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EDITORIAL
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BREASTFEEDING THROUGH THE CENTURIES

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Proper infant nutrition means providing the baby with proteins, fats, carbohydrates, vitamins, minerals and other essential substances that support normal growth, survival, functioning and development to the fullest of the infant's potential, as well as resistance to infections and diseases promoting normal functioning [1].

Mother's milk is the optimal source of nutrition in the first months of the baby's life. Breastfeeding is a natural continuation of intrauterine life and represents the biological unity between the mother and her child [2]. From the beginning of mankind, caring for the offspring was done by constant mother-child contact, and breastfeeding was there to provide the newborn with food, warmth, protection and a place in the society **(Figure 1)**.

Breastfeeding is the foundation for survival and health of a child and it provides essential and irreplaceable nourishment for child's adequate growth and development. It is the first immunization that protects the child against respiratory, gastro-intestinal, and other potentially life-threatening diseases. Also, breastfeeding offers protection against obesity and certain non-contagious diseases later in life [3].

As mammals, human beings have always depended on mother's milk for survival. Throughout the history, the practice of breastfeeding was shaped by cultural values, some of which are viewed today as damaging both for breastfeeding itself and the child's health. In order to demonstrate the importance of breastfeeding for health professionals and their role in its promotion, it is important to understand why some societies had supported, and still support certain beliefs and practices around infant feeding, while others offered no such support.

Breastfeeding, as the most natural way to feed infants, offers an insight into the development, progress and perfecting the process of feeding infants in the first year of life and brings us to a conclusion that breastfeeding must be supported in various ways within a society and regulated by law [4].

If we were asked today what food is given to the baby that is not breastfed, the most likely answer would be the non-human milk. However, if we were to go back to the prehistoric period we would discover that such answer was not acceptable. Prehistory is a period in human civilization in which humans hunted and gathered food to survive [5, 6]. If. at that time, a mother could not breastfeed, her newborn baby would be condemned to parish unless some other woman took her place. Likewise, mothers that had sufficient milk would continue breastfeeding their children up to the time when they were capable of finding their own food.

In the Neolithic Age, when humans tried to find solution to everyday problems with planting, harvesting and raising cattle, they still did not come up with an idea to use milk from animals in their own diet or feed it to their children [4–6]. When domestic animal herds were established, children began surviving thanks to animal milk [7–9]. The story of Moses, as told in the Old Testament, tells how the Jews and Egyptians sought healthy wetnurses in order to secure survival of children who were separated from their mothers. Another story gives approximate description of how long children were breastfed. For example: a thousand years before Christ (BC), when he was three years old. Samuel was taken to live with Eli, after he had been weaned (I Samuel 1: 22–24) [10].

Teachings in the Talmud, some 200 BC, supported and encouraged mothers to breastfeed their children for 2 years, stressing that by doing so the mothers "preserved life" of their children [8].

The people of Mesopotamia, Egypt and Hebron looked after their offspring in a similar manner that has remained unchanged and supported by their

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cultures for millennia. These people considered children to be divine gifts, so they treated them accordingly.

After Egypt had fallen under the Roman rule, the Greco-Roman culture became dominant and children lost their value. Families would make contracts with wetnurses, who would take their children to their own homes and returned them to their parents years later. This custom had spread throughout the Greek colonies and the Roman Empire and was eventually accepted in Europe. If there were no wetnurses available, children were fed from feeders or directly from an animal's udder. During the nursing period, some children were given animal milk and eggs and after weaning fruits and vegetables would be introduced [6–8]. Customs and traditions associated with child care have their roots in the Greco-Roman and Arab medical traditions.

According to Hippocrates, children should be fed solid foods as soon as they cut their first teeth [11]. In his work "Historia Animalium" Aristotle expressed his opinions, among other things, on human and non-human milk and discussed their quality and composition. He noted that milk contained whey and coagulum, that milk with a higher percentage of coagulum was more nutritious, but that milk with less coagulum was healthier for babies [12]. He also advised mothers, in case of a new pregnancy, not to breastfeed their children before they turned seven months old, because the colostrum in the milk becomes adequate only after childbirth. Little is known what food was given to children in that period. However, Fields presumes that infants were fed with milk combined with honey, cereals, chewed food or by directly suckling from animals [13].

In the first century of the *Anno Domini* the first Roman texts, by Soranus and Galen, discussed childcare [14]. Philosophers and moralists of that age were against wetnurses. Pliny, Plutarch, and Tacitus considered milk to be the best food for infants and that breastfeeding helped mother and child establish and strengthen emotional bonds "avoiding future problems" [6]. According to these authors, a mother should be relieved from her breastfeeding duty only in case of illness or new pregnancy [8]. Plutarch established the first moral movement supporting breastfeeding [15]. Physicians of that time were less demanding than their fellow philosophers when it came to breastfeeding. They believed that by suckling the child absorbed characteristics of the wetnurse. Therefore, attention was paid not only to their qualities as milk providers and the quality of milk, but also to personal traits of the wetnurse, her age, health, temperament, and morals [6, 8].

The knowledge of Ancient Greece arrived into the Arab world in the 9th century BC. To be more precise, Islamic authors of the medical texts were predominantly Persians. Notable among them was Avicenna, the author of the "Canon of Medicine", a five volume encyclopedia that represented a skilfully organized medical knowledge of that period [6, 8, 14, 16]. Avicenna believed that health and other characteristics of the nursing mother affected the health of the baby. He advised that children should be breastfed as long as possible, because he believed the mother's milk was the optimal food for infant growth and development [8, 16].

Medical writings of the Middle Ages are based on the knowledge of Galen, and later Avicenna that have been translated into the Latin and used at the European universities up to the 17th century [14, 16]. Discovery of the printing machine stimulated book publishing during the Renaissance (13th – 17th century). Among medical texts of the time, especially significant are four treatises on pediatrics known as "Pediatric Incunabula" [6, 17]. Authors of the new books followed the recommendations of Avicenna, they supported breastfeeding, but failed to recognize the significance of colostrum. The fact that books were printed in other languages, apart from Latin. was a great advancement that made information more accessible. In one of these books, from 1429, there is a drawing of a baby being fed from a receptacle similar to today's feeding bottles [8, 18].

During the Renaissance and Reformation, traditions gradually changed, with the appearance of the first handbooks for midwives. After the publication of "The Accomplished Midwife" in 1668, the whole concept of baby nutrition began changing [6]. The author of this book. Mauriceau expressed his opinion on nutrition of children whose mothers had no milk. Paps and other substitute foods were presented as an advantage over milk, while the advantage of breastfeeding gave way to the relationship between the mother and child [4].

In 1748, almost one hundred years later, in the book titled "An Essay upon Nursing, and the Management of Children, from Their Birth to Three Years of Age". by Cadogan, colostrum was recognized as a substance responsible for the elimination of meconium, and prevention of illnesses of mothers (milk fever) and children (gastro-intestinal infections). Also, he believed in the importance of the emotional bond that was established if the mother breastfed her child from the hour it was born. He opposed wetnurses and introducing non-milk food before the baby turned six months. He also believed that by boiling non-human milk the milk lost its properties and therefore might be harmful to the baby [6, 8].

In the period between 1675 and 1750, there was a gradual decline in infant mortality rate in England and Sweden. This phenomenon was attributed to the doctors and midwives that supported breastfeeding [4, 18]. This was the period when mortality rates among newborns were cut by half due to the change of habits related to infant nutrition. Infirmaries were set up (1747), where mothers spent several days after childbirth in order to establish lactation and

where the babies were placed on their mothers' breast within the first hour after being born [5].

During the 16th and the 17th centuries, mothers without milk often fed their children with paps and soups than by using services of wetnurses. Recipes for such paps included liquid ingredients (milk, beer, wine, vegetable and meat broth, and water), cereals (rice, wheat and corn flower, and bread) and supplements (sugar, honey, eggs, meat, and spices) [6, 8]. This type of nutrition was acceptable, only lacking vitamin C due to insufficient intake of fruits and vegetables [8].

During the 17th century, a nutritive status of children worsened because non-human milk and meat broth was gradually replaced by water. Eggs, butter, and animal fat, as sources of vitamin A and D, proteins, calcium, and iron, were no longer used. As a result of such diet, children started suffering from rickets, scurvy, and kidney stones. Contamination of utensils and food increased the incidence of tuberculosis. brucellosis and other gastro-intestinal infections [8, 19]. Non-dairy food that was introduced during 7–9 months of age was in the 16th century being introduced to babies between 2 and 4 months old.

The Industrial Revolution in England started in the 18th century. This was the time when migration from villages to towns took place and that irreversibly changed the habits of feeding infants that had been common practice for centuries. Urbanization changed the family life. People were poorer, they lived in inadequate facilities, in populous families, and in unhygienic conditions. People were exploited for minimum wages and, as a result, women were forced to go to work daily. Children were left behind at homes or in institutions. Wetnurses were nowhere to be found, as was the money to pay them. At that time techniques that would preserve the milk during the transport from the villages to the towns, or for storing milk at home were still unknown. This affected milk quality and safety [4].

At the end of the 19th century, scientist believed that high rate of malnourishment and mortality among infants was associated with the decreased percentage of children being breastfed and increased percentage of children being fed by non-human milk. In 1863, in Manchester, Jelliffe wrote that 60% of breastfed children were well-nourished at 9 months [19]. According to Radbill, feeding with paps or non-human milk caused 100% of mortality during the first week of life [20]. Simon's discovery in 1838 that cow's milk contained more protein and less carbohydrate than human milk propelled the argument that non-human milk should be introduced in human diet [21, 22].

What was the situation like in our region? There is a breastfeeding culture in the region. Between the 12th and the 15th century, the Serbian medieval medicine was thriving. In the 14th century, an Icon of the Mother of God the "Milk-Giver" was discovered in the Sopoćani Monastery where the Mother of God is depicted breastfeeding a baby. This image speaks of breastfeeding as a cultural heritage from that time. The "Milk-Giver" is one of the most beautiful pieces of Byzantine art and has a great artistic and spiritual value. Many Orthodox Christians offer their prayers to the icon, believing it would bring salvation to them. Young women pray to the icon in order to receive a blessing for health and happiness, and some women believe that the icon helps them during childbirth, or if they lack milk for breastfeeding, or when bringing up children, as well as for salvation of their souls [23].

With the fall of the medieval Serbian state, the folk medicine became even more non-scientific leading to degradation of science, culture and medical knowledge. People started turning to witchcraft again. One of the examples of superstitious beliefs was the practice of mothers taking their newborns to the river on the third day of their postnatal life in order to cleanse the evil, believing that witches took mothers' milk. It was also believed that such practice would make the milk flow like water ("Beliefs of the South Slavs about Childbirth and Infant Health" by Dr. Milorad Dragić) [24]. Also, breastfeeding was often part of numerous epics and stories. An example of one of the most beautiful and exalting epics is "The Building of Skadar" in which a young walled-up bride. wife of Gojko Mrnjavčević, begs her brothers in law:

…"A window for my bosom leave. Draw out for me my two white breasts. So when my tiny Jovo comes. He still can suckle from my breasts"… [25].

In the 18th century, the Renaissance in culture and medicine brought Enlightenment and the sorcerers and the healers gradually disappeared, whereas the first medical professionals started appearing. They were educated individuals from Vojvodina who spread their influence among the Serbs who were under the Ottoman rule for centuries. In the 19th century, a book titled "Čadoljub", about child care in the first year of infant life, was published in Budapest by a physician Gavrilo Pekarović, as a part of the general cultural advancement. The book was intended for Serbian mothers and included recommendations and advice related to nutrition and child care [26]. In 1881, in Sombor, Dr. Milan Jovanović Batut initiated a journal "Health" that featured an article about breastfeeding in one of the first issues [27]. Many years later (1936) the importance of natural diet and benefits of mother's milk were topics of many discussions. Well known professors of medicine (Ambrožić, Čupić, Kostić, Ružičić...) pointed out that "natural diet should be the first chapter of pediatrics and that the entire healthcare should be based upon it" [28].

As time passed by, cow's milk has proved indigestible. because it contained more whey and it was blamed for deaths due to "intoxication" by milk protein or due to excessive electrolytes [29]. This led physicians to prescribe diluted cow's milk before giving it to the infants. This practice generated the following problem: it was discovered that with such diet mortality rates dropped, but it was soon discovered that children were not gaining weight. In order to overcome these shortcomings, it was

recommended to add sugar or cream to the diluted milk. Thereafter, the cow's milk became the dominant milk in the nineteenth century because there were so many arguments in its favour [21]. Between 1850 and 1910, scientific advances in the field of bacteriology led to the process of pasteurization to be considered. This idea was suggested by Appert (1795), and by Pasteur (1864). They exposed wine to high temperatures thereby eliminating the bacteria that turned it to vinegar [9, 22]. This process was used to stop milk from going sour. Many physicians, however, opposed to the method because they believed it reduced the nutritional value of milk, making it low in vitamins C and D, Pasteurization only became a routine practice in the United States after 1915. Another huge idea of the nineteenth century in this area was supported by Gail Borden who discovered a method for making condensed milk. The milk was heated to high temperatures to remove half of the water content, and large quantities of sugar were added. The condensed milk was sterile and could be stored because it was bacteriologically safe. It was used to feed soldiers in the American Civil War in the period between 1861 and 1865 [22]. As with any new ideas, there were sceptical physicians who observed that infants were not thriving because of the low fat content in the milk [21]. The first commercial infant formula was developed by Liebig. He managed to produce a combination of ingredients that resulted in a powder. which, when added to milk, became food "identical" to breast milk. In other words, the formula contained wheat flour, sugar and potassium bicarbonate that were mixed with preheated milk [22,

30]. In 1874, the first complete artificial formula for infants was produced. In this formula ingredients were no longer mixed with milk because it already contained powdered milk (along with wheat flour, and sugar) [22]. Industrial advertising did the rest. This milk was presented to the mothers as "humanized milk" in order to confuse the terms "human" milk and "humanized" milk. This formula was easy to make, because it only required the powder to be mixed with water [30]. However, this product was not affordable to the general population in Europe and America because of its high cost.

Unfortunately, all the above mentioned factors, together with the promotion of the formula, resulted in the decrease of breastfeeding [6, 21]. In 1940, in the United States, the industrially produced milk formula was fortified with vitamin D and children were given juice in order to overcome small concentration of vitamin C in the milk. These were the reasons why physicians believed that using formula was safe [31].

In search for higher profits and due to falling birth rates caused by the Second World War, manufacturers began "perverse" promotion of breast milk substitutes [21]. The formulae that predominated between 1950 and 1960, were similar to evaporated milk, but with added vitamins, enriched with vegetable oil and minerals, and with low protein concentration [4].

After 1960, the birth rates started falling again. This time the reason was the contraceptive pill and the feminist movement. Breasts, which had had only functional connotations, gained esthetic and sexual roles. Feeding bottles were adopted as a symbol of women's liberation. Due to new advances, composition of formula was changed (lactose, fat, minerals, vitamins, and lactic acid) and they became more present in infant diet. Markets were also expanded. All of these changes contributed to the decline in breastfeeding rates and early introduction of supplementary foods in infant diet [19, 32, 33]. Although the real reason is unknown, the things started changing for the better in the 1970s. The reasons appear to be rooted in the change of mentality, which accused the industry of interfering in breastfeeding using aggressive advertising campaigns. Breastfeeding became popular again! Cow's milk was being introduced later into the infants' diet, because mothers opted to breastfeed their infants [31]. The reasons for this were probably the studies that linked cow's milk to anemia [2]. Formula fortified with iron was being recommended. In 1979, Fomon et al., found that there was a risk of overweight associated with introducing formula into infant diet. Obesity is caused by inability of children to refuse food after being full.

With the support of breastfeeding, nutritional recommendations for children were changing. For example, in 1976, 60% of children in the United States were already eating solid foods at 1 month, while in the early 1990s this rate was below 10% [31]. We need to stress that the prevalence of breastfeeding reached its lowest point in 1972, when it was 22%. In the following years the rates inclined,

Figure 1. Breastfeeding mother, painted by Vasja Milankov
Slika 1. *Majka-dojilja, naslikala Vasja Milankov*

Figure 2. Icon of the Mother of God the "Milk-Giver"
Slika 2. Ikona Bogorodice Mlekopitateljnice

reaching 34% in 1975, while in 1984 the prevalence was as high as 59.7% [34]. Among the factors most responsible for this increase in breastfeeding are most certainly the Natural Childbirth Movement (1960) and Baby Friendly Hospital Initiative launched by the World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF). Their goals were defined by Ten Steps to Successful Breastfeeding (1990) in order to promote, protect and support breastfeeding [35]. It was the initiative of these organizations to prohibit advertising baby milk, bottles, and pacifiers. Under such pressure, the industry adopted the following advertising slogan "breast milk is the best food for infants", emphasizing that these products should only be used if mothers did not have sufficient milk and if they could not breastfeed [21, 32]. In 1993, the WHO observed that breastfed children had a different pattern of growth and it defined the growth curves for breastfed children. Between 1997 and 2003, data were collected from children of six different ethnic groups to create international reference curves. The study showed that children from different ethnic groups had similar growth curves if given satisfactory conditions [36].

Science advances rapidly, and health professionals are obliged to follow such advances and make new ones. At present, WHO and the Pan American Health Organization currently recommend feeding infants only by breast milk until 6 months. Solid foods, non-dairy foods should be introduced from 6 months onwards (cereals, fruits, vegetables, meat). Salt and sugar, processed meat, juices, and canned food should be avoided [2, 37, 38]. Food consistency should be thickened gradually, while home cooked food should be preferred to processed foods as the latter contain additives, preservatives, and antibiotics [2, 39]. It is recommended that breastfeeding should be encouraged until 2 years of age [4]. In 2017, the WHO adopted the resolution WHA65/6, a Comprehensive Implementation Plan on Maternal Infant and Young Child Nutrition that lists six global targets concerning child nutrition by 2025. The target number 5 is to increase the rate of exclusive breastfeeding until 6 months postpartum to at least 50%. The exclusive breastfeeding is defined as exclusively breastfeeding a child until 6 months of age (without other foods and water), starting from the first hour of life and to be continued until the second year of life [40–42].

Globally, only 38% of children are exclusively breastfed until 6 months of age [43, 44]. There is a possibility to increase the rate of exclusive breastfeeding. Between 1985 and 1995, the rate of exclusive breastfeeding increased from 14% to 38%, but unfortunately decreased subsequently. However, 25 countries increased the rate of exclusive breastfeeding by 20%. The increase of exclusive breastfeeding rate may be of assistance in attaining the global nutrition targets and be a strong influence for the improved population health and state economy. It is necessary to examine the knowledge on the benefits of breastfeeding and based on it adopt measures and set priorities that would increase the rate of exclusive breastfeeding by at least 50% until 6 months postpartum [43].

In the end, for the sake of cultural and traditional heritage of our people, it is worth mentioning that the icon from the Sopoćani Monastery has become a symbol of the movement dedicated to breastfeeding, and that on March 14, 1992 the icon was used as a theme for a postage stamp and a poster "Breastfeeding is the Best" in the UNICEF and WHO breastfeeding campaign **(Figure 2)**.

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ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

EVALUATION OF SPIROMETRIC PARAMETERS AND MAXIMUM OXYGEN CONSUMPTION IN ATHLETES AND NON-ATHLETES

ANALIZA RESPIRATORNIH PARAMETARA I MAKSIMALNE POTROŠNJE KISEONIKA KOD SPORTISTA I OSOBA KOJE SE NE BAVE SPORTOM („NESPORTISTA")

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Summary

Introduction. There is a great interest to identify factors that influence the value of maximum oxygen consumption. The goal of this research was to assess the body composition, pulmonary parameters, and maximum oxygen consumption in different types of sports and in non-athletes. **Material and Methods.** The research included 149 male participants: aerobic athletes (n = 55), anaerobic athletes (n = 53) and non-athletes (n = 41). The participants were tested at the Department of Physiology, Faculty of Medicine of the University of Novi Sad. Anthropometric parameters and body mass index were measured. Also, the body fat mass was determined by bioelectrical impedance. pulmonary parameters by spirometry and maximum oxygen consumption on a bicycle ergometer. **Results.** The body mass index values in non-athletes were the highest and significantly different compared to the aerobic athletes (p = 0.01). Also, non-athletes had significantly higher values of body fat mass compared to athletes (p < 0.001). The pulmonary parameters were not significantly different between the tested groups (p > 0.05). However. the values of maximum oxygen consumption were significantly different between all three tested groups (aerobic athletes 53.75 ± 7.82 ml/kg/min; anaerobic athletes 48.04 ± 6.79 ml/kg/min; non-athletes 41.95 ± 8.53 ml/kg/min) (p < 0.001). A low degree of correlation was found between maximum oxygen consumption and pulmonary parameters in the tested groups. **Conclusion.** Body composition has an impact on the pulmonary parameters. The values of maximum oxygen consumption depend on the type of sport and training. and the highest values are in aerobic sports. There is a low degree of correlation between maximum oxygen consumption and pulmonary parameters in the tested groups.
Key words: Spirometry; Oxygen Consumption; Athletes; Body Composition; Body Mass Index; Sports; Anaerobic Threshold; Respiratory Function Tests

Sažetak

Uvod. Postoji velika zainteresovanost za identifikovanje faktora koji utiču na vrednost maksimalne potrošnje kiseonika. Cilj rada bio je procena telesnog sastava, respiratornih parametara i maksimalne potrošnje kiseonika kod osoba koji se bave različitim sportovima i osoba koje se ne bave sportom („nesportisti"). **Materijal i metode.** Istraživanje je obuhvatalo 149 ispitanika muškog pola: aerobni sportovi (n = 55), anaerobni sportovi (n = 53) i „nesportisti" (n = 41). Testiranje je sprovedeno na Zavodu za fiziologiju Medicinskog fakulteta Univerziteta u Novom Sadu. Izmereni su: antropometrijski parametri i izračunat je indeks telesne mase. Procenat masne mase je određen bioelektričnom impedancom, respiratorni parametri pomoću spirometra, dok je vrednost maksimalne potrošnje kiseonika merena na bicikl-ergometru. **Rezultati.** Najviše vrednosti indeksa telesne mase imale su osobe u grupi „nesportista" i u poređenju sa osobama iz grupe aerobnih sportova statistički se značajno razlikuju (p = 0,01). „Nesportisti" su imali statistički značajno više vrednosti procenta telesnih masti u odnosu na sportiste (p < 0,001). U sve tri grupe ispitanika nije dobijeno postojanje statistički značajne razlike (p > 0,05) u vrednostima respiratornih parametara. Međutim u pogledu vrednosti maksimalne potrošnje kiseonika između sve tri posmatrane grupe ona postoji (aerobna grupa 53,75 ± 7,82 ml/kg/min; anaerobna grupa 48,04 ± 6,79 ml/kg/min; „nesportisti" 41,95 ± 8,53 ml/kg/min) (p < 0,001). U sve tri grupe zabeležen je nizak stepen koeficijenta korelacije između vrednosti maksimalne potrošnje kiseonika i respiratornih parametara. **Zaključak.** Telesna konstitucija ima uticaj na parametre plućne funkcije. Vrednost maksimalne potrošnje kiseonika zavisi od vrste sporta i tipa treninga i najviša je kod osoba koje se bave aerobnim sportovima. Postoji nizak stepen koeficijenta korelacije između vrednosti maksimalne potrošnje kiseonika i parametara plućne funkcije unutar svih grupa.
Ključne reči: spirometrija; potrošnja kiseonika; sportisti; telesna kompozicija; indeks telesne mase; sport; anaerobni prag; testovi respiratorne funkcije

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Introduction

Morphological characteristics and functional abilities change due to physical activity, as a result of adaptation of the body to different training and competition requirements. and depend on the type of sports activity [1]. Aerobic capacity is an integral indicator of functional capacities of all systems involved in supply, transportation and energetic oxygen transformation (cardio-respiratory and functional ability of muscles to create adenosine triphosphate (ATP) in the presence of oxygen) [2]. Maximum oxygen consumption (VO_2max) is the best indicator of aerobic capacity of an organism [3, 4]. Considering the usage of VO_2max in diagnostic and therapeutic purposes there is a great interest to identify factors that affect the degree of physical competence [5, 6]. Physiological factors that could limit the VO_2max are respiratory diffusion capacity, maximal minute heart volume, oxygen transport capacity of the blood, and skeletal muscles properties [7, 8].

