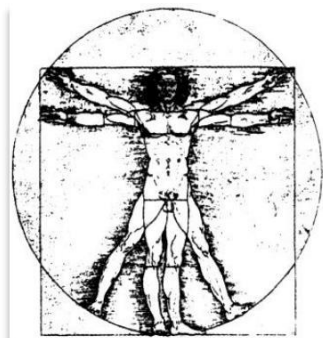


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## PALMAR RIDGE COUNT IN DIFFERENT NATIONALITIES

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### ABSTRACT

This paper presents data on finger and palm ridge count of both hands of a representative sample of healthy examinees with different ethnic origin.

The aim of the study was to establish and analyze the differences in palmar ridge count found in healthy examinees with different ethnic origin.

Ridge count from 600 palm prints was read on the palms taken from healthy individuals with Macedonian, Albanian and Roma nationality, 300 males and 300 females. Prints were taken using Cummins and Midlo's ink method. Ridge count was calculated and comparison was made between different ethnic groups. Ridge count for the fingers (TRC) and (ATRC) was the highest in Macedonians, lower in Albanians and the lowest in Roma examinees. AB ridge count was the highest in Macedonian males and females, lower in Albanians and the lowest in Roma as well as values for BC and CD ridge counts. The results obtained for Macedonian examinees were similar to those of the Albanians and more different than those we counted in Roma examinees.

In conclusion, the ridge count on the palm prints in three ethnic groups is presented. We made a comparison with other ethnic groups and we discussed the differences between them. The results can serve as a basis for the dermatoglyphic status of nationalities in Macedonia. At the same time they can be used in medico-biological investigations for theoretical and scientific applied purposes.

**Key words:** ridge count, ink method, palm prints

### INTRODUCTION

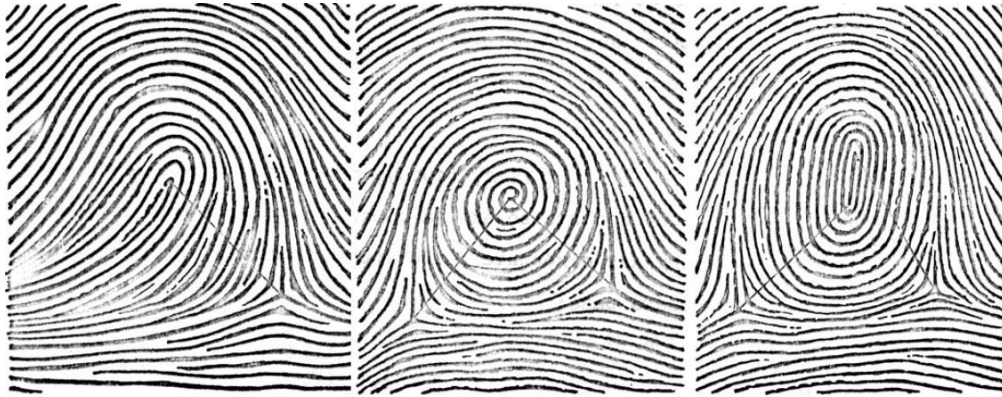
During the past decades the use of dermatoglyphics in anthropology has increased. The questions raised and the methodological approaches have become more sophisticated. The anthropological dermatoglyphics have been summarized in excellent papers [1]. Dermatoglyphics are formed during the first and the second trimester of the developing embryo and once formed remain permanent and never change throughout the life except in the dimension in commensurate to the growth of an individual [2]. Such traits are poligenetically determined and phenotypic variability in the expression of genes influencing anthropometric and dermatoglyphic variables represent the genome to a certain degree. The genetic basis of majority of quantitative traits is not precisely known. Generation and examinations of these variables involve little cost in comparison to the generation of molecular genetic markers. Thus, it is necessary to assess the relative usefulness of quantitative traits in portraying patterns of population structure expected from ethnohistorical information [3].

Macedonian population structure is remarkable in that the population is divided into three strictly defined ethnic groups. One of the more neglected aspects of dermatoglyphic research has been the study of the ridges of palmar surfaces. The lack of data on healthy Macedonian, Albanian and Roma nationality palmar ridge count led us to undertake this study in order to find out the ridge count differences in some ethnic groups, to compare them with each other and to ascertain whether the information obtained from the palmar study provide additional useful anthropological data.

The group consisted of six hundred examinees, the inclusion criterion being randomly chosen examinees from Macedonian, Albanian and Roma nationality.