The goal of this study was to evaluate the body composition, respiratory parameters and values of VO_2max in athletes and non-athletes, in various types of sports, as well as to evaluate the degree of correlation between values of VO_2 max and parameters of respiratory function.

Material and Methods

This research included 149 male subjects who were divided into three groups: aerobic sports group (n = 55), anaerobic sports group (n = 53) and non-athletes (n = 41).

The tests were conducted at the Department of Physiology, Faculty of Medicine of the University of Novi Sad. All participants were informed about the procedures, the purpose of the examination and the confidentiality of personal data and signed a written consent to participate in the research. The approval of the Ethics Committee of the Faculty of Medicine. University of Novi Sad was obtained for conducting this research.

A clinical examination was performed and anthropometric parameters, body fat percentage, respiratory parameters, and VO_2max were measured. Body weight (BW) was measured with a medical balance decimal beam scale (accuracy 0.1 kg), body height (BH) using anthropometer according to Martin's technique with a precision of 0.5 cm, and body mass index (BMI) was calculated. Bioelectrical impedance, (OMRON BF300) was used for body composition analysis.

Parameters of the respiratory function: forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and percentage of the forced vital capacity – Tiffeneau index (FEV1%) were measured by spirometry (MIR Spirolab Enraf Nonius Holland).

Measurement of the VO_2max (ml/kg/min) was carried out by FITmate Pro device. In the first 2 minutes, respondents were pedaling a bike ergometer (Ergoselect 100 Cosmed, Ergoline GmbH, Germany) without any resistance, which was progressively increased by 25 W per minute thereafter. During the whole test subjects were supposed to maintain the cadence of 60 revolutions per minute (RPM). The heart rate was continuously monitored during the whole test by pulse meter.

The results were processed using the Jeffrey's Amazing Statistical Program (JASP) 0.8.0.1. The arithmetic mean (X), standard deviation (SD), single-factor analysis of variance (ANOVA) and Pearson correlation coefficient (r) were used in this study.

Results

Average values of BW, BH, BMI, age, and sport experience of all participants are presented in **Table 1**. We noticed that there was a significant difference in terms of BW and BH between the groups of aerobic and anaerobic athletes (p = 0.03) and in terms of BW between non-athletes and aerobic athletes (p = 0.001).

Values of BMI significantly differed between non-athletes and aerobic athletes (p = 0.01). A significant difference was observed comparing the percentage of body fat mass in aerobic and anaerobic athletes with the group of non-athletes (p < 0.001). Average values of spirometric parameters are shown in **Table 2**. The values of FVC, FEV1 and FEV1% in all three groups were not significantly different (p > 0.05).

Analyzing the values of VO_2 max significant difference (p < 0.01) between tested groups was found **(Graph 1)**.

Examining the relation between VO_2 max and FVC, FEV1 and FEV1% in tested groups a low degree of correlation was determined.

Discussion

This research shows that the values of BW and BH in the anaerobic compared to aerobic athletes are statistically significantly high. Aerobic sports are characterized by activities where the endurance is dominant, while in anaerobic sports development of explosive strength is emphasized. This can explain the observed difference [9]. In non-athletes with a sedentary lifestyle, changes in body composition are unavoidable. In our study, non-athletes were statistically significantly heavier with higher values of BMI compared to the aerobic athletes. When it comes to body fat mass, non-athletes had significantlly higher values of body fat mass than athletes, while the difference between aerobic and anaerobic athletes was not observed. Previous studies have shown that physical activity contributes to a reduction of body fat

Table 1. Anthropometric parameters and percentage of body fat mass
Tabela 1. Antropometrijski parametri i vrednosti procenta telesne masti

Parameters *Parametri*	Body weight (kg)/*Telesna težina (kg)*	Body height (cm)/*Telesna visina (cm)*	Body mass index (kg/m²)/*Indeks telesne mase (kg/m²)*	Body fat (%)/*Telesna mast (%)*	Age (years) *Starost (godine)*	Sport experience (years)/*Sportsko iskustvo (god)*
Aerobic sports/*Aerobni sportovi* X±SD	74.77±8.89	178±0.06	23.40±2.39	11.11±4.66	21.98±5.65	8.09±4.84
Anaerobic sports *Anaerobni sportovi* X±SD	79.80±11.87†	182±0.06†	24.14±2.96	11.08±3.93	20.94±2.53	7.25±4.02
Non-athletes *Nesportisti* X±SD	82.6±10.78*	181±0.06	25.05±2.69*	14.78±5.39*‡	21.19±1.72	/

Legend:† p < 0.05 between aerobic and anaerobic sports;* p < 0.05 between non-athletes and aerobic sports; ‡ p < 0.05 between non-athletes and anaerobic sports

Legenda:† p < 0,05 između aerobnih i anaerobnih sportova; p < 0,05 između nesportista i aerobnih sportova; ‡ p < 0,05 između nesportista i anaerobnih sportova*

mass. The lowest values of body fat mass were recorded in aerobic sports (triathlon, marathon, cross-country skiing, cycling) [10–12].

It is known that parameters of the respiratory function vary depending on the age, height, weight, gender and ethnicity [13]. The parameters of the respiratory system were not significantly different in physically active individuals compared to the sedentary population as it was reported in earlier study [14]. However, according to recent literature, the respiratory volumes can vary considerably depending on the type, intensity, duration and frequency of sports activities [15, 16]. Durmić et al, showed that the type of sport has a significant impact on the adaptation of the respiratory system [17]. Athletes who are engaged in sports where the endurance is dominant (rowing and canoeing, swimming, long-distance running and marathon, cycling, triathlon) have higher values of respiratory functions compared to athletes who train sports where the development of explosive strength is most important [18]. Our results did not show a statistically significant difference in the values of respiratory parameters between athletes
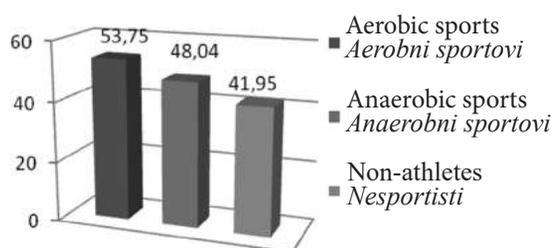
Graph 1. Maximum oxygen consumption in all three groups
Grafikon 1. Vrednosti maksimalne potrošnje kiseonika ispitivanih grupa

and non-athletes, as well as between different types of sports, compared to previous studies. These results can be explained by the difference in body composition of the participants.

Regular physical activity increases the values of VO_2max which is the main indicator of the fitness level [19, 20]. According to the literature data, the value of VO_2 max can be increased by 20–30% during 8–10 weeks of training and even by 40–50% during the

Table 2. Average values and standard deviation of spirometric parameters in investigated groups
Tabela 2. Prosečne vrednosti testova plućne funkcije sa standardnom devijacijom kod ispitivanih grupa

Parameters/*Parametri*	Aerobic sports/*Aerobni sportovi*	Anaerobic sports/*Anaerobni sportovi*	Non-athletes/*Nesportisti*
FVC (L) X±SD	5.10±0.64	5.16±0.76	5.39±0.71
FEV1 (L) X±SD	4.76±0.54	4.83±0.56	5.03±0.64
FEV1% X±SD	93.41±5.33	94.19±6.12	93.54±6.17

Legend: FEV1 - forced expiratory volume in the first second. FVC - forced vital capacity. FEV1% - percentage of the forced vital capacity (Tiffeneau index)

Legenda: FEV1 - forsirani ekspiratorni volumen u prvoj sekundi, FVC - forsirani vitalni kapacitet i FEV1% - Tifnoov indeks

period of 1–4 years of intense physical activity [21–23]. Our results showed significantly lower values of VO_2max in non-athletes compared to athletes engaged in different types of sports. Intensive physical activity causes expansion of the heart chambers and muscle hypertrophy and increases the density of the capillary network and the number of mitochondria which leads to an increase of VO_2max [24]. Numerous studies showed that values of VO_2max are significantly lower in the group of non-athletes compared to the aerobic and anaerobic athletes, which is in agreement with our results [25–31].

Analyzing the values of VO_2max in this study, we found that participants from the aerobic sports group have significantly higher values compared to the anaerobic group. Ranković et al., also proved that the values of VO_2max were significantly higher in aerobic sports (football players 51.70 ml/kg/min) compared to the anaerobic sports (volleyball players 45.40 ml/kg/min) [25]. Other authors reported that rowers achieved the best results of VO_2max (55.8 ml/kg/min) compared to football players (53.6 ml/kg/min) and judo athletes (47.2 ml/kg/min), because it is a sport that requires high aerobic capacity. The lowest values of VO_2max were found in judo athletes, which can be attributed to the anaerobic character of this sport [26]. Lazović-Popović et al., showed that football players have significantly higher VO_2max values (57.1 ml/kg/min) compared to karate players (48.98 ml/kg/min) [27]. Other researches showed that handball players (51.90 ml/kg/min) achieved significantly higher values of VO_2max compared to volleyball players (45.50 ml/kg/min) [28].

In this research, there is also a very low degree of correlation between the value of VO_2max and the parameters of the respiratory function in all tested groups. The same results were presented in previously conducted researches [27, 32]. MacAuley reported that there was a significant correlation between the respiratory function and physical activity, however, the relation between respiratory parameters and physical fitness has not been established. Our study included testing in the maximum load area, unlike other researches, which included testing in the mid-load zone. Previously, it was considered that there was a possibility that the degree of load may affect the respiratory function, and that the mid-load zone was not sufficient to push the respiratory function to the limits where it was a limiting factor in assessing physical capacity. However, our results showed that the degree of load was not a limiting factor. A low degree of correlation between VO_2max and respiratory parameters can be explained by the fact that the cardiovascular system actually limits VO_2max much more than the respiratory system [33, 34].

Conclusion

Considering values of the respiratory parameters, there was no significant difference between the tested groups. The value of maximum oxygen consumption in non-athletes was significantly lower compared to both groups of athletes. Subjects in the aerobic group had significantly higher values of maximum oxygen consumption compared to the anaerobic group. A low correlation between maximum oxygen consumption and respiratory parameters was observed in the tested groups.

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LIP PRINT PATTERN VARIATIONS IN THE POPULATION OF VOJVODINA PROVINCE, SERBIA – A PILOT STUDY

VARIJABILNOST OTISAKA USANA U POPULACIJI VOJVODINE, SRBIJA – PILOT STUDIJA

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Summary

Introduction. Lip prints are considered to be an important form of transfer evidence, analogous to fingerprints, and can be very useful in forensic investigations and personal identification. Although previous studies have confirmed that lip print patterns are individual and unique for each person, they show similarities between family members, strongly indicating the possibility of inheritance pattern of lip prints. Since heredity may play an important role in lip print development, ethnic groups geographically closely located tend to share similar patterns of lip prints in comparison to more distant populations, so a characteristic lip pattern may indicate a person's geographical and racial origin. **Material and Methods.** Lip prints of 211 healthy individuals (107 females and 104 males), residents of Vojvodina Province, Serbia, were analyzed and classified using the Suzuki and Tsuchihashi classification. **Results.** In the studied sample, type II pattern was the most common in both the upper and lower lip, being predominant in 45.85% of the studied samples. It was followed by types III, I, and IV accounting for 31.28%, 15.28% and 4.62%, respectively. The results of the current study are in accordance with the results of previous studies of European populations. The Pearson chi-square test showed a statistically significant difference between the lip print patterns in males and females. **Conclusion.** A comparison of lip print patterns between males and females showed a statistically significant difference, supporting the hypothesis that lip prints may be useful in sex determination.
Key words: Lip; Inheritance Patterns; Biometric Identification; Ethnic Groups; Sex Characteristics; Dermatoglyphics; Forensic Anthropology

Sažetak

Uvod. Otisci usana smatraju se značajnim oblikom transfernih tragova, analognih otiscima prstiju, koji mogu biti veoma korisni u forenzičkim istraživanjima i identifikaciji osoba. Iako su prethodne studije pokazale da su obrasci šara usana individualni i jedinstveni za svaku osobu, otisci usana pokazuju sličnosti među članovima porodice, snažno ukazujući na mogućnost postojanja obrasca nasleđivanja. Pošto nasledni faktori mogu imati značajnu ulogu u razvoju usana, geografski bliske etničke grupe mogu pokazivati međusobne sličnosti u morfologiji linija usana, u poređenju sa geografski udaljenijim populacijama. Karakteristični obrasci otisaka usana mogu ukazivati na geografsko poreklo i rasu osobe. **Materijal i metode.** Otisci usana 211 zdravih osoba (107 žena, 104 muškarca), stanovnika Vojvodine, Srbija, analizirani su i klasifikovani prema klasifikaciji Suzukija i Cukihašija. **Rezultati.** U analiziranoj populaciji, tip II najzastupljeniji je i na gornjoj i donjoj usni, čineći 45,85 ukupnog broja uzoraka. Prema zastupljenosti slede tipovi III, I i IV, sa učestalošću od 31,28%, 15,28% i 4,62%. Dobijeni rezultati u skladu su sa rezultatima prethodnih istraživanja vršenih u evropskoj populaciji. Pirsonov hi-kvadrat test ukazao je na statistički značajne razlike između zastupljenosti pojedinih tipova otisaka usana unutar muškog i ženskog pola. **Zaključak.** Poređenje između tipova obrazaca ženskog i muškog dela uzorka ukazalo je na statistički značajne razlike, potvrđujući hipotezu o primenljivosti analize otiska usana u identifikaciji pola.
Ključne reči: usna; obrasci nasleđivanja; biometrijska identifikacija; etničke grupe; polne karakteristike; dermatoglifi; forenzička antropologija

Introduction

Lips are two highly sensitive mobile folds, composed of skin, muscle, glands and mucous membrane, surrounding the oral orifice and forming the anterior boundary of the oral cavity. In the transition zone of human lips. known as vermilion. between the inner labial mucosa and outer skin, normal lines and fissures form wrinkles and grooves. These lip features have been named "sulci labiorum rubrorum" and the examination of lip prints is referred to as „cheiloscopy", from the Greek word *cheilos* (χείλος) – lip [1].

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Despite the fact that the different lip lines were first noticed and described by R. Fisher at the beginning of the 20th century, subsequent years have not lead to a detailed study of the uniqueness or permanence of lip patterns, their genesis in the pre-natal period or their practical application [2, 3]. In 1932, the French criminologist Edmond Locard first acknowledged the importance of cheiloscopy. In 1947. Snyder suggested the possibility of lip print analysis as a method in personal identification, while Santos, in 1967, concluded that lip patterns could be classified into different groups, and each group could be further divided into several subtypes [4, 5].

During the seventh decade of the 20th century, two Japanese scientists, Tazuo Suzuki and Yasuo Tsuchihashi, examined lip print pattern variations in a sample of 1.364 persons at the Department of Forensic Odontology at the Tokyo University. Based on this research, it was concluded that the arrangement of lines on the vermilion is individual and unique for each human being [6]. In 1973, Renaud studied 4.000 lip prints and confirmed the conclusions of Japanese scientists, supporting the idea of lip print singularity [7]. Two identical twins seemed to be indistinguishable by every other means, except their lip prints, which significantly differed [6].

In 1974, Tsuchihashi performed another study which resulted in a simple classification of lip patterns **(Figure 1)**. The results of this study enabled the author to confirm not only lip print singularity. but also lip response to trauma. The author observed that after healing, the lip pattern was equal to that prior the injury [8]. In the following years, several other classifications were suggested, but the classification based on the research of Suzuki and Tsuchihashi is still the most widely used in forensic practice and anthropological studies.

Studies of lip print variations are, in general, rarely conducted in European populations. This is the very first study on the lip pattern polymorphism in Serbia, to our best knowledge.

The aim of the present investigation was to classify the lip print patterns in the sample of the population from Vojvodina Province, Serbia, and to evaluate the potentials of lip print patterns in human identification and in forensic cases. In addition, the study was intended to verify the potential significance of lip print configuration for sex determination in forensics and to contribute to the cheiloscopy literature with the specific characterization of the studied population.

Material and Methods

This study included 211 healthy individuals (107 females and 104 males), residents of Vojvodina Province, Serbia, aged 19 – 58 (mean age 26.1). Written informed consent was obtained from all participants.

Subjects with known hypersensitivity to lipsticks or previous cosmetic or surgical lip treatment were not included in the study. Also, subjects with an inflammatory process or trauma of the lips were excluded.

Lip print collection was done after all the participants cleaned their lips with a wet napkin and a thin layer of lipstick was applied on dry lips. The impressions of the relaxed and slightly separated lips were taken on the copy paper. Two to five lip prints were taken from each participant, in order to obtain at least one complete print sufficient for identification of different lip areas.

Each lip print was divided into four areas, assigned with the numbers 1 – 4 in a clockwise sequence starting from the right half of the upper lip. Thus, 844 segments from 211 individuals were obtained for lip pattern print analysis. Each area was studied separately to determine the type of the grooves.

Lip prints were studied with a standing magnifying lens with an autonomous light source. The lip print pattern was determined by two observers independently using Suzuki and Tsuchihashi classification, based on the predominant type of lines for each area. In case of conflicting results, the third observer held the responsibility of determining the final type of the lip print pattern.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 19.0 software (IBM Corp., Armonk, NY, USA). A Pearson's chi-square test was used to compare qualitative data and determine statistical significance between males and females, regarding the upper and lower lip. The level of statistical significance was set at $p < 0.05$. Post hoc analyses were done after the basic statistical analysis.

Results

The obtained results showed that type II pattern was the most common in both lips, being predominant in 45.85% of the studied samples, followed by types III, I, and IV (31.28%, 15.28% and 4.62%, respectively). The least common patterns were types I' and V, accounting for 1.78% and 1.18% **(Table 1)**. The Pearson's chi-square test of goodness of fit was performed to determine whether the six lip pattern types were equally distributed among our population. As expected, they were not equally distributed, (χ^2 (5, N = 844) = 847.60, $p < 0.001$)).
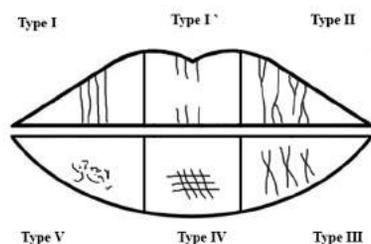
Type I - complete vertical, type I'- incomplete vertical, type II - branched, type III - intersected, type IV - reticular pattern, type V - irregular
Tip I - potpuni vertikalni, tip I'- nepotpuni vertikalni, tip II – razgranati, tip III - ispresecani, tip IV - retikularni (mrežasti), tip V - nepravilni

Figure 1. Suzuki and Tsuchihashi classification of lip print patterns
Slika 1. *Klasifikacija otisaka usana po Suzukiju i Cukihašiju*

Table 1. Prevalence of lip print pattern types
Tabela 1. *Prevalencija različitih oblika otisaka usana*

Pattern type *Tip otiska*	Females – lip areas/*Žene – regije usana*		Males – lip areas/*Muškarci – regije usana*		Total/*Ukupno*	
	n	%	n	%	Total *Ukupno*	%
I	91	21.26	38	9.13	129	15.28
I`	9	2.10	6	1.44	15	1.78
II	216	50.47	171	41.11	387	45.85
III	99	23.13	165	39.66	264	31.28
IV	10	2.34	29	6.97	39	4.62
V	3	0.70	7	1.68	10	1.18

In males, the lip prints indicated an almost equal predilection of branched and intersected patterns (41.11% and 39.66%, respectively), followed by complete vertical (9.13%) and reticular grooves (6.97%). The irregular and incomplete vertical patterns were infrequent, found in 1.68% and 1.44% of the sample, respectively **(Table 1)**.

In females, the branched pattern was predominant, accounting for 50.47% of the studied lip prints. In contrast to the male sample, similar prevalences of type III and type I were found (23.13% and 21.26%) in the analyzed female lip prints. The incomplete vertical and irregular patterns were found in 2.1% and 0.7% of cases, respectively.

The Pearson's chi-square test showed a statistically significant difference between genders in lip print pattern types (χ^2 (5, N = 844) = 54.80, p < .001)). The post hoc Bonferroni adjustment analysis was done (p < 0.005), and it was found that types I, III and IV statistically significantly differed between genders [9, 10].

In this study, the upper lip in both genders showed a predominance of type II pattern, followed by type III and type I **(Table 2)**. with statistically significant results of Pearson's chi-square test (χ^2 (5, N = 412) = 20.12, p <.05)). Bonferroni post hoc analysis (p < 0.0042) revealed that the statistically significant difference in the upper lip pattern between genders was due to the difference in pattern types I and III. On the lower lip, analysis showed that the lip pattern types significantly differed (χ^2 (5, N = 412) = 44.536, p < 0.001)), as the branched pattern was predominant in females (53.27%), while type III pattern was the most common in males (40.86%), followed by type II (36.6%). The type I pattern was more often recorded on both lips in females (20.09% and 22.43%, respectively) in comparison to the male lip prints (7.69% and 10.58%. respectively). Post hoc Bonferroni adjustment analysis (p < 0.0042) showed that lower lip pattern significantly differed between genders in all lip pattern types except type V and type I'.

Discussion

Lip prints are considered to be an important form of transfer evidence, analogous to fingerprints, and can be very useful in forensic investigations and personal identification, being often present on objects such as drinking glasses, cutlery items, paper napkins, cigarette butts or tissues. They can be also found in less typical places, such as the surface of windows, paintings, doors and plastic bags, establishing a link between the subject and the crime scene. These prints are found not only as visible lipstick marks, but as well as marks of humidity present in lips through saliva, mixed with the oiliness secreted by neighboring salivary and sebaceous glands. These substances, particularly the lipids and fatty acids, are transferred to an object through lip contact which becomes visible by using different forensic techniques [11–13].

Although previous studies have confirmed that lip patterns are individual and unique for each person. lip

Table 2. Lip print pattern types of upper and lower lips with sex distribution
Tabela 2. *Zastupljenost tipova otisaka usana gornje i donje usne prema polu*

Pattern type *Tip otiska*	Upper lip/*Gornja usna*		Lower lip/*Donja usna*	
	Female n (%) *Žene (%)*	Male n (%) *Muškarci (%)*	Female n (%) *Žene (%)*	Male n (%) *Muškarci (%)*
I	20.09	7.69	22.43	10.58
I`	2.34	0.96	1.87	1.92
II	47.66	46.15	53.27	36.06
III	25.23	38.46	21.03	40.86
IV	3.74	5.29	0.94	8.65
V	0.94	1.44	0.47	1.92

print similarities between family members strongly indicate the possibility of inheritance patterns. In 2008, Augustine et al. evaluated a possible hereditary lip print pattern, and found a significant resemblance between parents and their offspring [14]. Vats et al. also concluded that there is a similarity of lip prints among parents and their offspring, with no clear association in lip print patterns of siblings, including monozygotic twins [15]. Ghalaut et al. reported an 83% resemblance of lip patterns and no statistically significant difference in the parents/offspring study, indicating the influence of heredity on wrinkles and grooves morphology present in the red part of human lips [16]. These findings implicate that, since heredity may play an important role in lip print development, geographically close ethnic groups may tend to share similar lip print patterns in comparison to distant populations. Thus, a characteristic lip pattern may indicate the geographical and racial origin of a person [17].

Several studies have confirmed that lip print patterns may significantly vary among distinct populations. A collaborative study of populations from India, Saudi Arabia, Spain and Nigeria showed significant inter-ethnic differences [18]. The Indian prints revealed an almost equal propensity for bifurcated and incomplete vertical patterns (corresponding to types II and I') accounting for approximately 30%. The principal pattern observed in the population of Nigeria was the complete vertical type (corresponding to type I), which was found in 50% of analyzed segments. The bifurcated pattern was the most prevalent in the populations of Saudi Arabia and Spain (38% and 66%, respectively). A study of Malay population showed that the most common lip print pattern among the study group was type I (29.84%) followed by type II and type III [19]. Costa et al. [1] reported the prevalence of types II and III (35.5% and 34%, respectively) in the Portuguese population, while Popa et al. [20] noted similar results in the population of Romania, with the predominance of type III, followed by type II.

The results of the current study are in accordance with the results of previous studies of European populations, showing the prevalence of bifurcated and intersected lip print patterns.

In several recent studies gender differences were recorded in lip print patterns, suggesting that variations in patterns among males and females may help in the context of personal identification and sex determination. In European population [1, 20] patterns I and II were dominant in females, while patterns III and IV were more characteristic for males. However, the most prevalent type for each gender was not the same in every study, suggesting population-specific characteristics of lip patterns [1, 3, 20–22]. Although some researchers claimed high success rate in the detection of gender based on the lip print pattern type, a number of studies reported that there was no statistically significant difference between male and female lip print patterns [18, 23, 24]. Analysis of lip patterns for sex estimation can be a subjective process which must be performed with great caution, since a false estimation can prejudice a forensic case [25].

The results of this study showed that the upper lip in both genders showed a predominance of type II pattern. Statistical analysis revealed a significant difference in upper lip patterns between genders due to type I and III patterns. In addition, lower lip patterns significantly differed between genders in all lip pattern types except type V and type I, supporting the hypothesis that lip prints may be useful in gender determination.

Conclusion

Being permanent and distinctive, lip print patterns may be used to distinguish individuals and they are an important form of transfer evidence which can be found at crime scenes and provide a direct link to a suspect.

Since heredity may play an important role in lip print development, the characteristic lip pattern may indicate the geographical and racial origin of a person.

The current study showed the prevalence of the bifurcated and intersected lip print patterns in the population of Vojvodina Province, which is in agreement with the results of previous studies in European populations.

Cheiloscopy requires more long-term studies with larger samples in order to be substantially documented and provide more reliable and accurate results.

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BIOFEEDBACK IN THE TREATMENT OF LOWER URINARY TRACT SYMPTOMS IN CHILDREN

BIOFIDBEK U TRETMANU SIMPTOMA DONJEG URINARNOG TRAKTA KOD DECE

Marina ĐERMANOV[1,2] and Dragana ŽIVKOVIĆ[1,2]

Summary

Introduction. Bladder and bowel dysfunction describes a large spectrum of lower urinary tract symptoms along with fecal elimination issues. The aim of the study was to analyze the effects of biofeedback treatment in children with lower urinary tract symptoms. **Material and Methods**. A prospective study analyzed the effects of biofeedback treatment conducted in children with lower urinary tract symptoms. Questionnaires and voiding diaries were collected prior to the treatment. The patients were followed for two weeks on daily basis. After the completion of the treatment, the data from voiding diaries and questionnaires were analyzed. **Results.** A total of 18 children were referred for biofeedback treatment. Seven patients had an overactive bladder. seven had isolated dysfunctional voiding, and in the third group three had difficulties starting to void and one had daily incontinence with dysfunctional voiding. A total of 14 patients presented with improvement of symptoms. The analyzed data showed no measurable improvement in one patient, even though he reported a personal feeling of improvement. Three patients without positive effects of the therapy were immature and non-cooperative. In six out of seven patients with overactive bladder with urine leakage, the symptom disappeared by the end of the treatment. **Conclusion**. Biofeedback is a very useful tool in the treatment of lower urinary tract symptoms in pediatric population. Although the main indication for initiating this therapy is dysfunctional voiding, the study showed an improvement of symptoms in patients with overactive bladder as well.
Key words: Lower Urinary Tract Symptoms; Biofeedback. Psychology; Urinary Bladder. Overactive; Urinary Incontinence. Urge; Urination Disorders; Child

Sažetak

Uvod. Sindrom disfunkcije mokraćne bešike i creva predstavlja široki spektar različitih simptoma donjeg urinarnog trakta zajedno sa teškoćama u eliminaciji stolice. Cilj ove studije bio je da se analizira efekat biofidbek terapije kod dece sa funkcionalnim poremećajem mokrenja. **Materijal i metode.** Sprovedena je prospektivna studija za analizu efekta biofidbek terapije kod dece sa funkcionalnim poremećajem mokrenja. Sakupljani su upitnici i dnevnici mokrenja pre terapije. Pacijenti su svakodnevno praćeni tokom dve nedelje tretmana. Po završetku terapije analizirani su podaci dobijeni iz dnevnika mokrenja i upitnika. **Rezultati**. Kod ukupno 18 pacijenata sprovedena je biofidbek terapija. Sedam pacijenata je imalo hiperaktivnu bešiku. Drugih sedam pacijenata imali su izolovano disfunkcionalno mokrenje. U trećoj grupi pacijenata, tri pacijenta su imali teškoće u započinjanju mokrenja i jedan pacijent je imao dnevnu inkontonenciju sa disfunkcionalnim mokrenjem. Kod 14 pacijenata je registrovano poboljšanje simptoma. Analizom podataka uočeno je da kod jednog pacijenta nije bilo merljivog poboljšanja, iako je pacijent imao subjektivni osećaj poboljšanja simptoma. Tri pacijenta kod kojih nije registrovan pozitivan efekat terapije bili su nezreli i nekooperativni. Kod šest od sedam pacijenata sa hiperaktivnom bešikom sa prisutnim oticanjem urina, simptomi su u potpunosti nestali do kraja tretmana. **Zaključak.** Biofidbek se pokazao kao veoma dobra metoda lečenja pedijatrijskih pacijenata sa funkcionalnim poremećajem mokrenja. Iako je glavna indikacija za ovaj vid terapije disfunkcionalno mokrenje, studija je pokazala poboljšanje simptoma i kod pacijenata sa hiperaktivnom mokraćnom bešikom.
Ključne reči: simptomi donjeg urinarnog trakta; povratna informacija; hiperaktivna bešika; disfunkcionalno mokrenje; poremećaji mokrenja; dete

Introduction

Bladder and bowel dysfunction (BBD) describes a large spectrum of lower urinary tract symptoms (LUTS) along with fecal elimination issues such as constipation and encopresis [1]. Children without neurological or anatomical abnormalities of the urinary tract frequently have voiding disorders. Children with voiding disorders may present with a urinary tract infection and/or different LUTS, usually dysuria, urgency, urinary frequency, daytime incontinence, enuresis, dribbling, straining and urinary retention [2, 3]. Underlying urological conditions responsible for LUTS are most commonly overactive bladder (OAB) and dysfunctional voiding (DV) [1].

The diagnosis of voiding dysfunction is made by detailed medical history, voiding diary analysis, clinical examination, ultrasound examination, uroflow and urodynamic investigations [4]. Voiding diaries kept by the parents help in evaluation of voiding schedule, relationship between voiding and daily

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Abbreviations

BBD	– bladder and bowel dysfunction
LUTS	– lower urinary tract symptoms
OAB	– overactive bladder
DV	– dysfunctional voiding
PVR	– post void residual
EMG	– electromyography
BF	– biofeedback
VUR	– vesicoureteral reflux
UTIs	– urinary tract infections

events such as meals, breaks at school and play activities, the occurrence of urgency or incontinence, as well as the voided volume [4, 5]. The physical examination includes abdominal palpation for masses, detection of full bladder or full rectal ampulla. The patient's back is inspected for signs of occult spinal dysraphism. The penis should be evaluated for earlier surgery, meatal stenosis and palpable urethral abnormalities (stricture. diverticulum). The vaginal introitus should be inspected for the presence of labial adhesions, recessed urethra, urine pooling, infection and signs of sexual abuse [4, 6]. Urine analysis is used to detect glycosuria, proteinuria. diabetes insipidus or infection. Ultrasound examination of the bladder is performed when a child feels that his/her bladder is "full", and can be used to estimate functional bladder capacity. Measured capacity is compared with the expected bladder capacity for the age, while post void residual (PVR) urine can be assessed after voiding. PVR measurement helps not only to identify patients who need further evaluation. but also to evaluate the effects of the treatment during the follow-up [5, 6]. A non-invasive uroflowmetry, with or without electromyography (EMG), allows the best assessment of detrusor contraction coordination with voluntary relaxation of the external sphincter [1, 6].

Treatment of any kind of LUTS starts with urotherapy that encompasses education about urinary tract physiology and dysfunctions, behavioral training regarding adequate fluid intake, voiding habits and postural training. Behavioral interventions are well suited for the primary health care. Elimination of bladder irritants from the diet, management of fluid intake, weight control, bowel management and timed voiding regimens are some of behavioral interventions which are leading to healthy bladder habits [7]. A lifestyle modification may be the only therapy needed in the majority of patients. Antimuscarinic agents are most commonly used for the treatment of OAB, with or without behavioral treatment [8].

Biofeedback (BF) therapy is a nonsurgical. non-pharmacological treatment of lower urinary tract dysfunction. Frequently, it is defined as a bladder re-education or rehabilitation [9]. Animated BF uses video-computerized systems to teach patients about controlling their body and normal physiological processes [10]. Electromyographic instruments electrically measure levels of muscle activity. Pelvic-floor exercise consists of tightening the pelvic muscles and holding the contraction for a period of time, followed by a resting period [11]. These changes in the electrical muscle activity are transformed into visual and audio signals [12, 13]. Using surface electrodes to identify changes in muscle activity, the user is visually or audibly warned [12]. Individuals learn to control the level of muscle activity in the body and in doing so they learn to achieve state of willing relaxation [11].

Material and Methods

Patients with LUTS were referred for BF treatment after 2 weeks of urotherapy. Our aim was to analyze the effects of BF treatment in children with LUTS.

After the approval by the Ethics Committee, a prospective study on the effects of BF treatment in patients with LUTS was conducted. Voiding diaries and questionnaires were collected prior to the BF treatment. The patients were followed throughout the treatment and diaries and questionnaires were analyzed after the therapy. The treatment was conducted daily for two weeks. According to patient's ability to control pelvic floor muscles, they underwent either pediatric (in most cases). or medium pediatric protocol (in three patients). The pediatric protocol included 40 repetitions, with both contraction and relaxation phase, each lasting for 5 seconds, whereas the medium pediatric protocol included 20 repetitions, with both contraction and relaxation phase lasting 10 seconds each. Patients were able to choose between different animations modes. The data obtained in the study were statistically analyzed.

Results

A total of 18 children underwent BF treatment. The youngest patient was 4 years old, and the oldest was 13 years old, 7.6 years on average. All the patients were completely evaluated, including urodynamic examination. Seven patients had OAB with involuntary detrusor contractions during filling, complicated with an increased activity of the pelvic floor muscles registered on EMG during voiding. The other seven patients had isolated DV. The third group of four patients was a heterogenic group. One patient had spina bifida with insufficient external sphincter, one patient had an episode of transverse myelitis, one complained of painful voiding and the forth one had difficulties starting to void **(Table 1)**.

A total of 14 patients presented with improvement of symptoms. There was no measurable improvement in one patient, even though he reported a personal feeling of improvement. Three patients without positive effects of the therapy were either immature and/or non-cooperative. In six of seven patients with OAB, leakage was noticeable during contractions at the first few sessions, but it disappeared by the end of the treatment.

An increase in the strength of pelvic floor muscles was noted in all the patients. The mean contractions in all the patients over time are presented in **Graph 1**.

Discussion

Epidemiological studies reported LUTS in 21.8% school-age children [3]. Up to 40% of the pediatric patients in urology clinic have LUTS [4]. Seventy-

Table 1. Indications for biofeedback
Tabela 1. Indikacije za biofidbek

Indications/*Indikacije*	OAB/DV/*HAB/DM*	DV/*DM*	Other/*Ostalo*
Number of patients/*Broj pacijenata*	7	7	4

Legend: OAB – overactive bladder; DV – dysfunctional voiding
Legenda: HAB – hiperaktivna bešika; DM – disfunkcionalno mokrenje

five percent of these patients are evaluated between 3 and 10 years of age, and about 20% is between 11 and 17 years of age [14]. Symptoms appear more predominantly in girls compared to boys [3].

The BBD is a potential cause of significant physical and psychosocial burden for children and their families [1]. The condition may have a negative impact on self-confidence and quality of life, feeling of shame, poor progress at school, aggression. The quality of life of the patients with LUTS and their families is profoundly impacted but can be easily improved with adequate treatment [1, 8, 15].

Pharmacological agents used for the treatment of DV include alpha-adrenergic blockers (acting on the smooth muscle of the external sphincter) and anticholinergic agents (acting on the detrusor muscle). Although alpha-blockers are routinely used in adult population for facilitating bladder emptying. their use in children is currently off-label; yet, several studies have shown encouraging results [16].

Another pharmacological approach to facilitate bladder emptying is botulinum-A toxin (Botox®). Botox inhibits acetylcholine release at the presynaptic neuromuscular junction and results in flaccid muscle paralysis. Clinically, Botox injections have been used safely for the treatment of focal dystonia, muscle spasm and spasticity. Botox has been subsequently applied in patients with LUTS and there are several reports of Botox treatment in children with detrusor-external sphincter dyssynergia [16].

Urotherapy may be the only therapy needed in the majority of patients with LUTS. It has been shown to decrease urinary tract infections (UTIs), improve constipation and decrease the need for intervention in patients with vesicoureteral reflux (VUR) [16].
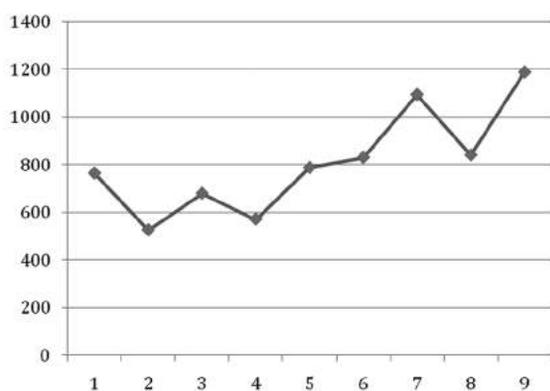
Graph 1. Mean contractions in all the patients over time
***Grafikon 1**. Prikaz srednje vrednosti kontrakcija kod svih pacijenata tokom vremena*

Rehabilitation of LUTS includes prompted voiding. timed voiding with bladder training and lifestyle modification. The combination of standard urotherapy with BF therapy significantly improves the results [17, 15]. Our study investigated the effectiveness of a combination of urotherapy and BF therapy in 18 patients with LUTS. By evaluating the results of pelvic floor muscles EMG prior to and following the BF therapy, 14 out of 18 participants gained significant improvement. Authors have described a significant improvement in UTIs, urge incontinence, fractionated voiding, constipation, voided volume, maximum flow rate, average flow rate as well as postvoid residue in both patients with DV and OAB, but better results are observed in patients with DV [18].

Biofeedback has become a modality for the treatment of DV, DV has been associated with UTIs and VUR. Various studies have shown a great improvement in symptoms of DV after BF therapy. The results have shown a decrease of daytime and nighttime incontinence, patients were infection free and VUR was cured [19].

In patients with OAB, initial therapy consists of regulation of voiding frequency and voiding charts. Anticholinergic medications can be added, and if this fails, pelvic floor training with BF may be proposed [19]. Training to achieve pelvic floor relaxation during voiding may have a role in treating OAB. Some authors suggest that long term pelvic floor hyperactivity results in neural remodeling, causing end-organ histologic changes, resulting in clinical symptoms. BF helps patients to visualize the movements of their pelvic floor and therefore teaches them how to control the contraction and relaxation [3, 10].

In our study, three patients with OAB and one patient with DV showed no significant improvement. Higher rate success has been found in patients who understood the concept of BF. Good prognostic factors were associated with patient's motivation, cooperation and maturity [10].

There was no measurable improvement in one patient. even though he reported a personal impression of improvement. Some authors explain that patients, who find the setting where the testing is done uncomfortable. may have worse performance during examinations. Also, some patients may come unprepared for testing. They are either not well hydrated, or may feel expectation to void and express urgency sooner than in a more typical setting [20].

Patients with difficulties in starting to void and with painful voiding have recovered completely after BF therapy, while patients with transverse myelitis and spina bifida have shown an immediate improvement after the therapy, but for a short period of time. These

patients may be considered for a life long treatment to sustain sufficient control of the symptoms. Patients may present with a combination of abnormalities that impact bladder emptying, but that are not always purely pelvic floor dysfunctions. Many of these patients can also benefit from urotherapy and BF [16, 21].

Conclusion

Biofeedback serves as an important method in the treatment of children with lower urinary tract symptoms. It is a good complementary method in education and reeducation for establishing physiological functions of the urinary bladder. The results can give an encouragement for implementation of this method in treating patients with lower urinary tract symptoms. Although the main indication for initiating this therapy is dysfunctional voiding, the study showed an improvement of symptoms in patients with overactive bladder as well. It is of utmost importance that patients are well prepared, well educated how biofeedback works, motivated and able to understand the purpose of the treatment.

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SOCIAL AND MENTAL FUNCTIONING IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

SOCIJALNO I MENTALNO FUNKCIONISANJE ŽENA U POSTMENOPAUZI SA SMANJENOM MINERALNOM KOŠTANOM GUSTINOM

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Summary

Introduction. Osteoporosis is a systemic, metabolic, progressive bone disease characterized by reduced bone mineral density leading to bone fragility and reduced quality of life. The objective of this study was to examine the quality of social and mental functioning in postmenopausal women with reduced mineral bone density. **Material and Methods.** This prospective cross-sectional study included 210 postmenopausal women aged ≥ 50 years, who were referred for osteodensitometry to the Special Hospital for Rheumatic Diseases Novi Sad, Serbia. The study was conducted in the period from February 24 to April 3, 2017. All women completed the Serbian version of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (41). They all underwent bone mineral density measurement in two regions of interest, and the results were interpreted according to the current definition of osteoporosis. The participants' social and mental functioning was analyzed including the following variables: age, place of residence, educational attainment, employment, nutritional status, bone mineral density, and low-trauma fractures. Statistical processing and analyses were performed using Statistical Package for the Social Sciences, version 20. **Results.** A statistically significant negative correlation was noted between social functioning and the T-score for the femoral neck (r = -0.438), hip (r = -0.412) and spine (r = -0.226), as well as mental functioning with the T-score for the femoral neck (r = -0.424), hip (r = -0.454) and spine (r = -0.319). Patients with a history of fractures had a poorer quality of social functioning (t = 2.17, p < 0.05). **Conclusion.** The examinees of older age, with poor socio-demographic status, reduced bone mineral density, history of low-trauma fractures presented with lower quality of social and mental functioning.

Key words: Postmenopause; Osteoporosis, Postmenopausal; Bone Density; Social Participation; Mental Health; Surveys and Questionnaires; Quality of Life; Demography

Sažetak

Uvod. Osteoporoza je sistemsko, metaboličko, progresivno koštano oboljenje čija je karakteristika smanjenje mineralne koštane gustine koje dovodi do fragilnosti kosti i smanjenja kvaliteta života. Cilj rada je ispitivanje kvaliteta socijalnog i mentalnog funkcionisanja kod žena u postmenopauzi koje imaju smanjenu mineralnu koštanu gustinu. **Materijal i metode.** Prospektivna studija preseka obuhvatila je 210 ispitanica, starosti ≥50 godina, koje su upućene na osteodenzitometrijsko snimanje u Specijalnu bolnicu za reumatske bolesti u Novom Sadu. Studija je sprovedena u periodu od 24. 2. do 3. 4. 2017. godine. Sve ispitanice su popunile upitnik koji je sastavio ispitivač i srpsu verziju Upitnika za procenu kvaliteta života Evropske fondacije za osteoporozu (41). Svima je merena mineralna koštana gustina na dve regije od interesa i dobijeni rezultati interpretirani su prema važećoj definiciji osteoporoze. Analizirali smo socijalno i mentalno funkcionisanje ispitanica, uključujući sledeće varijable: starost, mesto boravka, stepen obrazovanja, zaposlenost, nutricioni status, mineralnu gustinu kostiju i frakture usled manje traume. Statistička obrada i analiza podataka urađena je korišćenjem softvera Statističkog paketa za društvene nauke, verzija 20. **Rezultati.** Postoji statistički značajna negativna korelacija socijalnog funkcionisanja sa T skorom vrata butne kosti (r= - 0,438; p<0,001), T skorom kuka (r= -0,412; p<0,001) i T skorom kičme (r= -0,226; p<0,001), kao i mentalnog funkcionisanja sa: T skorom vrata butne kosti (r= -0,424: p<0,001), T skorom kuka (r= -0,454; p<0,001) i T skorom kičme (r= -0,319; p<0,001). Kada je u pitanju kvalitet socijalnog funkcionisanja postoji statistički značajna razlika između ispitanica sa i bez preloma kostiju (t= 2,17, p<0,05). **Zaključak.** Ispitanice starije životne dobi, sa lošijim sociodemografskim karakteristikama, sa nižom mineralnom koštanom gustinom i prethodnim prelomima imaju lošiji kvalitet socijalnog i mentalnog funkcionisanja.

Ključne reči: postmenopauza; postmenopauzalna osteoporoza; gustina kosti; socijalna participacija; mentalno zdravlje; ankete i uptinici; kvalitet života; demografija

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Introduction

Osteoporosis is a systemic, metabolic, progressive bone disorder characterized by a reduction in bone mineral density (BMD) and changes in the bone tissue microarchitecture, which in turn results in bone fragility and an increased risk of fractures [1]. Given that osteoporosis is common in postmenopausal women, it has a significant impact on their quality of life (QoL). Evidence suggests that it is associated with significant morbidity and mortality [2].

In clinical practice, BMD is assessed using dual X-ray absorptiometry (DXA), which is a gold standard for the diagnosis of osteoporosis. DXA scanning involves BMD measurement in two regions of interest, the lumbar spine and the proximal femur, whereas the obtained values are expressed in g/cm^2. The diagnosis is based on the T-score expressed in standard deviations (SDs) [3, 4]. According to the World Health Organization (WHO) diagnostic classification. BMD at the hip or lumbar spine ≤ 2.5 SDs below the mean for young adult population is indicative of osteoporosis. In sum, lower T-scores are associated with more severe BMD deficiency. Consequently, osteoporosis is recognized as a risk factor for fractures, in the same vein as hypertension is linked to a greater risk of stroke [4, 5].