### MATERIAL AND METHOD

In this paper we present the statistical analysis of palmar ridge count on the palms of 600 examinees (300 males and 300 females). The prints were taken from healthy examinees from different settlements in Skopje, aged from 18-24. Prints were taken by Cummins and Midlo's ink method from healthy individuals of Macedonian, Albanian and Roma nationality. Ridge count was calculated and comparison was made between different ethnic groups. Ridge count is the number of ridges which crosses the line between the triradii and the core of the pattern (TRC) (Fig.1.). Triradii are the center in which the line from three different regions meet and the angle between them is higher than 90 degrees. We marked the basic triradii as a, b, c and d, on the basis of each finger. In complex patterns with two triradii we counted both sides and we named this absolute ridge count (ATRC). Ridge count was counted for the fingers, configurational areas on the palm including palmar a-b b-c and c-d ridge count. Configurational areas of the palms are: Hy area, Th/I, II, III and forth interdigital. All results were statistically analyzed.



**Fig. 1.** Ridge count

## RESULTS

The total number of ridges (TRC) in Macedonian males was 63.05, in Albanians 58.71 in Roma males 52.35. TRC in Macedonian females was 52.93, in Albanians 44.28 ridges, in Roma female examinees 42.31. Absolute ridge count (ATRC) in Macedonian males was 76.59, in Albanians 69.55 and in Roma examinees 67.97. In females of Macedonian nationality ATRC was 64.64, in Albanians 53.82, and in Roma 55.22 ridges.

Ridge count in the configurational areas of the palms was: AB ridge count in Macedonian males was 20.75, in Albanians 21.23, and in Roma 15.92; in Macedonian females 20.09, in Albanians 17.67 and in Roma 16.37.

BC ridge count in Macedonian males was 14.76, in Albanians 13.72, and Roma males 10.24, whereas in Macedonian females BC ridge count was 15.98, in Albanians 11.77 and in Roma 10.48 ridges.

CD ridge count in Macedonian males was 18.61, in Albanians 17.27, and in Roma males 11.00. CD ridge count in Macedonian females was 21.68, in Albanians 15.37 and in Roma 11.10 ridges.

The results obtained for Macedonian examinees were similar to those of the Albanians and more different than those we counted in Roma examinees.

## DISCUSSION

The results have shown dermatoglyphic quantitative palmar characteristics in the Macedonian, Albanian and Roma populations. We have compared our with other author's findings.

Tornjova–Randelova's paper shows higher ridge count in Bulgarian examinees than in our study. Finger ridge count formula was  $I > IV > V > III > II$  for both hands, which was also different from the formula we got. Total number of ridges (TRC) was 137.84 for both hands, which are higher than our values. Palmar ridge count was higher in AB, then BC and CD. A-d ridge count was higher on the right hand. Total ridge count for both hands was 194, from minimum 100 up to 295 ridges. The results are presented as a basis for describing dermatoglyphic status of Bulgarian nationality. The authors potentiated the possibility of using them in clinical, medico-biological and other scientific researches [4].

Twelve variables have been studied in the populations in Macedonia (Vlachs), Bulgaria, Croatia, Greece, Hungary, Romania, Serbia and Slovakia. Macedonians are with lowest TRC compared to other nationalities (126 in males and 129 in females). AB ridge count was the lowest in Macedonians and the highest in Croatians (84 in males and 85 in females). There are differences among populations and both sexes. Macedonians are dermatoglyphically similar to Aromuns (Vlachs) and Bulgarians. Croatians, Slovaks and Greeks are in separate group with similarities among them [5].

Baltova and Kavgazova published some results for Bulgarians from different parts of the country. TRC (total ridge count) was from 114-135 in males and 123-134 in females. AB ridge count was 37 in males and 36 ridges in females. Values are higher than in our study [6, 7, 8].

Temaj has shown homogeneousness among three groups of Albanian population in different parts of Kosovo. Ab ridge count was 34 in females; BC-22; CD-30 in both sexes. TRC was from 103-113 in males and 100-112 in females.

In conclusion, principal components analysis of the quantitative dermatoglyphic variables in the examined group revealed a pattern of biological relations among groups which are consistent with their linguistic, historical and demographic backgrounds. There are some differences compared to the palmar dermatoglyphics in other nationalities and hence they can be interpreted as markings of the Macedonian, Albanian and Roma ethnic groups. That's the main objective of anthropological studies, giving answers to simple questions. It is hoped that further studies in dermatoglyphics will broaden some new possible applications of skin ridge count and provide comparison with other nationalities.

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## ANATOMY AND CLINICAL SIGNIFICANCE OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY

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### ABSTRACT

With the introduction of new techniques in diagnostic and interventional radiology and progress in micro neurosurgery, accurate knowledge of the brain blood vessels is essential in daily clinical work. The aim of this study was to describe the anatomical characteristics of the posterior inferior cerebellar arteries and to emphasize their clinical significance.

In this study we examined radiographs of 103 patients who had CT angiography at the University Clinic for Radiology in Skopje, R. Macedonia. This study included 45 females and 58 males, age range from 25 to 82 years; mean age 58.4±13.2 years.

The outer diameter of the posterior inferior cerebellar artery at its origin on the left side was in the range between 0.46 - 2.80 mm, mean 1.24 ± 0.42 mm. The outer diameter of the posterior inferior cerebellar artery on the right side was in the range between 0.54 - 2.50 mm, mean 1.18 ± 0.40 mm.

Thorough knowledge of the anatomy and variations of the posterior inferior cerebellar artery is important for clinicians as well as for basic scientists who deal with problems related to intracranial vasculature on daily basis for safe performance of diagnostic and interventional procedures.

**Key words:** posterior inferior cerebellar artery, anatomy, variations, diameter

### INTRODUCTION

The posterior inferior cerebellar artery (PICA) usually arises as the largest branch of the vertebral artery at the anterolateral margin of medulla oblongata, close to the lower cranial nerves, and courses through a series of deep fissures that lie between the tonsil, vermis, and cerebellar hemisphere. The PICA supplies the posterior inferior cerebellar surface, lateral medula and choroid plexus of the fourth ventricle [1]. The PICA has the most complex and variable course of all the cerebellar arteries. Radiologists, neurosurgeons and forensic pathologists must be aware of radiologic features and geographic territories of cerebellar arteries, as even minor variants may have important clinical and forensic consequences [2]. The aim of this study was to describe the anatomical characteristics of the PICA and to emphasize their clinical significance.

### MATERIAL AND METHODS

The study population included 103 patients referred to the University Clinic for Radiology in Skopje, R. Macedonia for computed tomography angiography (CTA). This study included 45 females and 58 males, age range from 25 to 82 years; mean age 58.43±13.2 years. We made an anatomical analysis of CTA images realized for medically justified goal, with the approval of the Macedonian Ethics Committee. The CTA was obtained using a CT scanner Somatom Definition AS Siemens Healthcare, Erlangen, Germany. Contrast material was injected through an 18- to 20-gauge IV catheter inserted into an arm vein, a total of 100 ml. at a rate of 3 ml/s with a pressure injector, followed by a flush of 40 ml of saline administered at the same injection rate. After the contrast medium was injected, by use of bolus tracking software, scanning was carried out automatically. The data were transferred to a workstation for post-processing. Reconstruction included the following: maximum intensity projection-MIP; four-dimensional CTA with volume rendering; reformatted multiplanar reformation-MPR. For the post-processing process we used SYNGO software. The PICA was clearly and directly shown in the high quality images, and satisfied the requirements of our study.

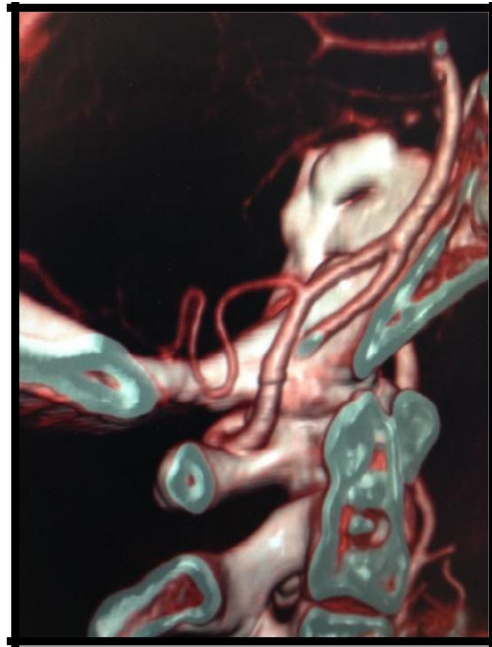
The anatomic features of the right and left PICA were analyzed, and anatomical characteristics were analyzed on each CT image.