Due to the large number of osteoporotic patients and a high potential for complications, osteoporosis is a major social and financial problem. The most prevalent osteoporosis complications are fractures that are usually caused by falls during walking, or from a sitting position, known as "low-trauma fractures". Owing to the nature of these falls, spinal vertebrae, hip, lower part of the forearm, and the upper section of the upper arm are the most common osteoporotic fracture sites [4, 6].

The QoL is a multidimensional concept that includes physical, emotional, mental, behavioral, and social components [7]. Social functioning, as a QoL domain, includes individual's interaction with the environment and the ability to perform workplace duties, as well as take part in social activities, and maintain healthy relationships with the partner and the family [8]. Mental functioning, as another QoL domain, refers to one's ability to realize his full potential, deal with everyday life stressors, remain productive and contribute to the community [9].

The Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41) is the original instrument for assessing the QoL in patients with osteoporosis. This questionnaire includes 41 items pertaining to pain, physical functions, social functions, general health perception and mental functions. As QUALEFFO has been validated in a multicenter study in seven countries, it is widely employed when assessing QoL [10].

Tadić and colleagues conducted a case-control study from June 2010 to October 2011, through which the Serbian version of QUALEFFO-41 was validated [11]. The main study objective was to examine the quality of social and mental functioning in postmenopausal women with reduced BMD.

Material and Methods

This prospective cross-sectional study was conducted at the Special Hospital for Rheumatic Diseases Novi Sad, Serbia, in the period from February 24th to April 3rd 2017. The study included 210 postmenopausal women aged ≥ 50 years who were referred to the Special Hospital for Rheumatic Diseases for osteodensitometry.

The study was conducted with the approval of the Ethics Committee of the Special Hospital for Rheumatic Diseases Novi Sad, and all respondents signed an informed consent prior to taking part in the study. Body height (cm), body weight (kg), and body mass index (BMI) in kg/m^2 were measured immediately prior to the DXA scanning. The BMD was measured in two regions of interest, the lumbar spine (L1 - L4) anterior-posterior projection, and the proximal femur. The results were expressed in absolute BMD values (g/cm^2) and T-scores. The obtained results were interpreted according to the adopted osteoporosis definition [4]. To increase validity of the findings yielded, the DXA scanner was subjected to daily calibrations. All respondents completed an identical questionnaire, developed by the researchers specifically for this investigation in order to obtain sociodemographic information, including the participants' age, age at menopause onset, place of residence (rural/urban), educational attainment, and occupation. In addition, low-trauma fracture history (fracture site and frequency) was obtained from medical records. All participants also completed the Serbian version of QUALEFFO-41 in order to assess their QoL. The aim was to examine the social and mental functioning QoL domains in relation to the aforementioned sociodemographic variables.

The reliability of the measuring instrument used in the present study was examined through internal consistency by calculating the Cronbach's alpha coefficient, for which values above 0.70 are deemed acceptable. The Cronbach's alpha coefficients for the mental and social functioning questionnaires were 0.726 and 0.867, respectively, confirming their reliability.

The quality of social and mental functioning is a part of the test measuring the QoL. The subtest pertaining to social functioning has seven, while that related to mental functioning consists of nine items, where the respondents express the degree of agreement/disagreement with individual statements on a 5-point Likert scale. In line with the test recommendations, the score is obtained by

recording responses for specific items, their summary, and finally convertion of these values to the scale ranging from 0 to 100. Consequently, subtest scores range from 0 to 100, whereby a higher value indicates a poorer quality of social and mental functioning.

The exclusion criteria were premenopausal stage, presence of metabolic bone disorders, and a BMD T-score less than 1 SD.

Statistical data processing: Descriptive statistics were calculated, and the arithmetic mean was used with the corresponding SD. The minimum and the maximum were also reported, along with frequencies and percentages.

Differences between groups were determined by single-factor analysis of variance (ANOVA). In addition to ANOVA, large independent samples were subjected to the t-test. The Pearson correlation coefficient was also calculated to examine the relationships between two continuous variables. Statistical significance was defined at the probability level of the null hypothesis of either $p < 0.01$ or $p \leq 0.05$.

Statistical processing and analyses were performed using the statistical software SPSS version 20 (Statistical Package for the Social Sciences), while Microsoft Office Excel and Word were used for graphical and tabular representations.

Results

The mean age of the 210 participants was 67.01 ± 7.49 years. The majority of the study sample were urban residents (75.2%) with secondary education (49.5%). Only 9.5% of the respondents were employed, and 70% of these women indicated that their job required prolonged standing or sitting. Almost half of the examinees were overweight (49.52%). In most cases, the mean T-score for the femoral neck, hip and lumbar spine (L1 - L4) was at the level of osteopenia. The average age of subjects at menopause onset was 48.01 ± 4.99 years. The history of low-trauma fractures was noted in 41.9% of the sample, while only two respondents had a hip fracture. Of the 11 respondents that suffered a vertebral fracture, 72.7% had one fracture. Finally, 72% of the participants with non-vertebral fractures had one such fracture **(Table 1)**.

Statistically significant differences were observed in the quality of social functioning between subjects of different ages (F = 8.88, p < 0.001), with the oldest respondents (M = 56.52), as well as those living in rural areas (M = 53.6 vs M = 44.3) having the lowest quality of social functioning.

Moreover, statistically significant differences in the quality of social functioning were found between respondents with different levels of educational attainment (F = 6.69, p < 0.001), whereby those with primary education (M = 57.4), as well as unemployed individuals (M = 47.8 vs, M = 35.4), reported the lowest quality of social functioning.

Single-factor analysis was conducted to establish whether there were statistically significant differences in the quality of social functioning based on the participants' BMI, and the findings confirmed

this hypothesis (F = 2.75, p < 0.05). Rather surprisingly, respondents in the normal BMI range were found to have the lowest quality of social functioning (M = 47.0), as shown in **Table 2**.

No statistically significant differences in the quality of mental functioning were found between subjects of different ages. However, respondents from rural areas had poorer quality of mental functioning compared to urban examinees (M = 41.6 vs. M = 35.1).

On the other hand, statistically significant differences between respondents with different levels of formal education were found with respect to their quality of mental functioning (F = 10.18, p < 0.001), since women with primary education reported the lowest quality of mental functioning (M = 57.4). Employment status had no bearing on the quality of mental functioning, as no statistically significant differences between employed and unemployed participants were established.

Single-factor analysis confirmed no statistically significant differences in the quality of mental functioning based on the participants' BMI, as shown in **Table 3**.

Analyses also revealed that the quality of social functioning statistically and negatively correlated with the femoral neck T-score (r = -0.438, p < 0.001) and BMD (r = -0.401, p <0.001), the hip T-score (r = -0.412, p < 0.001) and BMD (r = -0.399, p <0.001). and the spinal T-score (r = -0.226, p < 0.001). However, the spinal BMD was not statistically significantly related with the quality of social functioning.

A statistically significant difference in the quality of social functioning was found between subjects with and without history of bone fractures (t = 2.17, p < 0.05), whereby women who had experienced fractures had lower quality of social functioning (M = 49.6 vs, M = 44.3).

No statistically significant correlations between participants' quality of social functioning and the total number of fractures (r = 0.013, p > 0.05), number of vertebral fractures (r = 0.419, p > 0.05), or non-vertebral fractures (r = 0.07, p > 0.05) were established **(Table 4)**.

Analyses further revealed that the participants' quality of mental functioning statistically significantly and negatively correlated with the femoral neck T-score (r = -0.438, p < 0.001) and BMD (r = -0.401, p < 0.001), the hip T-score (r = -0.412, p < 0.001) and BMD (r = -0.399, p < 0.001), and the spinal T-score (r = -0.226, p < 0.001). However, the spinal BMD was not statistically significantly related with the quality of mental functioning.

On the other hand, no statistically significant differences in the quality of mental functioning were found between subjects with and without history of bone fractures (t = 0.92, p > 0.05).

Similarly. no statistically significant correlations between participants' quality of social functioning and the total number of fractures (r = -0.034, p > 0.05). number of vertebral fractures (r = 0.511, p > 0.05), or non-vertebral fractures (r = 0.15, p > 0.05) were noted.

There was no statistically significant correlation between the quality of mental functioning and the

Table 1. Sample characteristics
***Tabela 1.** Karakteristike uzorka*

Variables/*Parametri*	Frequency (%)/*Učestalost (%)*	Min	Max	M	SD
Age/*Godine*	210 (100%)				
50 - 60	36 (17.1%)				
61 - 70	115 (54.8%)	51.00	83.00	67.01	7.49
71+	59(28.1%)				
Menopause/*Menopauza*	210 (100%)	29.00	56.00	48.01	4.99
BMI/*ITM*					
Underweight/*Pothranjenost* (<18.5 - 25)	2 (1.00%)				
Normal nutritional status/*Normalna uhranjenost* (18.5 - 25)	60 (28.5%)				
Overweight/*Prekomerna uhranjenost* (25 - 30)	104 (49.5%)	17.56	50.20	27.38	4.65
Obesity/*Gojaznost* (>30)	44 (21.0%)				
Place of residence/*Mesto stanovanja*					
Rural/*Selo*	52 (24.8%)				
Urban/*Grad*	158 (75.2%)				
Level of education/*Nivo obrazovanja*					
Primary school/*Osnovno*	47 (22.4%)				
Secondary school/*Srednje*	104 (49.5%)				
Post-secondary education/*Više*	27 (12.9%)				
Higher education/*Visoko*	32 (15.2%)				
Employment/*Zaposlenost*					
Yes/*Da*	20 (9.5%)				
No/*Ne*	190 (90.5%)				
Employment type/*Način obavljanja posla*					
Sitting/Standing/*Sedi/Stoji*	14 (70%)				
Walking/Physical/*Hoda/Radi fizički*	6 (30%)				
Descriptive indicators of measurement parameters/*Deskriptivni pokazatelji mernih parametara*					
T-score for the femoral neck/*T-skor vrata butne kosti*		-4.10	0.40	-1.6976	0.74078
T-score for the hip/*T-skor kuka*		-4.10	2.20	-1.5362	0.82915
T-score for the spine (L1-L4)/*T-skor kičme (L1-L4)*		-6.20	2.30	-1.9990	1.09684
BMD for the femoral neck/*MKG vrata butne kosti*		0.34	1.03	0.7743	0.09294
BMD for the hip/*MKG kuka*		0.51	1.11	0.8141	0.09557
BMD for the spine (L1-L4)/*MKG kičma (L1-L4)*		-0.98	1.66	0.9396	0.18877
Fracture/*Prelom*	210 (100%)				
Yes/*Da*	88 (41.9%)				
No/*Ne*	122 (58.1%)	1	5	1.5	0.871
Hip fracture/*Prelom kuka*					
Yes/*Da*	2 (1%)				
No/*Ne*	208 (99%)				
Number of vertebral fractures/*Broj vertebralnih preloma*	11 (100%)				
1	8 (72.7%)				
2	2 (18.2%)				
3	1 (9.1%)				
Number of non-vertebral fractures *Broj nevertebralnih preloma*	82 (100%)				
1	59 (72.0%)				
2	14 (17.0%)				
3+	9 (11.0%)				

Legend: N – number of patients; Min – minimum; Max – maximum; M – mean value; SD – standard deviation; BMD – Bone Mineral Density; BMI – Body Mass Index
Legenda: N – broj ispitanika; Min – minimum; Max – maksimum; M – medijana; SD – standardna devijacija; MKG – mineralna koštana gustina; ITM – indeks telesne mase

Table 2. Social functioning and sociodemographic variables
Tabela 2. *Socijalno funkcionisanje i sociodemografske varijable*

Variables/*Parametri*	M	SD	F	p
Age/*Godine*				
50 – 60	40.0885	22.72416		
61 – 70	43.6591	20.45831	8.885	0.000*
71+	56.5204	23.19639		
Total/*Ukupno*	46.6604	22.44848		
Place of residence/*Mesto stanovanja*				
Rural/*Selo*	53.6881	22.12535		
Urban/*Grad*	44.3475	22.13777	6.967	0.009*
Total/*Ukupno*	46.6604	22.44848		
Level of Education/*Nivo obrazovanja*				
Primary school/*Osnovno*	57.4782	20.95613		
Secondary school/*Srednje*	45.9936	20.56668		
Post-secondary education/*Više*	42.5112	23.95000	6.693	0.000*
Higher education/*Visoko*	36.4398	23.61347		
Total/*Ukupno*	46.6604	22.44848		
Employment/*Zaposlenost*				
Yes/*Da*	35.4848	27.39116		
No/*Ne*	47.8368	21.61547	5.599	0.019**
Total/*Ukupno*	46.6604	22.44848		
BMI/ITM				
Underweight/*Pothranjenost* (<18.5 – 25)	26.2202	11.82720		
Normal nutritional status/*Normalna uhranjenost* (18.5 – 25)	47.0784	23.77554		
Overweight/*Prekomerna uhranjenost* (25 – 30)	43.7365	21.02357	2.754	0.044**
Obesity/*Gojaznost* (>30)	53.9305	22.74495		
Total/*Ukupno*	46.6604	22.44848		

Legend: M – mean value; SD – standard deviation; F – single-factor analysis of variance; p – statistical significance; *p < 0.01; **p < 0.05; BMI – Body Mass Index

*Legenda: M – medijana; SD – standardna devijacija; F – jednofaktorska analiza varijanse; p – statistička značajnost; *p<0,01; **p<0,05; ITM – indeks telesne mase*

number of fractures (r = -0.034, p > 0.05); similarly, no statistical correlation was noted between the quality of mental functioning and the number of vertebral (r = 0.511, p > 0.05) or non-vertebral fractures (r = 0.15, p > 0.05) **(Table 5)**.

Discussion

Osteoporosis is a condition characterized by reduced BMD. which contributes to bone fragility and increases fracture risk. Assessment of functional status and QoL is highly important for the evaluation of disease progression and the development of new treatments, in particular when they pertain to chronic conditions such as osteoporosis. QoL assessments of osteoporotic patients are used in conjunction with biomechanical and radiographic evaluations following each fracture [12].

The present study included 210 women aged 67.01 ± 7.49 years. Our investigation indicated that older participants had a significantly poorer quality of social functioning. Patients living in rural areas

and those with lower educational attainment also had a poorer QoL in both domains, while social functioning quality was compromised for unemployed individuals. Nutritional status, as determined by the BMI score, also affected the participants' quality of social functioning, but had no impact on the quality of their mental functioning.

The world population is rapidly aging. According to the earlier statistics, it was estimated that, globally, the number of individuals aged 65 years and over would double from 2010 to 2014, with the greatest increase in the developing countries. If this trend continues, osteoporosis will become even more prevalent as will bone fractures, resulting in a decline in QoL and rise in the mortality rate [13, 14]. In a study conducted in eastern Poland, BMD of women living in rural and urban areas was estimated and compared. failing to reveal statistically significant differences in the mean BMD values of the two groups. However, the prevalence of osteoporosis and osteopenia was associated with age [15].

Urošević et al. (2015) analyzed and compared the QoL among elderly individuals living in urban

Table 3. Mental functioning and sociodemographic variables
Tabela 3. *Mentalno funkcionisanje i sociodemografske varijable*

Variables/*Parametri*	M	SD	F	p
Age/*Godine*				
50 – 60	36.8056	15.62026		
61 – 70	34.5894	15.04111	2.856	0.060*
71+	40.8192	18.81334		
Total/*Ukupno*	36.7196	16.42336		
Place of residence/*Mesto stanovanja*				
Rural/*Selo*	41.6132	17.09233		
Urban/*Grad*	35.1090	15.92542	6.292	0.013**
Total/*Ukupno*	36.7196	16.42336		
Level of Education/*Nivo obrazovanja*				
Primary school/*Osnovno*	46.9267	16.28214		
Secondary school/*Srednje*	35.4434	14.87842		
Post-secondary education/*Više*	32.7160	17.30154	10.187	0.000*
Higher education/*Visoko*	29.2535	14.26872		
Total/*Ukupno*	36.7196	16.42336		
Employment/*Zaposlenost*				
Yes/*Da*	31.6667	12.00363		
No/*Ne*	37.2515	16.75703	2.103	0.148
Total/*Ukupno*	36.7196	16.42336		
BMI/*ITM*				
Underweight/*Pothranjenost* (<18.5 – 25)	40.2778	5.89256		
Normal nutritional status/*Normalna uhranjenost* (18.5 – 25)	37.9167	17.26655		
Overweight/*Prekomerna uhranjenost* (25 – 30)	35.6571	14.49389	0.308	0.820
Obesity/*Gojaznost* (>30)	37.4369	19.80098		
Total/*Ukupno*	36.7196	16.42336		

Legend: M – mean value; SD – standard deviation; F – single-factor analysis of variance; p – statistical significance; *p < 0.001; **p < 0.05; BMI – Body Mass Index

*Legenda: M – medijana; SD – standardna devijacija; F – jednofaktorska analiza varijanse; p – statistička značajnost; *p<0,001; **p<0,05; ITM – indeks telesne mase*

and rural areas in Serbia. The authors reported significantly higher anxiety/depression scores in the rural population. However, no statistically significant differences in the average QoL scores were noted in urban and rural areas [16]. It is widely assumed that better education helps reducing the risk of a wide range of chronic illnesses, including osteoporosis. This hypothesis was tested in a study conducted in China, whereby the link between educational attainment of 685 postmenopausal women and their BMD and osteoporosis prevalence was examined. The findings yielded by this population-based, cross-sectional study revealed that higher educational attainment, particularly tertiary education. was strongly and positively related with higher BMD values and thus lower likelihood of osteoporosis. These relationships remained significant after adjusting for the most relevant confounders, such as body weight, age, and years since menopause onset [17]. Nutritional status is an important predictor of bone metabolism, which is adversely affected by both obesity and weight loss. Given that in the developed

world, the percentage of overweight individuals is rapidly growing and many of these individuals are undergoing some weight loss regimen, these findings are important, as they indicate that further research into bone metabolism is needed. The link between BMI and bone quality, and thus fracture risk, in obese individuals is presently insufficiently understood, and must be further explored by well-designed prospective trials. In particular, it is necessary to elucidate the mechanisms that regulate the effect of excess adiposity on bone quality [18].

Analyses of the measured parameters obtained through DXA scanning and the participants' history of fractures revealed that patients with lower BMD tend to have lower quality of social and mental functioning, while prior experience of fractures has a significant adverse impact on social functioning.

As a part of their study conducted in Morocco. Abourazzak and colleagues assessed the health-related QoL in postmenopausal women with osteoporosis using the Arabic version of the QoL questionnaire. The study sample included 357 postmenopausal women

Table 4. Social functioning and the measured parameters
***Tabela 4.** Socijalno funkcionisanje i mereni parametri*

Variables/*Parametri*	N	M	SD	t	F	r	p
T-score for the femoral neck/*T-skor vrat butne kosti*						-0.438*	0.000
T-score for the hip/*T-skor kuka*						-0.412*	0.000
T-score for the spine (L1-L4)/*T-skor kičme (L1-L4)*						-0.226*	0.001
BMD for the femoral neck/*MKG vrat butne kosti*						-0.401*	0.000
BMD for the hip/*MKG kuka*						-0.399*	0.000
BMD for the spine (L1-L4)/*MKG kičme (L1-L4)*						-0.101	0.143
Bone fracture/*Prelom kosti*							
Yes/*Da*	88	49.6899	24.08054	2.17			0.043**
No/*Ne*	122	44.3988	23.82408				
Total number of fractures/*Ukupan broj preloma*						0.013	0.906
Number of vertebral fractures/*Broj vertebralnih preloma*						0.419	0.20
Number of non-vertebral fractures/*Broj nevertebralnih preloma*						-0.076	0.498

Legend: N – number of patients; M – mean value; SD – standard deviation; t-test; F – single-factor analysis of variance; r – Pyreson coefficient of correlation; p – statistical significance; *p < 0.01;**p < 0.05; BMD – Bone Mineral Density
*Legenda: N – broj ispitanika; M – medijana; SD – standardna devijacija; t – t test; F – jednofaktorska analiza varijanse; r – Pirsonov koeficijent korelacije; p – statistička značajnost; *p<0,01; **p<0,05; MKG-mineralna koštana gustina*

Table 5. Mental functioning and the measured parameters
***Tabela 5.** Mentalno funkcionisanje i mereni parametri*

Variables/*Parametri*	N	M	SD	t	F	r	p
T-score for the femoral neck/*T-skor vrat butne kosti*						-0.424*	0.000
T-score for the hip/*T-skor kuka*						-0.454*	0.000
T-score for the spine (L1-L4)/*T-skor kičme (L1-L4)*						-0.319*	0.000
BMD for the femoral neck/*MKG vrat butne kosti*						-0.389*	0.000
BMD for the hip/*MKG kuka*						-0.453*	0.000
BMD for the spine (L1-L4)/*MKG kičme (L1-L4)*						-0.104	0.134
Bone fracture/*Prelom kosti*							
Yes/*Da*	88	40.3314	21.75011	0.928			0.355
No/*Ne*	122	37.6776	19.47008				
Total number of fractures/*Ukupan broj preloma*						-0.034	0.752
Number of vertebral fractures/*Broj vertebralnih preloma*						0.511	0.109
Number of non-vertebral fractures/*Broj nevertebralnih preloma*						-0.154	0.166

Legend: N – number of patients; M - mean value; SD – standard deviation; t-test; F – single-factor analysis of variance; r – Pyreson coefficient of correlation; p – statistical significance; *p < 0.01; BMD – Bone Mineral Density
*Legenda: N – broj ispitanika; M – medijana; SD – standardna devijacija; t – t test; F – jednofaktorska analiza varijanse; r – Pirsonov koeficijent korelacije; p – statistička značajnost; *p<0,01; MKG-mineralna koštana gustina*

aged 58 ± 7.8 years, 30.1% of whom had been diagnosed with osteoporosis. The authors reported that three risk factors were associated with lower QoL, namely low educational attainment. and history of both vertebral and non-vertebral fractures. The lowest QoL scores were found in subjects with vertebral fractures, especially among those with a greater number and severity of these fractures [19].

Similar results to those reported in this study were obtained by Ferreira and associates in 2009. These authors compared the scores of 220 post-menopausal women obtained by QUALEFFO-41 and Short Form Health Survey 36 (the SF-36 questionnaire). Their findings revealed that BMI > 25 and a sedentary lifestyle were the only factors associated with poor QoL, as measured by QUAL-EFFO-41. Women suffering from osteoporosis had a poorer QoL, especially in relation to physical, psychological and social aspects [20].

In 2014, Palacios et al. conducted a study on the impact of osteoporosis on QoL. Their sample included 3.328 Spanish women who had osteoporosis for at least two years. Analyses of their BMD measurements and QoL scores revealed that women with osteoporosis, lower BMD and history of osteoporotic fractures had poorer QoL (in terms of physical and mental functioning) compared to women with osteoporosis who had not experienced fractures [21].