### RESULTS

In this study we determined the origin of the left and right PICA. Absence of PICA was noticed in 8.73% of patients. In 94.67% of patients the left PICA had origin from the vertebral artery and in 5.31% of patients the left PICA had origin from the basilar artery. On the right side in 91.48% of patients PICA had origin from the vertebral artery and in 8.51% of patients it had origin from the basilar artery. No double origin, duplication of PICA, origin from internal carotid artery was noticed in this study.

The minimal value of the outer diameter of the left PICA was 0.46 mm. The maximal recorded value of the outer diameter of the left PICA was 2.80 mm. The average value of the outer diameter of the left PICA was  $1.24 \text{ mm} \pm 0.42 \text{ mm}$ .

The minimal recorded value of the outer diameter of the right PICA was 0.54 mm. The maximal value of the outer diameter of the right PICA was 2.50 mm. The mean outer diameter of the right PICA was  $1.18 \text{ mm} \pm 0.40 \text{ mm}$ .



**Fig. 1.** Origin of the right PICA from the right vertebral artery

## DISCUSSION

The PICA has the most complex and variable course of the cerebellar arteries [3]. The PICA arises from the vertebral artery at the anterolateral aspect of the brain stem near the inferior olive and passed posteriorly around the medulla. At the anterolateral margin of the medulla, it passes rostral or caudal to or between the rootlets of the hypoglossal nerve, and at the posterolateral margin of the medulla it passes rostral to or between the fila of the glossopharyngeal, vagus, and accessory nerves. It often has a tortuous course, and its area of supply is the most variable of the cerebellar arteries. Along its course, PICA divides into five segments: anterior bulbar segment, lateral bulbar segment, tonsillar bulbar segment, telovelotonsillar segment, cortical segment [3, 4, 5].

The PICA has a highly variable origin [4]. It usually originates from the vertebral artery, but it may also originate from the basilar artery and internal carotid artery [3, 5]. The PICA can be unilaterally absent in 2 to 26% of the cases and bilaterally absent in 2 - 2.5% of the cases [1, 3]. In our study group PICA was absent in 8.73% of the patients. The data from the previous published studies are in accordance with our study. Usually, if one of the PICA is absent, its territory was supplied either by the anterior inferior cerebellar artery, or by the superior cerebellar artery [2]. According to Lister, Macchi, Kayaci, PICA was defined as cerebellar artery that usually originates from the vertebral artery, and this condition occurs between 80 to 95% of patients [1, 3, 5, 6].

There are reports in the literature which describe origin of PICA from the basilar artery. Our literature search showed that PICA had origin from the basilar artery in 7 to 10% of the cases [3, 5].

Double origin of the PICA is reported rarely and, when it occurs it manifests as two separate vessels arising from the same vertebral artery that then converge and form the PICA proper. Double origin of the PICA can be confused with fenestration or duplication of the PICA. The prevalence of double origin of the PICA in the general population was in range between 0.36% to 1.45%. Double origin of PICA was described by Uchino, Lesley, Pasco et al. [7, 8].

Origin of PICA from the internal carotid artery was described by Ahuja, Nakanishi, Hui et al. [9, 10, 11]. The embryologic explanation postulated is the persistence of a primitive communicating vessel (presegmental artery) between the anterior and posterior circulation [9]. Ogawa et al. presented a case report where PICA had anomalous origin from the posterior meningeal artery [12]. Mercier et al. described cases of origin of PICA and AICA through a common trunk from the vertebral or basilar artery [13].

Recent studies have determined the diameter of PICA. According to Kayaci et al. the mean diameters of the right and left PICAs at their point of origin were calculated as  $1.50\pm 0.42$  mm and  $1.63\pm 0.34$  mm [5]. The average outer diameter of the PICA was 1.15 mm on the left side and 1.42 mm on the right in the study conducted by Grasso et al.

#### ***Clinical significance of the PICA***

The PICA may be exposed in surgical approaches to the 4th ventricle, cerebellar hemisphere, brain stem, jugular foramen, cerebellopontine angle, petrous apex, clivus and trigeminal nerve. The increasing use of surgical magnification for operations in these areas has created the need for a better understanding of the microsurgical anatomy of the PICA [3].

During the past few decades, there were rapid and continuous advances in the field of diagnostic subtraction angiography, CT and MR angiography techniques, and these methods have become more commonly used in analysis of the brain blood vessels pathology. The anatomy and variations of the PICA must be well known for accuracy of the interpretation of radiological findings and for planning and accomplishing endovascular procedures [3, 5, 6].

As double origin of PICA has rarely been reported, the significance of the finding is uncertain. But according to Lesley, Trivelato et al. double origin of PICA has an increased association with intracranial aneurysm and may represent a risk factor for subsequent development of intracranial aneurysm [8, 14].

Nassr et al. reported a case of aberrant PICA injured during C1 lateral mass screw placement, resulting in a cerebellar stroke of PICA distribution territory [15].

The PICA has the most complex relationship to the cranial nerves [3]. Microvascular compression of lower cranial nerves is believed to cause syndromes such as glossopharyngeal neuralgia (glossopharyngeal nerve compression), spasmodic torticollis (accessory nerve compression) and hemifacial spasm (facial nerve compression) [3, 4, 5, 16]. Batten reported an unusual case of facial pain and swelling caused by compression of the facial and vestibulocochlear cranial nerves due to the tortuous course of a branch of the PICA [17]. The symptoms were relieved after micro vascular decompression [3, 4, 5, 16, 17].

#### **CONCLUSIONS**

Thorough knowledge of the anatomy and variations of PICA is important for clinicians as well as for basic scientists who deal with problems related to intracranial vasculature on daily basis for safe performance of diagnostic and interventional procedures.

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## BIOFILMS MIGHT BE INVOLVED IN THE RECURRENCE OF URINARY TRACT INFECTIONS IN OUTPATIENTS PATIENTS

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### ABSTRACT

Biofilms are defined as functional consortiums of microorganisms that are attached to a surface enclosed in extensive hydrated polymeric matrix. Microbial biofilms have been implicated in the pathogenesis of a wide variety of infective diseases, by one estimate for 80% of all microbial infections and for over 60% of the urinary tract infections.

The ability of these bacteria to cause relapses of UTI directly correlates with their genetic capability for biofilm production on the urinary catheter surface or the uroepithelium.

In the present study our objectives were to investigate the difference between patients with recurrent UTI and those with a first time UTI in terms of the type of isolated bacteria and their ability for biofilm production.

The study included 120 urine samples from outdoor patients, having suspected UTI. A total number of 80 bacterial species, including 40 isolates from patients with first-time symptomatic UTI and 40 from patients with a history of recurrent UTI were examined.

For detection of biofilm production and biofilm cultivation/biofilm biomass determination, tube method and adherence assay on 96-well microtitre plate were used, respectively.

TM correlated well with the quantitative TCP for most of the biofilm producing strains, but the difference between strong, moderate and weak biofilm producers was more evident by the TCP. *E. coli* was most prevalent uropathogen in both groups of patients. The biofilm producing strains isolated from patients with recurrent UTI had higher ODs than correlated groups of biofilm producers among the patients with first time infection.

According to the criteria for biofilm-forming ability, after 24-h incubation, 45 strains were slime producers: 15 (37.5%) from the first-time symptomatic UTI and 30 (75%) from the recurrent UTI group of patients.

**Key words:** biofilm, urinary infections, slime, *E.coli*.

### INTRODUCTION

Urinary tract infections (UTIs) are among the most common urological disorders in both genders. They represent pathogenic invasion of the urinary tract, which leads to an inflammatory response of the urothelium. Infections may be acute or chronic and the clinical manifestations of UTI depend on the portion of the urinary tract involved, the etiologic organism(s), the severity of the infection, and the patient's immunocompetence [1, 2].

Patients with an episode of acute UTI might develop recurrent infection, defined as two episodes of UTI in a period of six months or three or more episodes of UTI during a twelve month period caused by the same (relaps) or different (re-infection) pathogens as that involved in the original UTI [3, 4] which represents a substantial burden to the healthcare system. Giving consideration these infections result in significant financial and personal costs multiple studies have been conducted to expand our knowledge on this medical entity, in particular on the recurrent UTI and to clarify the role of contributing risk factors as well as to determine the best therapeutic approach

Usually antibiotic treatment conducted in accordance with the findings of the conventional susceptibility testing is efficient at clearing symptoms of UTI, but in a case of frequent relapses where bladder colonization is inevitable, this access might result with unsatisfactory clinical respond [5].

The treatment failure is primarily due to the need for intermittent or permanent catheterization and consecutive biofilm formation.

Biofilms are sessile communities of prokaryotic and/or eukaryotic cells, attached to a substratum, interface or to each other, embedded in a matrix composed of selfproduced extracellular material, which exhibit an altered phenotype (with respect to growth rate and gene transcription) compared to planktonic cells [6, 7].