Grbović and colleagues conducted a study in 2016. aiming to establish the correlation between the QoL in postmenopausal women with osteoporosis and osteodensitometry parameters. Their study sample included 100 women whose BMD was measured by the DXA apparatus. FRAX index was employed to estimate the risk of osteoporotic fractures, and all participants completed the QUAL-EFFO-41 questionnaire. Subsequent data analysis revealed a correlation between BMD and the femoral neck T-score, as well as among pain level, social functioning and perception of health [22].

The results yielded by the present study support those reported by Vujasinović et al. in 2005. As a part of their investigation, the authors assessed the QoL of patients with osteoporosis and vertebral fractures and compared it to that of osteoporotic subjects that had not experienced fractures. The study included 63 patients whose osteoporosis was managed in the outpatient settings. The relevant data was obtained through DXA scanning, X-rays (confirming or ruling out the existence of fractures) and the QUALEFFO-41 questionnaire. Based on the patients' scores on the questionnaire, differences in QoL in these two groups were identified. Specifically, the authors noted that patients with history of fractures had a significantly lower QoL in the areas of pain, daily activities, and mobility, as well as social and mental functioning [23].

The influence of vertebral fractures on the QoL was also examined by Salaffi et al. (2007) in a sample of 234 and 244 women, with and without history of fractures, respectively. The data were gathered through the mini-Osteoporosis Quality of Life Questionnaire, the Medical Outcomes Study Short Form (SF-36) and the EuroQuol-5D. Based on the evaluation of all clinical variables and anthropometric data, physical functioning emerged as the most important determinant of poor QoL in patients with osteoporosis. Findings yielded by the SF-36 summary scales indicated that participants' mental and physical health was primarily affected by comorbid conditions. Moreover, even a single fracture had a significant adverse effect on the QoL. In addition, lumbar fractures were shown to be more strongly related to the QoL reduction compared to those in the thoracic segment. The authors concluded that the QoL in women with osteoporosis depends on the number of vertebral fractures, comorbidities and age [24].

In another study, the timing of which coincided with our investigations, QoL among patients with reduced BMD was examined. However, the authors focused on physical functioning using a sample of elderly undernourished women, all of whom had low BMD and poor socio-demographic characteristics, and suffered low-trauma fractures [25]. An extensive review of the available literature has failed to reveal any studies directly comparable to our research, making it difficult to contextualize our results. In the study published by other authors, the focus was mostly on the QoL in women with bone fractures and the effects of comorbidities on their treatment. Moreover, in most cases, the emphasis was placed on initiating timely and adequate therapy for chronic diseases, especially rheumatoid arthritis, which is an independent factor in the development of osteoporosis [26, 27].

A study published by Ramirez-Perez et al. in 2014, included 115 subjects with vertebral fractures and 135 without fractures, investigating effects of vertebral osteoporotic fractures on QoL. Their QoL was assessed using the QUALEFFO-41 questionnaire adapted for the Mexican population. Significant QoL reduction was established among respondents with a history of fractures, in the domain of pain, physical, social and emotional functioning, while age emerged as the main risk factor for deteriorating QoL in all domains [28].

Yoon et al. (2014) investigated the QoL in patients with osteoporosis and vertebral fractures, as well as the impact of fracture treatment on participants' QoL. According to the results of this study, fractures reduce QoL in all domains measured by the questionnaire. In addition, patients whose fractures were surgically treated had a significantly lower QoL compared to those whose fractures were managed conservatively [29]. Similar results were obtained in other studies.

Conclusion

In the present study, older age was significantly related to a poorer quality of social functioning, while having no effect on participants' mental functioning. Rural lifestyle and primary-level education also emerged as predictors of a poorer quality of social and mental functioning, while unemployment led to lower quality of social functioning.

Statistically significant differences were observed in the quality of social functioning (but not mental functioning) of examinees with different nutritional status. Lower quality of life in the social and mental domains was noted among women with lower bone mineral density, as well as those with history of fractures; however, mental functioning was not correlated with the existence of fractures.

Apart from timely diagnosis of reduced bone mineral density, adequate treatment, and prevention of osteoporotic fractures, it is also necessary to assess the quality of life of osteoporotic patients, with the aim of improving their quality of life in all domains of functioning.

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THE EFFICIENCY AND SAFETY OF A DIETARY SUPPLEMENT USED IN THE TREATMENT OF PRESCHOOL AND SCHOOL CHILDREN WITH ACUTE RESPIRATORY INFECTIONS

EFIKASNOST I SIGURNOST PRIMENE DIJETETSKOG SUPLEMENTA U LEČENJU PREDŠKOLSKE I ŠKOLSKE DECE SA AKUTNIM RESPIRATORNIM INFEKCIJAMA

Lidija SAGIĆ[1], Katarina MILOŠEVIĆ[2], Olivera OSTOJIĆ[3] and Anita AGIĆ[4]

Summary

Introduction. The aim of this research was to assess the efficiency and safety of a natural product N-acetylcysteine and propolis in the children with acute respiratory infections with increased mucus production and cough. **Material and Methods.** The research was conducted in the period April 2016 – February 2017 among 145 pediatric patients aged 3 to 14 years with symptoms of acute respiratory infection. They were divided into two groups. Group A – preschool and Group B – school children. The first clinical examination included demographic data, physical examination. filling out the quality of cough questionnaire, and taking nasal and pharyngeal swabs. After a ten-day therapy, physical examination was conducted, quality of cough questionnaire was refilled and swabs were taken. **Results.** Group A included 73 and Group B 72 children. No statistically significant difference was observed in the incidence of respiratory disease episodes. In Group B children received antibiotics less often. started school at an early age and more children had daily activities in regard to children in Group A. Statistically, both groups of children coughed early in the morning more than during the day. The results of control swab tests were negative in both groups. No side effects were reported in either group. **Conclusion.** The propolis combined with N-acetylcysteine in a pediatric syrup is a good choice in the treatment of acute respiratory infections in children with accompanied mucus production and cough. The product is efficient and safe for all age groups.
Key words: Respiratory Tract Infections; Dietary Supplements; Child. Preschool; Child; Cough; Propolis; Acetylcysteine; Surveys and Questionnaires; Herbal Medicine

Sažetak

Uvod. Cilj našeg istraživanja bio je da se proceni efikasnost i kvalitet života primenom prirodnog preparata propolisa i N-acetilcisteina kod dece sa akutnim respiratornim infekcijama praćenim povećanom produkcijom sekreta i kašljem. **Materijal i metode.** Istraživanje je sprovedeno u periodu april 2016–januar 2017. godine kod 145 dece, uzrasta od tri do 14 godina sa simptomima akutne respiratorne infekcije. Podeljena su u dve grupe, grupa A – deca predškolskog, a grupa B – deca školskog uzrasta. Pri prvoj poseti su uzeti demografski podaci, brisevi nosa i ždrela, urađeni fizikalni pregledi i popunjen upitnik o kvalitetu kašlja. Nakon desetodnevne terapije, pored fizikalnog pregleda, ponovljen je upitnik o kvalitetu kašlja i uzeti brisevi. **Rezultati.** U grupi A bilo je 73 i u grupi B 72 dece. Nije bilo statistički zanačajne razlike u učestalosti epizoda respiratornih bolesti. Deca u grupi B su ređe dobijala antibiotike, ranije su kretala u zajednički kolektiv i više dece je imalo dodatnih aktivnosti od dece grupe A. U obe grupe statistički više dece je kašljalo rano ujutru i tokom dana. Kontrolni brisevi bili su negativni u obe grupe. Nije zabeleženo nijedno neželjeno dejstvo u obe grupe. **Zaključak.** Kombinacija propolisa i N-acetilcisteina u sirupu za decu predstavlja dobar izbor u lečenju akutne respiratorne infekcije kod dece, praćenih produkcijom sekreta i kašljem. Preparat je efikasan i bezbedan za primenu u svim dobnim grupama.
Ključne reči: infekcije respiratornog trakta; dijetetski suplementi; predškolsko dete; dete; kašalj; propolis; acetilcistein; ankete i upitnici; biljna medicina

Introduction

Acute respiratory infection (ARI) in children is the most common reason for visiting a primary care physician. Children have ARI episodes 6 – 8 times per year, both in developed and developing countries [1]. About 80% of pediatrician visits are due to ARIs and cough. The average duration of an uncomplicated respiratory infection in young children is 7 – 9 days, and school children cough for about 58 days per year [2].

The ARIs occur all year round, being more common during the autumn and winter, Children who attend collective care services have more episodes of ARI than those who do not.

Cough is a protective reflex mechanism for clearing mucus and foreign bodies from the airways. It can be a symptom of upper respiratory tract infections or one of non-infectious conditions such as asthma, exposure to nicotine smoke, or aspiration of a foreign object. Acute cough episodes occur most frequently in conditions such

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as cold or acute viral infection of the upper airways. Differentiating coughs due to upper airway infection and cough due to bronchitis is of no importance, because in children, both above conditions are of viral origin and do not require antibiotic therapy. The clinical course is mostly mild, except when bronchitis is associated with a bacterial superinfection [3]. Inadequate use of antibiotics for viral respiratory infections is a big problem due to the increasing pathogen resistance and high costs for the healthcare system, with no effect whatsoever [4].

Differentiating wet from dry, or productive from unproductive cough, is of small therapeutic importance, especially in younger children who swallow the sputum. Cough may provide information on the possible cause of the disease, for example, prolonged cough accompanied by wracking is seen in pertussis, while hoarse or barky cough is typical for croup. Children with asthma may have a typical night cough, which requires a bronchodilator.

Coughing may cause symptoms like fatigue, insomnia, hoarseness, musculoskeletal pain, and sweating. What's more, cough can have undesirable effects on the quality of life of the patient [5].

Far away in the past, ARI required administration of antibiotics as soon as possible, based on the assumed bacterial cause. In modern countries, the percentage of severe complications is very low. In the 1990s, antibiotic use declined and antibiotic prescribing in the United Kingdom has reached the plateau, but it was higher than in the northern Europe [4]. A great number of patients with uncomplicated respiratory infections examined in the primary care still get antibiotics and many doctors and patients think that it is all right.

These are all reasons why we need alternative therapeutic options. Mucolytic and antitussive agents are the most common over-the-counter medications, as well as natural products for treating acute cough in children and adults.

The term "herbal medicine" is used to identify medicinal herbs or some substances obtained from such herbs that help the body to fight different diseases. including infections, and to improve overall health. The use of complementary or alternative medicinal products for infections is very popular [6, 7].

The aim of our research was to assess the efficiency of a natural product with propolis and N-acetylcysteine (NAC) (PropoMucil®) pediatric syrup and quality of life of children with ARI with increased mucus production and cough.

Material and Methods

The prospective study was conducted in the period April 2016 – February 2017 at the Municipal Institute for Lung Diseases and Tuberculosis, University Children's Hospital and Children's Hospital for Lung Diseases and Tuberculosis, Medical Center "Dr Dragiša Mišović" in Belgrade, Serbia. The study was approved by the Ethics Committees, and it was conducted in accordance with the Declaration of Helsinki [8].

The study included 145 children aged 3 to 14 with symptoms of ARI associated with productive cough. The children were divided into two age groups. Group A – preschool children (n = 73) and Group B – school children (n = 72). The inclusion criteria were as follows: patients younger than 18 years of age, with the diagnosis of ARI and productive cough, acute inflammation, without antibiotic therapy. The exclusion criteria: patients younger than 3 or older than 18 years of age, patients with asthma, and patients who were sensitive to propolis or/and NAC.

The first examination included medical history taking: demographic data (age, sex, number of family members, whether the child attended a public/private pre- or kindergarten and since what age), symptoms (cough quality, duration, time of occurrence), previous therapy and associated diseases (children with asthma were not included in the study), and obtaining written consent from parents. During the first visit, in addition to physical examination, nasal and pharyngeal swabs were taken for microbiological testing. The children were given PropoMucil® pediatric syrup (a combination of purified dried propolis extract standardized to contain 12% of total polyphenols and NAC with the addition of honey, marshmallow and rose hip extract, manufactured by Abela Pharm, Belgrade, Serbia) to take twice a day at the recommended therapeutic dose during 10 days. PropoMucil® contains propolis which is allergen and gluten free. The NAC is of natural, non-human, non-animal origin. produced by fermentation of special Escherichia coli strain culture.

During the second visit, in addition to physical examination, compliance data were collected, nasal and pharyngeal swab samples repeated, and the quality of cough questionnaire refilled. The parents gave their opinion on the therapy efficiency, its acceptance by the child (taste) and potential side effects of the therapy.

The obtained data were statistically processed using the Statistical Package for the Social Sciences (SPSS) (17.0 Inc., Chicago, IL, USA). The quantitative data were expressed as percentages and numbers, whereas the variable measures were compared at two time points (the first and follow up visits) using a single-factor analysis with repeated measurement analysis of variance (ANOVA). The results are shown using a figure and tables.

Results

The sex and age distribution of children is presented in **Graph 1**.
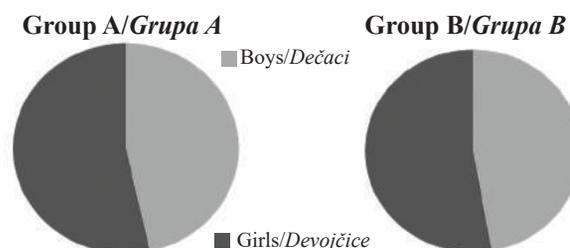
Graph 1. Age and sex distribution of children
Grafikon 1. Starosna i polna distribucija dece

Table 1. Age distribution of children
Tabela 1. *Starosna struktura dece*

General data/*Opšti podaci*	Group A/*Grupa A*	Group B/*Grupa B*	p/*p*
	n (%)/*br. (%)*	n (%)/*br. (%)*	
Age(years)/*Starost (god.)*/X ± SD; Med (min-max)	4.65 ± 1.01; 5 (2-7)	10.94 ± 3.88; 10 (7-18)	0.000*

Legend: n - number of subjects; % - percentage of subjects; X - medium value; SD - standard deviation; Med- median; min - minimum; max - maximum; p - statistical significance; * t-test of independent groups
*Legenda: br. – broj ispitanika; % – procenat ispitanika; X – srednja vrednost; SD – standardna devijacija; Med – medijana; min – minimum; max – maksimum; p – statistička značajnost; * t-test – za nezavisne grupe*

Table 2. Questionnaire
Tabela 2. *Upitnik*

Screening *Skrining*	Group A/*Grupa A*	Group B/*Grupa B*	p
	n (%)/*br. (%)*	n (%)/*br. (%)*	
Number of children in the family/*Broj dece u porodici* X ± SD; Med (min-max)	1.86 ± 0.73; 2 (1 - 4)	1.92 ± 0.69; 2 (1 - 4)	0.933*
Number of episodes of cough, sneezing, cold or withdrawal of secretion during the previous 30 days:/*Broj epizoda kašlja, kijanja, prehlada ili povlačenje sekrecije tokom prethodnih 30 dana:*			
Less than 3/*Manje od 3*	31 (42.5)	39 (54.2)	
3 to 5/*3 do 5*	37 (50.7)	22 (30.6)	
More than 5/*Više od 5*	5 (6.8)	11 (15.3)	0.771**
How many times did the child get an antibiotic during the previous 30 days?/*Koliko puta je dete dobilo antibiotik tokom prethodnih 30 dana?*			
Not once/*Nijednom*	11 (13.7)	15 (20.8)	
Once/*Jednom*	29 (39.7)	43 (55.6)	
Twice/*Dva puta*	20 (27.4)	12 (13.9)	
Several times/*Nekoliko puta*	13 (16.4)	5 (6.9)	0.007**
Does the child attend a kindergaten?/*Da li dete pohađa vrtić?*			
Yes/*Da*	68 (93.2)	67 (91.7)	
No/*Ne*	5 (6.8)	8 (8.3)	0.765**
If yes, what was the startup age?/*Ako pohađa, sa koliko godina je počelo?* X ± SD; Med (min-max)	1.52 ± 0.90; 1 (0 - 3)	1.14 ±0.79; 1 (0 - 3)	0.001*
Does the child have more than three respiratory infections per year since starting going to kindergarten/school?/*Da li dete ima više od tri respiratorne infekcije godišnje od početka odlaska u vrtić/školu?*			
Yes/*Da*	58 (79.5)	56 (74.7)	
No/ *Ne*	15 (20.5)	20 (25.3)	0.106**
Did the child have a respiratory infection during the previous year that lasted over 2 weeks accompanied by cough and secretion? *Da li je dete imalo respiratornu infekciju tokom prethodne godine koja je trajala više od dve nedelje i bila praćena kašljem i sekretom?*			
Yes/*Da*	66 (89.0)	59 (78.7)	
No/*Ne*	7 (11.0)	16 (21.3)	0.416**
How many times did the child have respiratory infection during the previous year that lasted more than 2 weeks which was accompanied by cough and secretion?/*Koliko puta je dete imalo respiratornu infekciju tokom prethodne godine koja je trajala više od 2 nedelje i bila praćena kašljem i sekretom?* X ± SD; Med (min-max)	2.49 ± 1.55; 2 (1-6)	2.54 ± 1.49; 2 (1-9)	0.666*
Is the mother a smoker and did she smoke in pregnancy? *Da li je majka pušač i da li je pušila u trudnoći?*			
Yes/*Da*	21 (28.8)	24 (35.3)	
No/*Ne*	22 (30.1)	23 (31.9)	0.068**

Legend: n - number of subjects; % - percentage of subjects; X - medium value; SD - standard deviation; Med - median; min - minimum; max - maximum; *p* - statistical significance; * *t*-test of independent groups; ** X^2test
*Legenda: br. – broj ispitanika; % – procenat ispitanika; X – srednja vrednost; SD – standardna devijacija; med – medijana; min – minimum; max – maksimum; p – statistička značajnost; * t-test – za nezavisne grupe*; ** X^2test

Table 3. First visit
Tabela 3. *Prva poseta*

First visit *Prva poseta*	Group A/*Grupa A* n (%)/*br. (%)*	Group B/*Grupa B* n (%)/*br. (%)*	p*
When does the child mostly cough?/*Kada dete uglavnom kašlje?*			
Early in the morning, after wakening/*Rano ujutru, nakon buđenja*	18 (24.7)	18 (24.0)	
During the day/*Tokom dana*	25 (34.2)	32 (45.5)	
In the evening, as soon as he/she goes to bed/*Uveče, čim legne u krevet*	16 (21.9)	17 (22.7)	
Whole night/*Tokom cele noći*	14 (19.2)	6 (7.8)	0.014
What does the sputum look like?/*Kakvog izgleda je sputum?*			
Yellowish, sticky/*Žućkast i lepljiv*	30 (41.1)	29 (38.7)	
Clear, slimy/*Beličast i sluzav*	23 (32.5)	19 (25.3)	
Fluid/*Tečan*	20 (27.9)	27 (36.0)	0.221
Does the child wake up during the night due to phlegm? *Da li se dete budi noću zbog sputuma?*			
Yes/*Da*	31 (37.0)	36 (48.0)	
No/*Ne*	42 (63.0)	39 (52.0)	0.236
Does cough with sputum interfere with child's daily activities *Da li kašalj sa sputumom ometa dnevne aktivnosti deteta?*			
Yes/*Da*	18 (42.5)	48 (64.0)	
No/*Ne*	55 (57.5)	27 (36.0)	0.000
Nasal swab:/*Bris nosa:*			
Negative/*Negativan*	65 (88.9)	72 (96.1)	
Staphylococcus aureus/*Staphylococcus aureus*	4 (5.5)	1 (1.3)	
Moraxella catarrhalis/*Moraxella catarrhalis*	1 (1.4)	0 (0)	
Streptococcus pyogenes/*Streptococcus pyogenes*	2 (2.8)	1 (1.3)	
Streptococcus pneumoniae/*Streptococcus pneumoniae*	1 (1.4)	1 (1.3)	0.717
Pharyngeal swab:/*Bris ždrela:*			
Negative/*Negativan*	65 (88.9)	73 (97.4)	
Staphylococcus aureus/*Staphylococcus aureus*	0 (0)	1 (1.3)	
Moraxella catarrhalis/*Moraxella catarrhalis*	3 (4.2)	0 (0)	
Streptococcus pyogenes/*Streptococcus pyogenes*	1 (1.4)	0 (0)	
Streptococcus pneumoniae/*Streptococcus pneumoniae*	4 (5.5)	1 (1.3)	0.655

Legend: n - number of subjects; % - percentage of subjects; p - statistical significance; * X^2test
*Legenda: br. – broj ispitanika; % – procenat ispitanika; p – statistička značajnost; * X^2test*

The Group A included 73 preschool children (39 boys and 34 girls, average age 4.65 ± 1.01), and Group B – 72 school children (38 boys and 34 girls, average age 10.94 ± 3.88) that is shown in **Table 1**.

No statistically significant difference was observed in the incidence of respiratory disease episodes. The Group B more rarely received antibiotics ($p = 0.007$), started school at earlier age ($p = 0.001$), and more children had daily activities ($p = 0.018$) than in Group A, which is shown in **Table 2**.

In Group A, children coughed during the day (34.2%) compared to school children (45.5%). Both groups had mainly yellowish and sticky sputum - Group A (41.1%), Group B (38.7%). Cough interfered with daily activities of school children (64%) more than in preschool children (42.5%); ($p = 0.0001$) **(Table 3)**.

Nasal and pharyngeal swabs were taken from all children for microbiological testing. At the first visit, 8 children in Group A, and 2 children in Group B had positive pharyngeal results **(Table 3)**. At follow-up, there were no positive swabs in either group **(Table 4)**.

At follow-up, a statistically significant difference between groups was observed only for wakeups at night due to sputum **(Table 4)**. Namely, more chil-

dren in Group A woke up during night (37%) due to sputum-induced difficulties than in Group B (21.3%) **(Table 4)**.

The majority of children were regularly taking the recommended therapy, more in Group B. In their opinion, the syrup had a pleasant and acceptable taste, 79.4% in Group A and 82.7% in Group B. At follow-up, the majority of parents and children said they felt better than before the therapy. None of the children had any side effects of the applied therapy **(Table 4)**.

Discussion

The ARIs, especially in preschool children, are accompanied by cough and nasal secretion. They are mainly caused by viruses and do not require antibiotic therapy. They occur more frequently in children who attend kindergartens, in families with two or more children. In our study, households were mostly with two children (Group A 1.52 ± 0.90; 1 (0 – 3) and Group B 1.14 ± 0.79; 1 (0 – 3)). The majority of children attend a kindergarten and 93.2% of them are preschool children. The children in Group A started attending a kindergarten at an earlier age; however, the number of

Table 4. Follow-up visit
***Tabela 4.** Kontrolni pregled*

Follow-up visit *Kontrolni pregled*	Group A/*Grupa A* n (%)/*br. (%)*	Group B/*Grupa B* n (%)/*br. (%)*	p*
What did the child think about the syrup?/*Kako je dete opisalo sirup?*			
Pleasant/*Prijatan*	13 (17.3)	20 (26.7)	
Acceptable/*Prihvatljiv*	38 (52.1)	42 (56.0)	
Unpleasant/*Neprijatan*	22 (30.6)	13 (17.3)	0.002
Did the child build up sputum?/*Da li je dete iskašljavalo sputum?*			
Yes/*Da*	21 (28.8)	19 (25.3)	
No/*Ne*	52 (72.2)	56 (74.7)	0.521
Does frequent cough and sputum interfere with child's daily activities? *Da li čest kašalj i sputum ometaju svakodnevne aktivnosti deteta?*			
Yes/*Da*	22 (30.1)	24 (32.0)	
No/*Ne*	51 (69.9)	51 (68.0)	0.694
Does the child wake up during the night due to sputum? *Da li se dete budi noću zbog sputuma?*			
Yes/*Da*	27 (37.0)	16 (21.3)	
No/*Ne*	49 (63.0)	59 (78.7)	0.017
How does the child feel?/*Kako se dete oseća?*			
The symptoms have improved/*Simptomi su se poboljšali*	42 (57.5)	59 (78.7)	
There are no changes/*Nema razlike*	13 (17.8)	4 (5.3)	
The symptoms are worse/*Simptomi su se pogoršali*	18 (24.7)	12 (16.0)	0.816
Nasal swab:/*Bris nosa:*			
Negative/*Negativan*	73 (100.0)	75 (100.0)	
Staphylococcus aureus/*Staphylococcus aureus*	0 (0)	0 (0)	
Moraxella catarrhalis/*Moraxella catarrhalis*	0 (0)	0 (0)	
Streptococcus pyogenes/*Streptococcus pyogenes*	0 (0)	0 (0)	
Streptococcus pneumoniae/*Streptococcus pneumoniae*	0 (0)	0 (0)	
Pharyngeal swab:/*Bris ždrela:*			
Negative/*Negativan*	73 (100.0)	75 (100.0)	
Staphylococcus aureus/*Staphylococcus aureus*	0 (0)	0 (0)	
Moraxella catarrhalis/*Moraxella catarrhalis*	0 (0)	0 (0)	
Streptococcus pyogenes/*Streptococcus pyogenes*	0 (0)	0 (0)	
Streptococcus pneumoniae/*Streptococcus pneumoniae*	0 (0)	0 (0)	

Legend: n - number of subjects; % - percentage of subjects; *p* - statistical significance; * X^2 test
*Legenda: br. – broj ispitanika; % – procenat ispitanika; p – statistička značajnost; * X^2 test*

coughing episodes and cough with sputum, over 5 during the previous month, was lower in the younger group (6.8% versus 15.3%). The majority of studies have shown that children who start school at an earlier age demonstrate higher incidence of respiratory infections compared to their peers who do not attend kindergartens [9, 10]. At the age of 2 to 5, the risk of infection is tripled if they do, comparing to their peers who stay at home [11, 12]. Our research has also shown that the incidence of respiratory infections in both groups of children is higher since they started attending a kindergarten: 79.5% of preschool children had more than 3 infections per year, the infections lasted longer than 2 weeks in 89% of children in Group A and 78.7% of those in Group B. Antibiotics were more frequently prescribed to preschool children (p = 0.007).

Cough was a dominant symptom in all studied children. It started mostly in the morning, after waking in 24.7% of preschool children, and during the day in 45.5% of school children. It interfered with sleep in both groups, so that 63% children in Group A and 52% of children in Group B woke up during the night due to

coughing. It interfered with daily activities of school children (64%). After a ten-day use of the pediatric syrup PropoMucil® (combination of purified 20% dried propolis extract standardized to 12% of total polyphenols incorporated with NAC and with the addition of honey. marshmallow and rose hip extract, manufactured by Abela Pharm, Belgrade), improvement of symptoms was observed in both groups: 57.5% in Group A and 78.7% in Group B. Cough still interfered with daily activities of school children, but only in 32%. Nighttime cough dropped to 37% in Group A and 21.3% in Group B. None of the children had any adverse reactions to the therapy.

Nasal and pharyngeal swabs were taken from all children for microbiological testing. At the first visit, 8 children in Group A, and 2 children in Group B had positive pharyngeal results. The most frequent pathogens causing infections in children of that age were Staphylococcus aureus, Moraxella catarrhalis, Streptococcus pyogenes and Streptococcus pneumoniae. The follow-up results were negative in all children, thus confirming the literature data that propo-

lis has anti-inflammatory and antibacterial properties, especially against Staphylococcus aureus [13–16]. which can be explained by the fact that the complex mixture of different compounds produces a synergistic reaction contributing to its anti-inflammatory effects [13]. In addition to propolis and NAC, the syrup also contains marshmallow acting on the dry unproductive cough, and on the inflammation of the upper airway. Owing to containing polysaccharides, marshmallow exerts its immunomodulating effect by increasing the phagocytic activity [17, 18]. As an integral part of the syrup, rose hip has anti-inflammatory and antioxidative properties [19]. Propolis found in commercial products showed to be very efficient in the treatment of inflammatory processes of the airways, so it is recommended for acute respiratory infections [20], which can be explained by the fact that it is a complex mixture of different compounds with synergistic action contributing to its anti-inflammatory effect [21, 22].

The results of a recent study, that included adults and children older than 3 years of age, showed that PropoMucil® has good clinical efficacy in reducing symptoms, predominantly cough and sputum production, after only 7 days of usage for ARI [23].

Conclusion

The combination of propolis and N-acetylcysteine in PropoMucil® pediatric syrup is a good choice in the treatment of uncomplicated pediatric acute respiratory infections accompanied by sputum production and cough. The demonstrated bactericidal and antiviral properties of the product can reduce the irrational use of antibiotics, especially in preschool children. It also showed to be efficient and safe for all ages.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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LUNG ULTRASOUND IN THE ASSESSMENT OF HYPERVOLEMIA
IN HEMODIALYSIS PATIENTS – TWO CASE REPORTS

*ULTRAZVUK PLUĆA U PROCENI HIPERVOLEMIJE KOD PACIJENATA
NA HEMODIJALIZI – PRIKAZ DVA SLUČAJA*

Vladimir VESELINOV[1], Igor IVANOV[2, 3], Jadranka DEJANOVIĆ[2,3] and Dejan ĆELIĆ[3, 4]

Summary

Introduction. Hemodialysis patients often have chronic volume overload, hypervolemia, which may cause severe complications. In some patients hypervolemia is masked, without any signs and symptoms, such as hypertension, edema and bibasilar crackles on lung auscultation. Lung ultrasound can be used to detect these patients. Pre- and post-dialysis lung ultrasound can be used to quantify lung congestion using the B line score. High post-dialysis B line score can identify patients with residual hypervolemia and adequate measures can be taken (increasing ultrafiltration, extended duration of hemodialysis, additional dialysis sessions). **Case Reports**. The first patient was a 57-year-old male. The hemodialysis vintage was 4 years. His interdialytic weight gain was 2.8 kg. The lung ultrasound was performed before and after dialysis and B line score was calculated. The pre-dialysis score was 15 and post-dialysis score was 2. The second patient was a 72-year-old male. The hemodialysis started 5 years before. This patient was noncompliant with the medical advice of his physician regarding diet and medications. His interdialytic weight gain was 5.6 kg. His pre-dialysis score was 26 and post-dialysis score was 15. Both patients were without signs and symptoms of hypervolemia after dialysis. Nevertheless, the second patient was 1.6 kg over his dry weight after dialysis. An additional dialysis session was scheduled, after which his post-dialysis B line score fell to 5. **Conclusion**. Lung ultrasound can be used to assess volume status in dialysis patients. It can identify hypervolemia in asymptomatic patients and allow necessary corrections.

Key words: Lung; Ultrasonography; Renal Dialysis; Kidney Failure, Chronic; Plasma Volume; Water-Electrolyte Imbalance; Pulmonary Edema; Edema; Signs and Symptoms

Sažetak

Uvod. Hronično opterećenje volumenom se često registruje kod pacijenata na hemodijalizi, često i sa komplikacijama. Hipervolemija kod pacijenata na dijalizi može biti skrivena. Pacijenti bez hipertenzije, bez perifernih edema i bez patološkog auskultatornog nalaza na plućima i dalje mogu imati ozbiljnu hipervolemiju. Ultrazvukom pluća pre i nakon hemodijalize možemo identifikovati pacijente sa rezidualnom hipervolemijom pomoću patološki visokog postdijaliznog B-linijskog skora, uprkos odsustva drugih simptoma i znakova hipervolemije. Potom možemo preduzeti potrebne mere kao što su povećanje ultrafiltracije, produženje trajanja hemodijalize ili čak zakazivanje vanredne hemodijalize. **Prikaz slučaja.** Prvi pacijent je muškarac star 57 godina, sa dijaliznim stažom od 4 godine i interdijaliznim prinosom od 3 kg. Pre i posle dijalize urađen mu je ultrazvuk pluća i izračunat B-linijski skor. Predijalizni skor je bio 15, a postdijalizni 2. Drugi pacijent je muškarac star 72 godine, sa dijaliznim stažom od 5 godina. Nedisciplinovan je, sa velikim interdijaliznim prinosom od 5,6 kg. Njegov B-linijski skor pre dijalize bio je 26, a posle dijalize 15. Oba pacijenta su bila bez simptoma i znakova hipervolemije nakon dijalize. Ipak, drugom pacijentu je ostalo 1,6 kg „viška" te mu je zakazana vanredna dijaliza, nakon koje je skor bio 5. **Zaključak.** Ultrazvuk pluća se može koristiti za procenu opterećenja volumenom kod pacijenata na hemodijalizi. On može da identifikuje pacijente sa skrivenom hipervolemijom, one bez jasnih simptoma i znakova hipervolemije, što je bitno zbog sprečavanja komplikacija koje su česte među ovom populacijom pacijenata.

Ključne reči: pluća; ultrasonografija; hemodijaliza; hronična bubrežna insuficijencija; volumen plazme; elektrolitski disbalans; plućni edem; edem; znaci i simptomi

Introduction

Chronic volume overload is frequent among hemodialysis patients. It leads to hypertension, left ventricular hypertrophy and heart failure [1]. Adequate volume control in these patients decreases morbidity and mortality [2].

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Dry weight is defined as the lowest tolerated post-dialysis weight and is reached with gradual lowering of weight to the value at which there are minimal signs and symptoms of hypo – or hypervolemia [3]. This clinical assessment of volume status is often inadequate [1]. New techniques for assessing dry weight have been developed, including bioimpedance, biospectroscopy [4], natriuretic peptide serum levels [5], and ultrasonography methods, the most common being inferior vena cava diameter [6]. A novel ultrasonography method described here is lung ultrasound (LUS) [7].

Lung ultrasound can detect extravascular lung water (EVLW), fluid present in lung interstitium, which is strongly dependent on the left ventricle filling pressure [2]. LUS detects EVLW by B lines on the screen of the device, B lines are well defined, dynamic, hyperechoic lines that stretch from the pleural line all the way to the bottom of the screen without any loss of intensity [8]. The sum of all B lines detected over the front and lateral sides of the chest represents the B line score (BLS), a numerical marker of pulmonary congestion [8].

This topic was chosen to demonstrate a simple method for detection of hypervolemia in hemodialysis patients, because of its high prevalence and associated complications. The aim of this paper is to show the use of LUS in two patients on chronic hemodialysis in Kikinda General Hospital.

Case Reports

The first patient was a 57-year-old male with end stage chronic renal disease due to nephroangiosclerosis. His hemodialysis vintage (time on dialysis) was 4 years, with three dialysis sessions per week, each lasting 4.5 hours. On patient's first weekly dialysis he was eupneic, normotensive (TA: 130/80 mmHg), with normal heart rate (80 bpm), normal lung and heart auscultation sounds and without peripheral edema. His average interdialytic gain was around 3 kg, and his marker of dialysis adequacy (kT/V) was 1.18. His comorbidities included hypertension and secondary anemia. On the day of the dialysis his interdialytic weight gain was 2.8 kg. His dialysis session lasted for 4.5 hours. Ultrafiltration was set to 3100 ml.

Lung ultrasound was performed before dialysis using a Samsung Medison MySono U6 ultrasound device, with a 3.5 MHz convex probe. The patient was placed in a semi recumbent position, with torso at 45 degree angle knee. The probe was placed longitudinally in the 2nd intercostal space on the left parasternal line and the classically described "bat sign" was seen **(Figure 1A)**. The "bat sign" is made up of the upper and lower ribs representing the

"wings" and the pleural line between them, resembling the "back" of the bat. The movement of the pleural line is also seen as a sliding motion back and forth, as well as acoustic shadows behind each rib. Hyperechoic horizontal lines appearing at equal distances below the pleural line are also seen. These reverberation artifacts represent the pleura and are called A lines. Thus far, it is a normal lung ultrasound finding. Placing the probe was continued along the 2nd intercostal space in the midclavicular, anterior axillary and midaxillary line and then in the same fashion along the 3rd and 4th intercostal spaces on the left and the 2nd, 3rd, 4th and 5th intercostal spaces on the right. B lines were detected over the lower parts of the chest. They are seen as hyperechoic dynamic vertical lines that start at the pleural line and spread to the bottom of the screen without loss of intensity. breaking the continuity of A lines **(Figure 1B)**. The total number of B lines in each of the 28 spaces was noted **(Table 1)**. The sum of these numbers represents the BLS which equaled 15 in our first patient. The dilaysis was uneventful. After dialysis the patient was symptom free, normotensive (TA: 120/60 mmHg), with normal heart rate (90 bpm). LUS was performed after dialysis and single B lines were detected over two lung fields. The BLS was 2.

The second patient was a 72-year-old male with end stage chronic renal disease due to nephroangiosclerosis. His hemodialysis vintage was 5 years with three dialysis sessions per week, each lasting 4 hours.

On his first weekly dialysis the patient complained of mild fatigue. He denied dyspnea in exertion, at rest or orthopnea. He was eupneic, hypertensive (TA: 150/90 mmHg), with normal heart rate (75 bpm), normal heart and lung auscultation, and with discrete crural pitting edema. He was noncompliant with medical advice on medications and dietary restrictions. His average interdialytic gain was around 6 kg, and his kT/V was 0.94. His comorbidities included hypertension and renal osteodystrophy. On the day of dialysis his interdialytic weight gain was 5.6 kg. Ultrafiltration was set to 4000 ml and the duration of dialysis to 4 hours. LUS examination was performed using the same method as in patient number one. The B line score in this case was 26. The dialysis was uneventful. After dialysis the patient was symptom free, normotensive
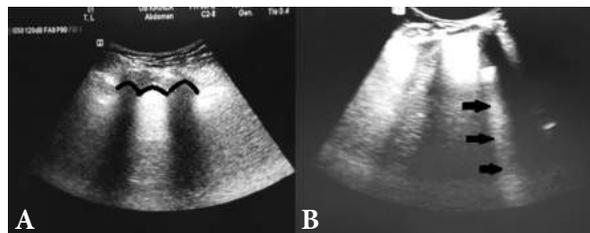
Figure 1 A. Normal lung ultrasound – bat sign visible; **B**. B line visible on the right, marked with arrows
Slika 1 A. *Uredan ultrazvuk pluća, vidljiv znak slepog miša; **B**. B linija desno, obeležena strelicama*

Table 1. Probe placement scheme
Tabela 1. Shema plasiranja sonde

Right hemithorax/*Desni hemitoraks*						Left hemithorax/*Levi hemitoraks*		
Mid-axillary line *Srednja pazušna linija*	Anterior axillary line *Prednja pauzušna linija*	Midclavicular line *Srednja ključnačna linija*	Para-sternal line/*Par-asternalna linija*	Inter-costal space *Međurebarni prostor*	Para-sternal line/*Paraster-nalna linija*	Midclavicular line/*Srednja ključnačna linija*	Anterior axillary line *Prednja pazušna linija*	Mid-axillary line *Srednja pazušna linija*
				II				
				III				
				IV				
				V	/	/	/	/

(TA: 120/70 mmHg), with normal heart rate (90 bpm). There was no edema. Lung ultrasound was performed after dialysis and a decrease in the number of B lines was registered. The BLS was 15.

Discussion

Dry weight assessment was never simple. Its definition changed frequently, and the current one is in use since 2009 [3]. Still, all definitions were based on arterial tension as an easily measured but imprecise volume indicator [9]. This led to a search for more objective methods of evaluating volume status and dry weight, respectively.

Standard ultrasound dogma, until recently, was that lung parenchyma cannot be visualized, due to the fact that ultrasound energy quickly dissipates in the air [7]. The only structure that can be visualized was the pleura [7]. Visualization of structures below the pleura is only possible if there is consolidation of lung parenchyma below it. Still the presence of air is responsible for several ultrasound artifacts that can be interpreted in different clinical context. Daniel Lichtenstein was one of the first to interpret these artifacts in intensive care patients, identified the key ones, and introduced LUS nomenclature [10]. The B lines are crucial for identifying lung congestion, but can also be seen in acute respiratory distress syndrome and lung fibrosis [11]. In our patients, increased number of B lines represents lung congestion due to hypervolemia. The B lines in this case occur when ultrasound waves meet thickened, edematous interlobular septa. This produces artifacts on screen which we see as B lines [8]. A greater number of B lines represent a greater degree of lung congestion [8]. For easier interpretation BLS was established, being the sum of all B lines detected over the 28 defined fields on the chest [12]. The BLS less than 8 is considered normal. Lung congestion is estimated as light if BLS is between 8 and 13, medium between 14 and 30, and severe if BLS equals or is above 30 [12].

Our first patient had a pre-dialysis BLS of 15 (medium lung congestion). This correlated with his lower interdialytic gain of 2.8 kg. Nevertheless, this patient had normal physical findings, no edema or pathologic lung sounds on auscultation. After adequate dialysis and ultrafiltration of 3100 ml his post-dialysis BLS equaled 2 (within reference range) meaning no lung congestion was present. We concluded that this patient reached his dry weight.

The second, noncompliant patient's pre-dialysis BLS was 26 (medium lung congestion). This was consistent with his physical findings including discrete pitting pretibial edema. Because his interdialytic weight gain was 5.6 kg, his dialysis duration was 4 hours, and maximal ultrafiltration was 4000 ml. After dialysis the patient was 1.6 kg above his dry weight. His post-dialysis BLS was 15 (medium lung congestion). No signs and symptoms of hypervolemia were present. An additional dialysis session was scheduled and at the end of it, the BLS was 5, meaning a significant BLS reduction.

These results are supported by the research of Basso et al. who demonstrated significant BLS reduction after dialysis in a 30-patient sample [1]. Mallamaci et al. showed a significant BLS reduction after dialysis as well as correlation of post-dialytic BLS with the ejection fraction and left atrial volume in a sample of 75 dialysis patients. They showed that cardiac function plays a significant role in EVLW control [12]. Trezzi et al. have performed a study that confirms these results [9].

Noble et al. followed the B line number dynamics during the course of a hemodialysis session on a sample of 45 patients. They measured BLS before, halfway through the dialysis and after dialysis. They showed significant BLS reduction during and after dialysis, which is in agreement with our observations [13].

Zoccali et al. followed a sample of 392 patients and showed that around 70% of dialysis patients with medium or severe lung congestion have no or very discrete symptoms. This is in accordance with what we saw in our two patients. In his prospective study, Zoccali et al. showed that BLS is a strong and independent mortality and adverse cardiac event predictor [14, 15]. Siriopol et al. went even further in the follow-up of dialysis patients and showed that a BLS is a significant predictor of survival time in dialysis patients, independent from heart function.

In this prospective study the author followed 96 patients during 400 days and showed that patients with high pre-dialysis BLS presented with significantly higher mortality [2].

Patients with end stage renal disease have a high mortality rate regardless of the chosen dialysis method [14, 15]. Chronic volume overload is frequent in patients on standard chronic hemodialysis (3 times a week, duration 4 – 4.5 h), so one of the main goals of dialysis is maintaining normal extracellular volume levels [16]. Prevention of volume overload is the central recommendation of all dialysis guidelines [2]. Additional information about the patients' volume status contributes to a better understanding of their general condition, and is even more important if we know that some of them can be hypervolemic and asymptomatic [1, 7]. Yet, there are no clear recommendations about monitoring the volume status of dialysis patients, or information if this monitoring and subsequent actions lead to a mortality reduction. The Lung Water by Ultra-Sound Guided Treatment to prevent death and cardiovascular complications in high-risk end-stage renal disease patients with cardiomyopathy study should provide answers to this question and clarify if there is a place for lung ultrasound and BLS in standard dialysis practice [17].

Conclusion

Lung ultrasound can be used to assess volume status in hemodialysis patients. It can identify hypervolemic patients without clear signs and symptoms of hypervolemia. Lung ultrasound could be an important step to decrease the high rate of complications in these patients.

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PRIMARY MALIGNANT MELANOMA OF THE FEMALE URETHRA − A CASE REPORT

PRIMARNI MALIGNI MELANOM ŽENSKE URETRE − PRIKAZ SLUČAJA

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Summary
Introduction. Malignant melanoma accounts for 3% of all cancers in Europe. Malignant melanoma of the genitourinary tract is very rare, accounting for 1% of all cases. In addition, primary malignant melanoma of the urethra accounts for 0.2% of all melanomas and 4% of all urethral cancers. The abnormal migration of melanocytes during the embryonic development may explain their occurrence in the urethra. Also, vulva contains a relatively high concentration of melanocytes, so it may be the reason for higher incidence of malignant melanomas in females than in males, especially located at the meatus or in the distal urethra. **Case Report.** A 60-year-old woman presented with a solid tumor protruding through the vaginal introitus. Computerized tomography revealed a 5 cm large tumor of the urethra, infiltrating the bladder neck and the anterior vaginal wall. In addition, a bilateral pelvic lymphadenopathy was observed. The patient underwent anterior pelvic exenteration with urethrectomy, bilateral pelvic lymphadenectomy and bilateral ureterocutaneostomy, followed by immunochemotherapy. Nonetheless, the patient died 10 months after the surgery. **Conclusion.** Urethral melanoma is a tumor with a very poor prognosis and high recurrence rate (71%), even after wide surgical resection, adjuvant radiotherapy, chemo and immunotherapy.
Key words: Melanoma; Urethral Neoplasms; Female; Surgical Procedures, Operative; Treatment Outcome

Sažetak
Uvod. Maligni melanom čini 3% svih karcinoma u Evropi. Maligni melanom genitourinarnog trakta je vrlo redak tumor i javlja se u 1% svih slučajeva. Pored toga, primarni maligni melanom uretre predstavlja 0,2% svih melanoma i 4% svih karcinoma uretre. Abnormalnom migracijom melanocita tokom embrionalnog razvoja se može objasniti pojava ovog tumora u uretri. Pored toga, vulva sadrži relativno visoku koncentraciju melanocita, što mogu biti razlozi za češće pojavljivanje malignog melanoma kod žena nego kod muškaraca i za pojavu tumora u distalnoj uretri i meatusu. **Prikaz slučaja.** Šezdesetogodišnja žena se javila urologu sa solidnim tumorom koji je prolabirao iz intoritusa vagine. Kompjuterizovana tomografija je pokazala tumor veličine 5 cm u ureteri, koji infiltrira vrat mokraćne bešike i prednji vaginalni zid. Pored toga, postojala je bilateralna limfadenopatija male karlice. Pacijentkinji je učinjena prednja egzentereza sa uretrektomijom, bilateralna pelvična limfadenektomija i bilaterlna ureterokutaneostomija. Nakon hirurškog lečenja primenjena je imunohemoterapija. Međutim pacijentkinja je preminula 10 meseci nakon hirurške intervencije. **Zaključak.** Maligni melanom uretre je tumor sa vrlo lošom prognozom i visokom stopom recidiva (71%), čak i nakon široke hirurške, adjuvantne radioterapije, hemoterapije i imunoterapije.
Ključne reči: melanom; karcinom uretre; žena; operativne hirurške procedure; ishod lečenja

Introduction

Malignant melanoma (MM) accounts for 3% of all cancers in Europe [1]. The incidence of MM in white females is 14.7 – 15.2 per 100.000, while it is less common in Asian and Black females [2]. However, MM of the genitourinary tract is very rare, accounting for 1% of all cases [3, 4]. In addition, primary MM of the urethra comprises 0.2% of all melanomas and 4% of all urethral cancers [5]. The MM of the urethra is rare due to its endodermal origin, as melanocytes arise from

neuroectodermal tissue. However, the abnormal migration of melanocytes during the embryonic development may explain their occurrence in the urethra [6]. In addition, vulva contains a relatively high concentration of melanocytes, so it may be the reason for higher incidence of MM in females, than in males (3 : 1) and for the occurrence of 8% at the distal urethra and the meatus [7–9]. The most common symptoms are urethral mass, dysuria, hematuria, local or vaginal bleeding and incontinence [10]. Primary urethral MM has a very poor prognosis due to delayed diagnosis and

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Abbreviations

MM　　　– malignant melanoma
CT　　　– computerized tomography

early metastasis [11–13]. At the time of diagnosis, about half of the patients have a metastatic disease. Melanomas may be confused with urethral polyps, mucosal prolapse or caruncles [14]. The histopathological diagnosis can be assisted by the use of immunohistochemical markers, such as HMB-45 and S-100. The MM is usually treated by extensive lesion excision and removal of the surrounding lymph nodes [15]. Surgery still remains the initial treatment of choice for localized disease. However, adjuvant local-regional and systemic therapy is necessary.