Most of the knowledge acquired over the years relates to single-cells in a free-floating state, but today it is generally accepted that microorganisms grow and survive in this type of organized communities where their physiology is very different [8].

Sessile bacteria in biofilms are particularly resistant to antibiotics and immune defenses, making them particularly recalcitrant to treatment which, correlates with extreme difficulties in eradication of biofilm-associated infections. It is frequent and frustrating occurrence that after treatment, surviving biofilm-associated bacteria will precede the disease [9, 10]. It is a well-recognized fact that biofilm formation is often tightly associated with persistent UTIs in patients with indwelling catheters [11].

Besides numerous data from studies conducted in hospitalized patients with UTI little is known of the incidence, related circumstances and processes of biofilm formation in ambulatory, non-catheterized patients.

This urges the necessity for studies which will elucidate the linkage between relapses of UTI in outpatients and biofilm formation of the isolated pathogen in order to consider developing new effective methods of prevention as well as different therapeutic approach in those patients [12].

#### **Study objectives:**

The study was carried out to evaluate the biofilm producing abilities among bacterial species isolated from outdoor patients and to relate the capacity of the microorganisms to form biofilm to the relapses of the urinary tract infection.

### **MATERIALS AND METHODS**

#### ***Samples and bacterial strains***

The study included samples from urine from 120 outpatients, from both genders, aged >18 years, having suspected urinary tract infection. All the patients were ambulatory patients who were referred for microbiological examination of urine at the Institute of Microbiology and parasitology.

Patients with urinary catheters, anatomical abnormalities of the urinary tract and those receiving immunosuppressive therapy, were excluded.

A total number of 80 bacterial species (isolated from 80 pure positive urine cultures) including 40 isolates from patients with first-time symptomatic UTI and 40 from patients with a history of recurrent UTI were examined. The remaining 40 urine specimens (out of 120 urine specimens analyzed in this study) were with mixed or no bacterial growth and did not undergo further investigation.

#### ***Isolation and identification of the strains***

Quantitative urine culture (Using a sterile calibrated loop, 1 µl of fresh, unprocessed urine was streaked onto blood sheep agar or chromogenic (UTI) agar to determine the number of colony-forming units (CFU) of bacteria per milliliter of urine.

All plates were incubated and read following standard laboratory procedures.

Additionally, microscopic Gram stain examination and standard biochemical tests were done where needed.

Specimen storage: following identification the selected strains were enumerated and sub cultivated on solid nutrition media to ensure purity prior to testing. From each species, one pure colony was selected for long preservation (frozen at -80°C in trypticase soya broth supplemented with 20% glycerol)

#### ***Qualitative assessment of biofilm formation: Tube method***

We used the qualitative method described by Christensen et al. for screening of biofilm production [13]. Suspension of each strain (loopful of test organism inoculated in 10 mL of trypticase soy broth) in glass tubes was incubated aerobically at the temperature of 37°C for 24 h. After incubation, the supernatant was discarded and the glass tubes were washed with phosphate buffer saline (pH 7.3) and dried. Tubes were then stained by 0.1% safranin solution, washed with distilled water three times and dried in inverted position. A positive result was defined as the presence of a visible layer of stained material adhered to the inner wall and the bottom of the tubes. Observation of a stained ring at the liquid-air interface was considered as negative result. The experiment was performed in triplicate and repeated three times.

#### ***Quantitative assessment of biofilm formation: Tissue culture plate assay***

Before each experiment, bacterial cultures were refreshed from stocks on nutrient agar (after defreezing, 5 µl of each bacterial suspension were streaked on Columbia agar and incubated aerobically for 18 hours at 37°C).

The ability to form biofilm was investigated using the microtiter plate assay- a most widely used method which is considered as standard test for detection of biofilm formation [13]. One colony from Columbia agar mentioned above was inoculated in 5 ml of trypticase soya broth and incubated for 18 h at 37 C.

Subsequently, 10 µl of stationary (18-h) TSB cultures were diluted 1:100 into 1000 µl of media (TSB was used as substitution of artificial urine/M63 media) to obtain suspension equivalent to the McFarland 0.5 turbidity standard containing approximately 10<sup>8</sup> CFUs/ml. After vortexing 100 µl from each bacterial suspension was inoculated into the wells of sterile, polystyrene, 96-well, flat-bottomed tissue culture plates.