Case Report

A 60 year-old female complained of obstructive voiding symptoms. intermittent urethrorrhagia and a painful mass protruding from the vagina. Physical examination revealed a 4 to 5 cm white polypoid mass in the vaginal introitus, originating from the external urethral meatus **(Figure 1)**.

Urethrocystoscopy revealed a mass that infiltrated the whole urethra, up to the bladder neck. After the biopsy, MM was established by histopathological examination. Computerized tomography (CT) revealed a 5 cm-large tumor of the urethra, infiltrating the bladder neck and the anterior vaginal wall, and enlarged bilateral pelvic lymph nodes.

Figure 1. White polypoid mass in the vaginal introitus originating from the external urethral meatus
Slika 1. Bela polipoidna masa u introitusu vagine, poreklom iz spoljašnjeg meatusa uretre

Figure 2. Anterior pelvic exenteration with urethrectomy
Slika 2. Prednja egzenteracija sa uretrektomijom

The patient underwent anterior exenteration with urethrectomy, bilateral pelvic lymphadenectomy and bilateral ureterocutaneostomy **(Figure 2)**. All lymph nodes were enlarged on both sides, and a total of 32 lymph nodes were removed, as the aortic branch was reached. Inguinofemoral lymphadenectomy was not performed, because metastases had already been found in all lymph nodes and the patient was already in poor physical condition, and an additional bilateral operation would compromise the earlier intervention without a positive benefit.

Pathological examination of the whole specimen confirmed MM of the urethra, infiltrating the anterior vaginal wall and the bladder neck, and all lymph nodes were positive for metastases **(Figures 3 and 4)**.

Following the surgery. the patient was referred to the Institute of Oncology and Radiology of Serbia. where chemo and immunotherapy were applied according to MM protocols of this institution. Dacarbazine, 140 mg/m^2 was administered for 5 days, vincristine, 0.8 mg/m^2 on day one, and injection of inter-
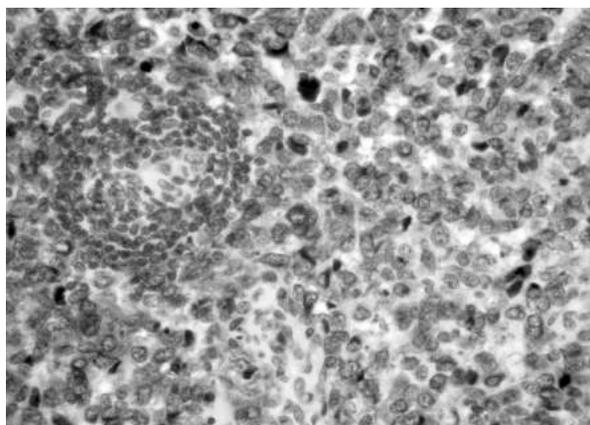
Figure 3. Malignant melanoma of the urethra infiltrating the anterior vaginal wall and the bladder neck
Slika 3. Maligni melanom uretrem koji infiltrira prednji zid vagine i vrat mokraćne bešike
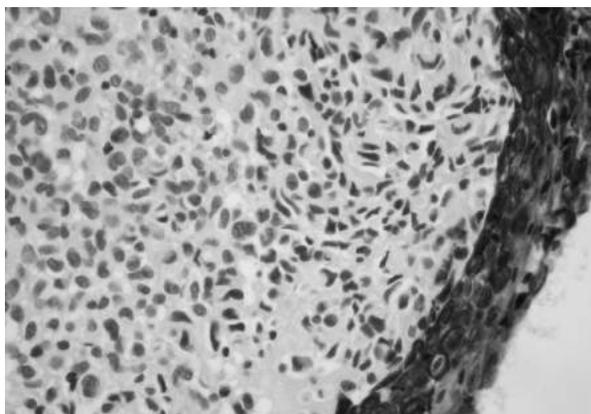
Figure 4. Malignant melanoma of the urethra with metastases in the pelvic lymph nodes
Slika 4. *Maligni melanom uretre - metastaze u pelvičnim limfnim nodusima*

feron-β 3.0 x 10^6 IU for 10 days. The cycle was repeated every four weeks. Nevertheless, the patient died 10 months after the surgery. The cause of death was metastatic liver disease, diagnosed 4 months after the surgery.

Discussion

The most common tumors of the female urethra are squamous cell carcinoma (60%) and transitional cell carcinoma (20%), while MM accounts for less than 2% of all cases [15]. In addition, female urethral MM comprises less than 0.2% of all melanomas [16].

The average age of presentation is 68 years [1]. and this type of tumor is more frequent in women than in men, with a female to male ratio of 3 : 1 [17]. El-Safadi found that the most frequent symptoms include urethral mass, dysuria, hematuria, local or vaginal bleeding and incontinence [18]. Oliva et al. reported melanomas being confused with urethral polyps, mucosal prolapse and urethral caruncle [14].

Sometimes, urethral MM may be interpreted as undifferentiated sarcoma and the diagnosis is confirmed by immunohistochemical staining. Because of poor prognosis, early diagnosis is essential, and clinicians need to include it in their differential diagnosis

when working up a patient with genitourinary complaints [18]. Microscopic examination of urethral MMs demonstrates a wide histologic spectrum with diffuse, nested, fascicular and storiform patterns of pleomorphic cells [10]. The histopathological diagnosis can be assisted by the use of immunohistochemical markers, such as HMB-45 and S-100. Due to its infrequency, there are no guidelines and recommendations for the diagnosis and treatment. It is usually treated by extensive lesion excision and removal of the contributory lymph nodes [15]. Sometimes, small urethral MMs are erroneously removed by local excision, since they may resemble caruncle. Distal urethrectomy following the excision did not reveal a residual tumor [16]. Amelanotic melanoma is a rare form of the urethral MM, and often resembles urethral caruncle. If the tumor is not locally invasive. radical surgery can be followed by continent urinary diversion and the reconstruction of the vulva [17]. Conventional prognostic factors, such as the depth of invasion or tumor stage, do not have an important role in predicting survival, due to the mucosal location and nodular growth, typical for this tumor. Melanoma of the urethra generally has a worse prognosis than the cutaneous melanoma [19]. This is mostly because of delayed diagnosis. Large, infiltrating, T4 tumors have poor prognosis, despite radical surgical treatment and postoperative immunochemotherapy [20]. DiMarco et al. reported a high recurrence rate of the primary urethral MM within the first year (60%) and advocated total urethrectomy in preference to partial, because of the associated high risk of relapse. In the series of 11 cases. DiMarco found that all women presented with a tumor in the distal urethra, while seven women had a local extension to the vagina. The authors described a 60% recurrence rate in the first year. and a cancer specific survival of 27 – 38% at 3 years [7]. The mean survival in two largest series was 16 months. Survival over 5 years was reported in 12 patients [7].

Conclusion

Urethral melanoma is a tumor with a very poor prognosis and high recurrence rate (71%), even after wide surgical resection, adjuvant radiotherapy. chemotherapy and immunotherapy.

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RUPTURED ABDOMINAL AORTIC ANEURYSM AFTER ENDOVASCULAR REPAIR

RUPTURA ANEURIZME ABDOMINALNE AORTE NAKON ENDOVASKULARNOG LEČENJA

Janko PASTERNAK, Vladan POPOVIĆ and Slavko BUDINSKI

Summary
Introduction. An aneurysm is a localized, permanent dilation of an arterial blood vessel with a diameter greater than 50% of the usual diameter for that aortic segment. It is treated with endovascular stent graft placement or open surgery. Endovascular stent grafting of the abdominal aorta has become popular as an elective treatment. but one of the complications is increased aneurysm diameter that may lead to rupture. **Case Series.** This case series reviews open reconstructive surgery of ruptured abdominal aortic aneurysms in three patients treated with endovascular repair. The diameter of the aneurysm increased due to endoleak or stent graft migration, leading to rupture. Due to the inability to extract the stent graft in two patients, the graft was transversely cut at the proximal part, where upper anastomosis was created using a Dacron graft prosthesis. **Conclusion.** Regular annual controls for the rest of patients lives are of great importance in order to avoid fatal complications after endovascular aneurysm repair. One of the methods after the abdominal aortic rupture after endovascular stent graft treatment that significantly shortens the duration of the surgery and gives a more stable upper anastomosis, is transverse stent graft cut in the proximal part. Complete prevention remains a challenge because a rupture may occur even if the abnormalities are not evident. The ultimate goal is to increase the survival rate after the ruptured abdominal aortic aneurysm.
Key words: Endovascular Procedures; Aortic Aneurysm. Abdominal; Blood Vessel Prosthesis; Postoperative Complications; Survival Rate; Vascular Grafting; Stents

Sažetak
Uvod. Aneurizma podrazumeva lokalno segmentalno stalno proširenje krvnog suda, sa svim slojevima, za više od 50% uobičajenog prečnika za pregledani segment i tretira se endovaskularnim stent-graftom i otvorenom hirurgijom. Endovaskularno lečenje aneurizme abdominalne aorte stent-graftom postalo je popularno kao elektivni tretman, ali jedna od komplikacija jeste dalje uvećanje dijametra aneurizme koje može dovesti do rupture. **Prikaz slučaja.** Ovaj rad je prikaz otvorene rekonstruktivne hirurgije u slučaju rupture aneurizme abdominalne aorte kod tri pacijenta koji su u prvom aktu lečeni endovaskularno te se, zbog endolika i migracije grafta, dijametar aneurizme i dalje povećavao i završio se rupturom. Zbog nemogućnosti izvlačenja stent-grafta kod dva pacijenta, graft je transverzalno presečen makazama na proksimalnom delu gde je naknadno kreirana gornja anastomoza interponiranog *Dacron* grafta. **Zaključak.** Redovne godišnje kontrole do kraja života pacijenata imaju veliki značaj kako bi se izbegle fatalne komplikacije nakon endovaskularnog lečenja. Jedan od načina nakon rupture abdominalne aorte nakon endovaskularnog tretmana stent-graftom, koji značajno skraćuje trajanje operacije i daje stabilniju gornju anastomozu, jeste da se poprečno preseče stent-graft makazama u proksimalnom delu. Kompletna prevencija ostaće izazov jer se ruptura može desiti i ako se abnormalnosti ne vide. Krajnji cilj je povećanje procenta preživljavanja nakon rupture aneurizme abdominalne aorte.
Ključne reči: endovaskularne procedure; aneurizma abdominalne aorte; vaskularna proteza; postoperativne komplikacije; preživljavanje; vaskularni graftovi; stentovi

Introduction

An aneurysm is a localized permanent dilation of an arterial blood vessel with a diameter greater than 50% of the usual diameter for that arterial segment. It is treated with endovascular stent graft placement or open surgery [1].

The main goal of treating abdominal aortic aneurysm (AAA) with surgical or endovascular repair is to reduce the risk of rupture and prevent the patient's death [1]. Endovascular aortic repair (EVAR) by stent graft placement is directed at removing the risk of rupture by its exclusion from arterial circulation [2].

Today, EVAR is a relatively safe and effective treatment of infrarenal AAA and it is considered to be the first choice therapy in patients with favorable morphology and poor health status unsuitable for open surgery. However, none of the currently available devices is completely effective in preventing rupture of aneurysm after EVAR [3], and it is also necessary to control these grafts and aneurysms for life. The goal of this paper was to substantiate this in regard to the occurrence of late ruptures.

Complications of endovascular repair include the appearance of endoleaks, stent graft migration, infection, and occlusion of the main arteries, which may increase the aneurysm diameter potentially leading to late rupture **(Table 1)** [4].

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Abbreviations
EVAR   – endovascular aortic repair
AAA   – abdominal aortic aneurysm
CTA   – computed tomography angiography
DUS   – duplex ultrasonography scanning

Computed tomography angiography (CTA) has been considered a gold standard in check-ups after endovascular treatment of abdominal aneurysm, but a protocol incorporating annual duplex ultrasonography scanning (DUS) was introduced, and CTA was performed only if abnormalities were identified or DUS was not diagnostic [5].

The aim of this paper is to point to the importance of regular annual follow-ups to avoid fatal complications, as well options for the operative treatment of AAA rupture after EVAR that significantly shortens the duration of the operation and provides a more stable upper anastomosis.

We present three cases of successfully performed treatment of ruptured aneurysms of the abdominal aorta that were previously treated with EVAR, and because of insufficient monitoring and follow-ups, the diameter has increased and resulted in ruptured aneurysms.

Patient number I

The first patient, 78 years of age, was treated for AAA with an endovascular stent graft (EVAR - Medtronic Endurant) six years ago, and in the first two years he was followed-up, but then stopped coming by his choice. He had no other chronic diseases or allergies and did not take any medications. He was admitted to the emergency department, conscious, oriented, hemodynamically hypertensive with TA 160/100 mmHg, heart frequency - 70 min, and with good oxygen saturation of 98% SaO_2.

Fugure 1. CT angiography of the abdominal aorta (Three-dimensional reconstruction) which confirmed the diagnosis of ruptured aneurysm of the abdominal aorta with a noticeable stent graft, and endoleak on distal and proximal anastomosis
Slika 1. Kompjuterizovana tomografska angiografija abdominalne aorte (Trodimenzionalna rekonstrukcija) koja potvrđuje dijagnozu rupture aneurizme abdominalne aorte sa uočljivim stent-graftom i endolikom na distalnoj i proksimalnoj anastomozi

He complained of a strong and sharp pain in the abdomen, followed by nausea 9 hours ago, and during the examination he presented with a painful abdomen with muscular defense and peritoneal suppression.

An emergency CTA (Siemens Somatom Sensation 16) was performed **(Figure 1)** which confirmed a ruptured AAA with the intraluminal presence of graft which corresponded to the stent graft and with the active extravasation of contrast at its distal end (type Ib endoleak) and less extravasation on the proximal end (type Ia endoleak).

The patient underwent xyphopubic laparotomy with intraoperative exposure of the abdominal aorta. A retroperitoneal hematoma was noticed. After the aneurysmectomy it was noticed that the stent graft was intact, the endoleak was on the proximal end on the posterior site, and the aneurysm rupture site was laterally to the left.

Because of the inability to extract the stent graft, it was cut transverse by scissors at the proximal part **(Figures 2A and 2B)** where the upper anastomosis of 20 mm Dacron graft prosthesis was created **(Figure 3)**.

The swab which was taken from a graft was negative. A passive drain in the Douglas space was set. Intraoperative blood cell salvage of 1400 ml was done and 600 ml of autologous blood was returned. The operation lasted 100 minutes.

Postoperatively, the patient remained in the intensive care unit and after hemodynamic stabilization and transition to spontaneous breathing, on the fourth

Figure 2A. Intraoperative finding with infrarenal transversal intersected stent graft, the location of the planned proximal anastomosis of the Dacron graft prosthesis
Slika 2A. Intraoperativni nalaz sa poprečno presečenim stent-graftom infrarenalno, mesto planirane proksimalne anastomoze interponiranog Dacron tubus proteze

Table 1. Classification of endoleaks
Tabela 1. Klasifikacija endolika

Type/*Tip*	Origin of the leak/*Poreklo endolika*
I	Inadequate seal at proximal (Ia) or distal (Ib) end of the graft *Neadekvatno zatvaranje na proksimalnom (Ia) ili distalnom (Ib) kraju grafta*
II	Retrograde flow from the inferior mesenteric artery, lumbar arteries, other collateral vessels of the aneurysm sac/*Retrogradni protok iz donje mezenterične arterije, lumbalnih arterija, drugih kolateralnih krvnih sudova aneurizmatske kese*
III	Component disconnection (IIIa) or fabric disruption (IIIb) *Diskonekcija komponenti endografta (IIIa) ili pucanje endografta (IIIb)*
IV	Graft material porosity/*Poroznost endografta*
V	Endotension: increase of the preassure without any visibile evidence of blood in the aneurysm sac *Endotenzija: porast pritiska bez ikakvog vidljivog dokaza prisustvo krvi u aneurizmatskoj kesi*

day he was transferred to the Vascular Surgery Clinic. Because of high inflammatory markers (PCT 0.11 ng/ml. CRP 51 mg/L) as well as ALT (115 U/L) and AST (114 U/L), the patient was examined by an infectologist who prescribed antibiotic therapy and the markers normalized during hospitalization. Patient with palpable distal pulses, without any pain and mobile, was released home in good general condition on the 10th postoperative day with antibiotic (Levomax) and antiaggregation (Cardiopirin) therapy.

The last follow-up was done using DUS twelve months after surgery, and the patient was free of any pain, with a prosthesis and with palpable distal pulses.

Patient number II

The second patient 82 years of age, was treated for AAA with endovascular stent graft (EVAR - Medtronic Talent) eight years ago and for the first four years he was controlled, but then stopped coming for check-ups as advised by his physician. He suffered from a chronic obstructive pulmonary disease and hypertension, which he claimed to be under control. He was admitted to the emergency department conscious, oriented, hemodynamically hypertensive with TA 170/110 mmHg, heart frequency – 85 min and with good saturation of oxygen SaO$_2$ 99%.

An emergency CTA (Siemens Somatom Sensation 16) was made **(Figure 4)** which confirmed a ruptured AAA with intraluminal graft which corresponded to the stent graft. The graft was not in the proper place, it migrated distally.

Xyphopubic laparotomy was performed for exposure of the abdominal aorta. A retroperitoneal

Fugure 2B. Stent graft extracted by transversal cutting the fixation site at the proximal part of the stent graft
Slika 2B. Izvađen stent-graft tako što je poprečno presečeno mesto fiksacije na proksimalnom polu stentgrafta

Figure 3. Intraoperative finding with the interposition of a 20 mm Dacron graft
Slika 3. Intraoperativni nalaz sa interpozicijom Dacron tubusa 20 mm

Figure 4. CT angiography of the abdominal aorta (Three-dimensional reconstruction) confirming the diagnosis of ruptured AAA with the visible stent graft and its distal migration
Slika 4. CT angiografija abdominalne aorte (Trodimen-zionalna rekonstrukcija) koja potvrđuje dijagnozu rup-ture aneurizme abdominalne aorte sa uočljivim stent-graftom i njegove migracije put distalno

hematoma was noticed. After the aneurysmectomy, it was noticed that the stent graft migrated distally, and that the aneurysm rupture was on the front site. After endostent graft extraction **(Figure 5)** inter-position of 22 mm Dacron graft prosthesis was cre-ated. A passive drain in the Douglas space was set. Intraoperatively, blood cell salvage of 1000 ml was done and 350 ml of autologous blood was returned. The operation lasted 120 minutes.

The patient was postoperatively in the intensive care unit until hemodynamic stabilization and transi-tion to spontaneous breathing, and on the eight day he was transferred to the Vascular Surgery Clinic.

The patient with palpable distal pulses and with-out any pain, mobile and in good general condition was discharged on the 15th postoperative day with antibiotic (Levomax) and antiaggregation (Cardi-opirin) therapy. The patient died two months after the surgery due to cardiopulmonary insufficiency, without postoperative complications.

Patient number III

The third patient was 82 years of age and treated for aneurysm of the abdominal aorta with an en-dovascular stent graft (EVAR – Medtronic Endur-atnt) 7 years ago and for the first three years he was controlled and then stopped coming by his choice. He suffered from hypertension, diabetes melitus, and had a coronary bypass surgery. He was admitted to the emergency department in a bad condition, with hypertension TA 160/100 mmHg, heart frequency – 100 min and with low saturation of oxygen SaO_2 90%, non-communicative, in soporous condition.

He complained of strong and sudden abdominal pain followed by nausea about 1 hour ago, and the clinical examination showed a painful abdomen with muscular defense and peritoneal suppression.

Fugure 5. Completely extracted stent graft with all its parts
Slika 5. Kompletno ekstrahovan stent-graft sa svim njegovim delovima

The abdominal ultrasound was urgently done and it confirmed a ruptured AAA with intraluminal presence of the graft which corresponded to the stent graft. The patient was randomized as the first order of priority, and the indication for surgery was made without CTA.

Xyphopubic laparotomy was performed for ex-posure of the abdominal aorta. An intraperitoneal hematoma was noticed. After the aneurysmomec-tomy, it was noticed that the stent graft was intact, and the aneurysm rupture was on the front site.

As in the first case, due to the inability to extract the stent graft, it was cut transversely through the proximal part where the upper anastomosis of 18 mm Dacron graft prosthesis was created. A passive drain in the Douglas space was set. Intraoperative-ly, blood cell salvage of 3400 ml was done and 1200ml autologous blood was returned. The opera-tion lasted 130 minutes.

After the surgery, the patient was hemodynami-cally unstable with continuous vasoactive support in the intensive care unit. The patient died 6 hours after the surgery.

Discussion

The EVAR technique has progressed rapidly over the past 20 years. With an increasing incidence of aortic aneurysms revealed due to screening, improve-ments in detection methods and an increase in the older population worldwide, it is expected that the rate of EVAR will increase further in the future [6].

which means a higher incidence of ruptures after EVAR because it is one of the complications.

The less invasive procedure and generally satisfactory early results have made EVAR an attractive therapeutic alternative to most patients with elective AAA [5]. Studies comparing the outcome of EVAR with open surgery consistently showed a significant reduction in morbidity with endovascular repair, so the endovascular procedure has rapidly advanced [7]. Patients with ruptured AAA after EVAR are hemodynamically more stable compared to patients with de novo ruptures of AAA [8].

Although the future prospect of EVAR seems extremely bright at this point, identifying risk factors for unwanted events, such as a need for conversion to open surgery and late post-EVAR ruptures. can lead to further improvement of this technique [7].