For biofilm formation the 96-well polystyrene microtitre plates were incubated for 24 h in a normal atmosphere at 37 °C without shaking. After the incubation time the supernatant was removed using a pipette and discarded and the plates were gently washed three times with 200 µl 1 85% NaCl to remove free-floating 'planktonic' bacteria.

In order to evaluate biofilm mass (including matrix, dead and living cells) and visualize the attachment pattern, each well of the microtitar plate was added 120  $\mu$ l of 0.1% (wt/vol) crystal violet and left at room temperature for 10-15 min. Excess (unbound) stain was removed and the wells were thoroughly washed with sterile distilled water. At this point, biofilms were visible as purple rings formed on the side of each well

The quantitative assessment of biofilm production was performed by adding 120  $\mu$ l 75% ethanol per well to solubilize the bound dye. Optical density of the eluted solution was read in a microplate spectrophotometer (ELISA microplate reader) at OD<sub>495</sub>. The amount of absorption was proportional with the amount of biofilm present.

Three wells inoculated with control strain in TSB served as positive control; wells containing sterile TSB served as a negative control during the experiment.

To compensate for the considerable variability in the assay, tests were done in triplicate on three separate occasions and the results averaged.

Optical density (OD) of stained adherent bacteria and the negative control was calculated as an arithmetical mean of the absorbencies of the three wells. The "cut-off" OD value (OD<sub>c</sub>) was defined as three standard deviations (SD) above the mean OD of the negative control i.e: OD<sub>c</sub>=meanOD of negative control+ (3x SD of negative control).

The OD<sub>c</sub> value in this study was 0.0047.

The results for biofilm production were interpreted and the isolates were classified as presented in the table below [14]:

**Table 1.** CLASSIFICATION OF Biofilm formation capacity according to the optical density

Strength of biofilm formation	Average OD value
Non-biofilm producers	$OD \leq OD_c$
Weak biofilm producers	$OD_c < OD \leq 2 \times OD_c$
Moderate biofilm producers	$2 \times OD_c < OD \leq 4 \times OD_c$
Strong biofilm producers	$4 \times OD_c < OD$

#### **Quality control**

Reference strains of known biofilm producers were used as positive controls: *Staphylococcus aureus* ATCC 29213 (for Gram positive isolates) and *E.coli* ATCC 25922 (for Gram negative isolates) as recommended by the National Committee for Clinical Laboratory Standards.

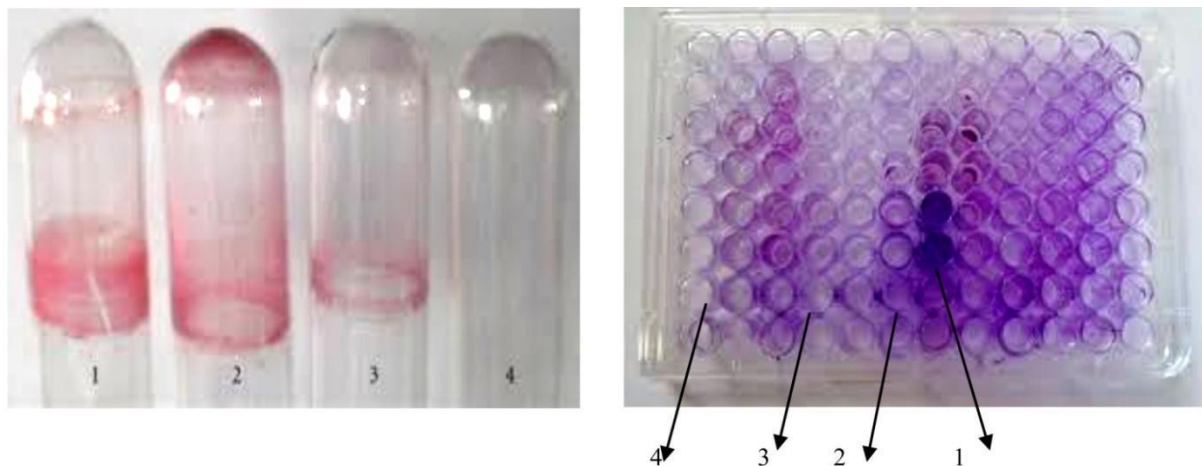
#### **RESULTS**

As previously mentioned, from the total number of 120 urine samples included in the study 80 bacterial species isolated from 80 pure urine cultures (40 from patients with first-time symptomatic UTI and 40 from patients with a history of recurrent UTI) were investigated for biofilm production by the tube method (TM) and tissue culture plate (TCP) method.