The CTA is considered the gold standard after EVAR. However. its limitations include expenses, the risk of contrast-induced nephropathy and exposure to radiation [5]. We have a modified protocol which first involves a 6-month postoperative follow-up with CT scanning enhanced by contrast, later followed by a 12-month follow-up. If there is no endoleak and the aneurysm diameter is stable, then annual ultrasound examination of the aorta is proposed. Increased aneurysm or a new endoleak should encourage more intensive imaging and treatment if necessary. Dias and associates suggested a CT after the first, third and sixth postoperative months, and in the case of positive findings. CT should be done annually [9].

Van Marrewijk and associates published that endograft check-ups should be done using the following techniques: contrast enhanced computed tomography (in 84%), angiography (in 4%), magnetic resonance angiography (in 3%), duplex ultrasound examination (in 8%) every year [7]. In our hospital, during the first year, check-ups are done during 6 months, then only DUS and CTA annually if the results are satisfactory. The biggest problem in the world as well as in our hospital is that patients commonly stop coming for check-ups.

Large cohort studies reported rupture rates between 0.5 and 1.2% of patient per year after EVAR. In the literature, ruptures of AAA after EVAR occurred about 24 ± 18 months after surgery, whereas we had three cases after 8 years. The average age of these patients was 74 ± 8.6 years at the time of AAA rupture (range 56 - 93 years). Most were men, as well as in our patients. The mortality after ruptured AAA treated with EVAR is about 50%, which is lower compared to aneurysms untreated by EVAR, where the mortality is over 80% [6, 7, 9].

The increasing diameter of aneurysm is considered as an evidence of unsuccessful endovascular treatment. While other reports often use an increase of 7 mm in diameter on the CT as the growth threshold for 6 months [7], we consider 5 mm or more as a threshold indicating a significant change, that is 1 cm or more on annual basis.

Low back pain and/or abdominal pain in patients with an AAA is a sign of possible rupture and requires urgent diagnosis. It is much better to find that there is no rupture intraoperatively, than to perform additional tests to create conditions for the rupture to really occur. If there is an AAA rupture (rAAA), more than half of the patients die before hospitalization [10].

Complications of endoleak, such as stent graft migration, stent fracture, dilation, or other aneurysms of the aortoilliac segment, require long-term follow-up of the patient, and secondary interventions are required in approximately 15% to 20% of patients. in most hospitals and in ours as well [3].

In previous studies, the authors pointed to the importance of follow-ups in the first two to three years [6], we emphasize the importance of regular check-ups to the end of life, due to the possibility of late rupture, which is lethal in most cases.

The failure of endovascular repair includes endoleak [7], stent graft migration [6], infection [11], and subsequent aneurysm enlargement, associated with permanent problems that may lead to late aneurysm rupture.

Fransen and associates reported cases of ruptured AAA after EVAR, where most patients were men of older age, caused by type I b endoleak, and in our patients both types of type I endoleaks were found [2].

Schloesser and associates reported that most ruptures of the AAA after EVAR were treated operatively, and that some of them underwent endovascular surgery. In our hospital, ruptures of the AAA are not treated by endovascular repair; that is the institution's policy because it is considered that immediate surgical treatment is an advantage and has better outcomes, which is also the attitude of many other countries.

Since rupture after EVAR is a relatively rare event. each rupture can offer enough new information to improve the monitoring and operational resolutions. So far, it has not been reported that due to the possible aneurysmal lesion after extraction of stent graft, it was cut out with scissors infrarenally and then implanted in proximal anastomosis. This provides faster setup of the clamps, shortens the entire surgery provides better stability of proximal anastomosis, avoiding the lesion and elimination of the wall of the abdominal aorta. The ultimate outcome is an increasing survival rate after aneurysm rupture.

The disadvantage of this case series is the small number of cases in our hospital, and in the next report the number of cases with this issue will be higher, since complications are inevitable and should be reduced to a minimum, which is the goal of this case series.

Conclusion

Regular annual follow-ups to the end of life are of great importance in order to avoid fatal complications after endovascular aortic repair. One of the methods after the abdominal aortic rupture after endovascular stent graft treatment that significantly shortens the duration of the surgery and provides a more stable upper anastomosis, is transverse cut of the stent graft with scissors in the proximal part. The ultimate goal is to increase the survival rate after the ruptured aneurysm of the abdominal aorta.

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POSTMENOPAUSAL OSTEOPOROSIS

OSTEOPOROZA U POSTMENOPAUZI

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Summary

Introduction. Postmenopausal women are at a great risk for osteoporosis and bone fractures. **Pathophysiology of osteoporosis.** The two main factors causing osteoporosis are aging and loss of the gonadal function. Postmenopausal osteoporosis is primarily the consequence of estrogen deficiency, whereas senile osteoporosis is related to the natural aging process. **Risk factors for the onset of osteoporosis.** Risk factors include: age of 50 years and over. female gender. Caucasian race, genetic predisposition, short stature, undernourishment, physical inactivity, amenorrhea, late menarche, early menopause, estrogen and androgen deficiency, alcohol consumption, cigarette smoking, calcium deficiency in the diet, use of some drugs. **Osteoporosis complications.** Osteoporosis is the main cause of bone fractures in older population. **Biochemical indicators of bone metabolism.** A great number of bone formation and resorption markers are listed. **Diagnostics.** Dual-energy X-ray absorptiometry measurements of the hip and spine are a worldwide standard in diagnosing osteoporosis. Dual X-ray laser heel measurement is an alternative to dual-energy X-ray absorptiometry. Quantitative computed tomography measures thin layers by cross-sectional scans. Quantitative ultrasonography is a good method, but the measurements are not as precise as by other imaging techniques. **Drug treatment of osteoporosis.** Modern treatment of osteoporosis includes application of bisphosphonates, selective estrogen-receptor modulators, calcium preparations, vitamin D, monoclonal antibodies, hormonal therapy, estrogens, and phytoestrogens. **Prevention.** Lifestyle changes and non-pharmacological measures are most important for healthy bones. Physical activity, nutrition rich in calcium and vitamin D, avoidance of smoking and alcohol consumption are of crucial importance for people of all ages. especially for the older ones.
Key words: Osteoporosis. Postmenopausal; Fractures. Bone; Age Factors; Risk Factors; Estrogens; Diagnosis; Drug Therapy; Biomarkers

Sažetak

Uvod. Žene u postmenopauzi su pod velikim rizikom za nastanak osteoporoze i preloma kostiju. **Patofiziologija osteoporoze.** Dva glavna faktora su starenje i gubitak gonadalne funkcije. Osteoporoza u postemenopauzi je primarno posledica nedostatka estrogena a senilna osteoporoza je povezana sa prirodnim procesom starenja. **Faktori rizika za osteoporozu.** Kao faktori rizika navode se: 50 i više godina, ženski pol, bela rasa, genetska predispozicija, nizak rast, pothranjenost, fizička neaktivnost, amenoreja, kasna menarha, rana menopauza, stanja nedostatka estrogena i androgena, konzumiranje alkohola, pušenje cigareta, ishrana siromašna kalcijumom, upotreba nekih lekova. **Komplikacije osteoporoze.** Osteoporoza je glavni uzrok preloma kostiju u starijoj populaciji. **Biohemijski markeri osteoporoze.** Opisani su brojni markeri izgradnje i razgradnje kostiju. **Dijagnostika.** Dvostruka apsorpciometrija X-zraka kuka i kičme je široko rasprostranjeni standard u dijagnostici osteoporoze. Merenja dvostruke apsorpciometrije X-zraka. uz primenu laserske tehnike petne kosti, alternativa je za dvostruku apsorpciometriju X-zraka. Kvantitativna kompjuterska tomografija meri tanke slojeve poprečnog skena. Kvantitativna ultrasonografija je dobra metoda, ali merenja nisu dovoljno precizna kao kod drugih imidžing tehnika. **Medikamentni tretman osteoporoze.** Savremeno lečenje osteoporoze uključuje primenu: bisfosfonata, selektivnih modulatora estrogenih receptora, preparata kalcijuma, vitamina D, monoklonalih antitela, hormonske terapije, primenu estrogena i fitoestrogena. **Prevencija.** Promena životnog stila i nefarmakološke mere su najznačajnije za postojanje zdravih kostiju. Fizička aktivnost, adekvatna ishrana bogata kalcijumom i vitaminom D, izbegavanje pušenja i konzumiranja alkohola su od neprocenjivog značaja kod osoba svih uzrasta, naročito u starijem životnom dobu.
Ključne reči: postmenopauzalna hemodijaliza; prelomi kosti; faktori godina; faktori rizika; estrogeni; dijagnoza; terapija; biomarkeri

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Introduction

Menopause is an inevitable and irreversible part of the general aging of the woman's reproductive system, followed by the permanent loss of menstruation. Menopause occurs as a result of losing ovarian sensitivity to stimulation with gonadotropins, with a consequent failure of folliculogenesis and steroidogenesis [1]. Changes in the number and quality of ovarian follicles start about 20 to 25 years after menarche. It is thought that the disturbed ovarian function in perimenopause, with the consequent oscillating changes in the estrogen level, and not only reduced production of estrogen, is the main cause of the menopausal syndrome. The syndrome is typically associated with a decline in the ovarian function, including vasomotor symptoms, psychic complaints, depressions, lowered concentration and insomnia, increase in body mass, urogenital disturbances and decline of the libido, as well as the skin and hair changes [2]. The shortage of estrogen leads to an increased osteoclast activity and bone resoprtion, while bone formation shows a decrease. Hence, postmenopausal women are at a great risk for the development of osteoporosis and bone fractures [3].

Osteoporosis is a common metabolic bone disorder which causes damages to the overall health, with physical, psychosocial and economic consequences. It is a chronic, progressive, and multifactorially conditioned disease. Most often it is diagnosed in older Caucasian women, although it also affects both genders, all races and all ages. Osteoporosis is a systemic bone disease which is characterized by a decrease in bone mass and decay of the microarchitecture of bone tissue, leading to an increase in bone fragility. Unfortunately, it is often detected only after a bone fracture.

Although osteoporosis is a disease of the elderly. its significance is often neglected. Namely, it should be kept in mind that osteopenia, as a state which is a consequence of menopause, can be prevented.

The World Health Organization (WHO) considers bone density measured by dual-energy X-ray absoptiometry (DXA) to be a criterion for the bone tissue status. The results are expressed via T-score or Z-score. The T-score is obtained by comparing the person's DXA density to that of control subjects at the moment of the highest bone mass density (BMD), whereas the Z-score, as the number of standard deviations in the BMD, compares these values of the given subjects with those of the subjects of the corresponding gender and age [4].

According to the WHO recommendations, the diagnostic classification is related to postmenopausal women and man above the age of 50. In this classi-fication, osteoporosis is defined as the BMD which is equal to or lower than 2.5 standard deviations compared to the maximum BMD (T-score). On the other hand, osteopenia is characterized by a BMD in the range of 1.0 - 2.49 SD below the T-score.

A decrease in the BMD occurs due to bone resorption, as a consequence of an accelerated degradation of bones, whereas the level of bone building remains within the premenopausal ranges. In the postmenopause, the bone degradation is accelerated by about 20% compared to that at younger age.

Pathophysiology of osteoporosis

As already said, the main cause of osteoporosis is the disbalance between the degradation and formation of bones. In physiological states, these two processes are balanced. Osteoporosis occurs when this balance is disturbed. i.e. when degradation is accelerated or when formation is decreased. It is important to point out that osteoporosis can be a consequence of reduced bone formation during the life and achieving full bone density in an earlier stage of life. The two main factors causing osteoporosis are aging and loss of the gonadal function. Postmenopausal osteoporosis is primarily the consequence of estrogen deficiency, whereas senile osteoporosis is related to the natural aging process [5].

Aging. After the age of 30, the process of bone resorption surpasses that of bone formation, which may lead to osteopenia/osteoporosis. Women lose about 40% of bone cortex and men about 15 – 20%. Also. trabecular bone loss in women is about 50%, compared with 25 – 30% in men. Age-related bone loss is characterized by a reduced supply of osteoblasts compared to the needs, whereas in the postmenopausal women it is associated with increased activity of osteoclasts [6].

Estrogen deficiency. It causes a decrease in BMD in women, but also in men, since osteoblasts, osteoclasts and osteocytes possess estrogen receptors. Besides, estrogens affect bones in an indirect way, via cytokines and growth factor. In the states of estrogen shortage, T-cells accelerate osteoclast recruitment, inhibit their differentiation, and extend their lifespan via interleukin-1, interleukin-6, and tumor necrosis factor alpha. Also, T-cells cause premature apoptosis of osteoblasts via interleukin-7. In the states of estrogen shortage, bones are more sensitive to the action of parathormone [7].

Calcium deficiency. Calcium, vitamin D, and parathormone maintain bone homeostasis. Calcium-poor diet or reduced calcium absorption, due to aging or some disease, may cause secondary hyperparathyroidism, which leads to increased absorption of calcium from bones by calcium excretion via kidneys [8].

Vitamin D deficiency. Vitamin D controls concentrations of calcium and phosphate, needed for healthy bones and teeth. Besides maintaining BMD. it is thought that this important biogenic element plays a role in prevention and development of cardiovascular, inflammatory and malignant diseases. Vitamin D is supplied in two ways – by the synthesis in the skin and through food. In the latter case,

we differ vitamin D2 (ergocalciferol) of plant origin, and D3 (cholecalciferol) of animal origin. Still, the main source of vitamin D is its synthesis in the skin under influence of ultraviolet B light [9].

The primary function of vitamin D is to regulate calcium absorption from the intestine and stimulation of its resorption from bones, to maintain the calcium serum level. The shortage of vitamin D leads to reduction of calcium absorption from the intestine and increased production of osteoclasts. which mobilize bone calcium. Due to its inadequate intake, vitamin D interacts with osteoblast receptors, causing an increase in the formation of osteoclasts.

Risk factors for the onset of osteoporosis [10–12]:
1. 50-plus years of age,
2. female gender,
3. Caucasian race,
4. genetic predisposition,
5. short stature,
6. undernourishment,
7. physical inactivity,
8. amenorrhea,
9. late menarche. early menopause,
10. deficiency of estrogen and androgen,
11. alcohol consumption,
12. cigarette smoking,
13. calcium-poor diet,
14. some drugs (steroids, insulin, anticonvulsants, chemotherapeutics, heparin).

Osteoporosis complications

Osteoporosis is the main cause of bone fractures in elderly people (more than 80% of cases in persons of 50-plus years of age). If not treated successfully, it leads to chronic painful conditions, limitation of movements, and in some cases to death (fractures of the spine and hip joints) [13].

Biochemical indicators of bone metabolism

There are markers of bone formation and markers of bone resorption. Bone formation markers are: total and bone-specific alkaline phosphatase (serum), osteocalcin (serum), C- and N-terminal propeptides of procollagen type 1, procollagen 1 carboxyterminal propeptide (PICP, serum), procollagen type 1N-terminal propeptide (P1NP, serum), and other non-collagen bone proteins. Bone resorption markers are: tartrate-resistant acid phosphatase (plasma), calcium (urine), hydroxyproline (urine), pyridinium crosslinks (urine), collagen type 1 telopeptide beta-crosslaps (urine, serum), C-terminal type-1 collagen telopeptide (ICTP – serum), collagen type 1 cross-linked 1 N-telopeptide (NTX, urine). The bone balance index (BBI) represents the relative values of the ratio of (osteocalcin/crosslaps x 1000). It indicates the degree of deviation of the ratios of the physiological processes of bone remodeling (formation and degradation of bones) from an ideally balanced state. In healthy population, the BBI is about 90 [14].

Diagnostics

Bone densitometry measures the difference in the absorption of gamma- or X-rays, ultrasound or laser in the bone and in the soft tissue. It is possible to measure the bone mineral content (g), and indirectly the bone density (g/cm^2).

The DXA is a very widespread method, which is characterized by extremely high resolution and precision. The measurement time is short, i.e. the method allows rapid measurement of the whole-body mineral content in a safe and reliable way, with very good reproducibility, while reducing the problem of superposition with the adjacent soft tissues. The apparatus uses X-rays as source of energy. The DXA measurements of the hip and spine are a worldwide standard in diagnosing osteoporosis [15]. Measurements by dual X-ray absorptiometry and laser technique (DXL) of the heel bone are an alternative to DXA. The technique has been developed with the aim of avoiding measurement errors of DXA due to the influence of the adjacent soft tissue [16].

The quantitative computed tomography measures thin layers by cross-sectional scans. The computer analysis provides data for BMD and estimates density of the trabecular and cortical bones [17].

Ultrasound densitometry is a method whose advantages are avoidance of irradiation and easily portable apparatus, but the measurements are not as precise as the ones obtained by other imaging techniques [18].

Drug treatment of osteoporosis

Modern treatment of osteoporosis includes application of [19–21]:
1. bisphosphonates (alendronate, etidronate, ibandronate, risedronate, zoledronic acid),
2. selective estrogen receptor modulators (raloxifene, lasofoxifene, arzoxifene),
3. calcium preparations,
4. vitamin D,
5. monoclonal antibodies,
6. hormonal therapy,
7. estrogens,
8. phytoestrogens.

Prevention

Lifestyle changes and non-pharmacological measures are most important for healthy bones. Physical activity, nutrition rich in calcium and vitamin D, avoidance of smoking and alcohol consumption are of crucial importance for people of all ages, and especially for the older ones [22]. The application of these measures also shows results in patients with osteoporosis. These subjects have enhanced bone strength and lower risk of bone fracture.

The prevention strategy includes optimal development of the skeletal system and achievement of maximal bone mass at the time of skeletal maturity; prevention of secondary causes for bone mass loss;

preservation of the structural integrity of bones, and fracture prevention.

A balanced and healthy diet ensures adequate intake of calcium and vitamin D. Malnutrition, anorexia and excessive aerobic activity of young girls leads to a later menarche and lower bone mass compared with those of the same age. A similar situation is also observed with the adults practicing restrictive diets and reducing body mass by surgery. The balanced protein intake (recommended daily intake is about 0.8 g/kg of body mass) can contribute to the minimization of the bone loss even in patients with advanced osteoporosis [23].

The main factor in the prevention of osteoporosis and its treatment is calcium. For women over the age of 50, the daily intake of calcium should be 1200 mg (diet + supplementation if necessary). If the diet does not supply sufficient amounts of calcium, its supplementation is indispensable. However, the pertinent data show that the daily diet intake in the majority of patients is only about 600 mg, which makes in fact only half of the necessary daily dose. In case of supplementation, to ensure optimal resorption, the calcium dose should not exceed 500 mg. It has been proved that calcium increases the BMD, but there are no scientific confirmations that its application without application of vitamin D decreases the risk of bone fracture [24]. Calcium supplementation is safe for the users. The risk of nephrolithiasis with these patients is minimal compared to general population (2.5% risk for development of nephrolithiasis in supplementation patients compared to 2.1 in general population).

Thus, apart from calcium, it is necessary to administer vitamin D. Many, apparently healthy persons, have a significantly lower serum 25-hydroxyvitamin D level compared to the optimum. This is primarily a consequence of inappropriate nutrition, since vitamin D is not so widely present in the foodstuffs. It is found in fish oil, cereals, and bread, Vitamin D is formed in the skin. According to the recommendations of the American National Academy of Sciences the daily intake of vitamin D should be 400 IU for healthy younger persons. For persons over 50 years of age, the recommendation is 800 to 1000

IU a day. However, some experts recommend even significantly higher daily doses of 1000 – 2000 mg of calcium. The correct recommendation for minimal 25-hydroxyvitamin D levels are 30–32 ng/ml, whereas the upper limit is up to 60 ng/ml. Some meta-analytic studies showed that postmenopausal women are at lower risk of fracture even if the daily supplementation dose is 700 – 800 IU. In the patients with severe vitamin D deficiency, the daily supplementation dose should be up to 2000 IU [25].

Increased alcohol consumption has negative effects on bones, since it increases the risk of bone fracture. The way how alcohol affects bones is complex and multifactorial, leading to an increased risk of accidental falls, deficiency of calcium, and liver overload. Also, it is not recommended to drink more than 1 – 2 cups of coffee a day, since some studies showed the existence of a positive relationship between caffeine and bone fracture, most probably due to a lower calcium intake.

Cigarette smoking also affects the bone health. The exact mechanism is not fully resolved yet, but it is thought that it increases the metabolism of estrogen and direct effect of cadmium on bone metabolism [26].

Regular physical activity, for example, everyday 30 minute walk and exercising for about 10 min several times a week contribute to the maintenance of healthy bone system. Studies have shown that muscle power in younger women is in a positive correlation with their BMD. Nevertheless, physical activity of older women should be individually adapted to the age, as well as to the general state of the subject [27].

Also, an important issue is education aimed at prevention of falls and consequent fractures. It is important to point out that phytoestrogens represent an option for preventing osteoporosis in women since there are indications that they have a positive effect on the bone health. Soybean isoflavon shows a functional activity similar to that of 17 beta-estradiol on osteoblasts and osteoclasts via genomic and non-genomic mechanisms [28]. Besides, they also exhibit a favorable effect on BMD and mechanical durability in postemenopausal women, contributing to bone formation via estrogen receptors on the cell surface.

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∗ Kompjuterska datoteka
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7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons. book reviews. extracts from foreign literature. reports from congresses and professional meetings. communications on activities of certain medical institutions. branches and sections. announcements of the Editorial Board. letters to the Editorial Board. novelties in medicine. questions and answers. professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript. including the text. all supplementary material and covering letter. is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper. that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study. a review article. a preliminary report. a professional article. a case report. history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*. page format A4. space 1.5 (for tables as well). margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper. without abbreviations. then a short title (up to 40 characters). full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s). full address. e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words. without abbreviations. with the precise review of problems. objectives. methods. important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper). materials and methods. results and conclusion

– Case reports should have the introduction. case report and conclusion

– Review papers should have the introduction. subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary. but the authors' keywords could be changed in accordance with the list of Medical Subject Headings. MeSH of the American National Medical Library.

The summary should be written in both languages. English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore. it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study). materials and methods. results. discussion. conclusion. list of abbreviations (if used in the text) and not necessarily. the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study). case report. discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance). with the relevant references and clearly defined objective of the investigation and hypothesis.

Materials and methods should contain data on design of the study (prospective/retrospective. eligibility and exclusion criteria. duration. demographic data. follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables. graphs. schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear. interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results. corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria. which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors. but if the number exceeds six. give the names of six authors followed by 'et al'.

<u>Articles in journals</u>

∗ *A standard article*

Ginsberg JS. Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension. insulin. and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F. Rossoni G. Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G. Cole JO. Haskell D. Marby D. Pame SS. Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA. Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

<u>Books and other monographs</u>

∗ *One or more authors*

Murray PR. Rosenthal KS. Kobayashi GS. Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J. Colombani J. eds. Histocompatibility testing 1972. Copenhagen: Munksgaard. 1973:12-8.

∗ *A chapter in a book*

Weinstein L. Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr. Soderman WA. eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S. Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA. Lutton E. Miller J. Ryan C. Tettamanzi AG. editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale. Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

<u>Electronic material</u>

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI. clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT. Maibach H. CMEA Multimedia Group. producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables. graphs. schemes and photographs).
THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables. graphs. schemes and photographs are to be submitted as separate documents. on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG. GIF. TIFF. EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title. text in tables. graphs. schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols ∗. †. ‡. §. | |. ¶. ∗∗. † †. ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table. graph. scheme or figure has been previously published. acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color. they will have to pay additional cost.

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SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW. THEIR PAPER WILL NOT BE PUBLISHED.