#### **Tube method**

We used this method for qualitative assessment and screening of the biofilm producing strains. All the isolates were investigated with the tissue culture plate method as well.

Over all, though qualitative TM correlated well with the quantitative TCP for most of the biofilm producing strains, difference (in the dye binding) between strong, moderate and weak biofilm producers was more evident by the TCP (illustrated in Figure 1). Also, most of the isolates were better biofilm producers by TCP compared to TM method (see Table 2)



1.Strong biofilm producers, 2.Moderate biofilm producers, 3.Weak-biofilm producers. 4.Non-biofilm producers.

**Fig. 1.** Screening of biofilm producers by TCP method: Strong, Moderate, Weak and Non-biofilm producers differentiated with crystal violet staining in 96 well microtiter plates.

Out of 80 urine isolates, 42 (52%) were confirmed as non-adherent by the TM vs. 35 (43.7%) by the TCP. Biofilm productions assessed by qualitative tube method compared to quantitative TCP method revealed 22.5% vs. 17.5% weak biofilm producers, 18.7% vs. 22.5% moderate producers, and 6.2% vs. 16.2% strong-biofilm producers (Table 2).

**Table 2.** Overall results for all the isolates for biofilm in TM and TCP test

<i>Phenotypic detection of biofilm production</i>	<i>N°of isolates</i>	<i>Ability to form biofilms</i>			
		<i>None</i>	<i>Weak</i>	<i>Moderate</i>	<i>Strong</i>
<i>Tube method –TM (%)</i>	80	42 (52%)	18 (22.5%)	15 (18.7%)	5 (6.2%)
<i>Tissue culture plate assay-TCP (%)</i>	80	35 (43.7%)	14 (17.5%)	18(22.5%)	13 (16.2%)

#### **Tissue culture plate assay**

The microtitre plate test correctly identified the positive reference bacterial strains as compared with the negative control.

In this study, the mean optical density value of the negative control wells measured at 495 nm was 0.003 and the optical density cut-off value was 0.0047. The ODs of the 24-h biofilm ranged from 0.0011 to 0.0079.

Based on the biofilm formation all the investigated strains were divided into four categories, the strains with  $OD_{495} < 0.0047$ ;  $0.0047 < OD_{495} \leq 0.00948$ ;  $0.0094 < OD_{495} \leq 0.0189$  and  $0.018 < OD_{495}$  were defined as none, weak, moderate and strong biofilm producers, accordingly (presented in Table 3).



**Table 3.** Optical density of the isolated strains from patients with first-time symptomatic UTI and from patients with recurrent UTI

Isolate	OD495	Biofilm formation	Isolate	OD495	Biofilm formation
<i>E. coli</i>	0.0011	None	<i>E. coli</i>	0.0035	None
<i>E. coli</i>	0.0020	None	<i>E. coli</i>	0.0027	None
<i>Klebsiella spp</i>	0.0032	None	<i>Enterococcus</i>	0.0038	None
<i>E.coli</i>	0.0018	None	<i>E. coli</i>	0.0018	None
<i>E.coli</i>	0.0035	None	<i>E.coli</i>	0.0022	None
<i>E.coli</i>	0.0037	None	<i>E.coli</i>	0.0029	None
<i>E.coli</i>	0.0029	None	<i>E.coli</i>	0.0030	None
<i>E.coli</i>	0.0041	None	<i>Klebsiella aerogenes</i>	0.0011	None
<i>Enterococcus spp.</i>	0.0022	None	<i>E.coli</i>	0.0024	None
<i>E. coli</i>	0.0036	None	<i>E.coli</i>	0.0033	None
<i>Enterococcus</i>	0.0040	None	<i>E.coli</i>	0.0059	Weak
<i>E. coli</i>	0.0033	None	<i>E.coli</i>	0.0061	Weak
<i>E. coli</i>	0.0041	None	<i>E.coli</i>	0.0051	Weak
<i>Enterococcus</i>	0.0044	None	<i>E. coli</i>	0.0082	Weak
<i>E. coli</i>	0.0026	None	<i>E. coli</i>	0.0077	Weak
<i>E. coli</i>	0.0045	None	<i>E. coli</i>	0.0069	Weak
<i>E. coli</i>	0.0037	None	<i>E. coli</i>	0.0091	Weak
<i>E. coli</i>	0.0033	None	<i>E. coli</i>	0.0098	Moderate
<i>E. coli</i>	0.0042	None	<i>E. coli</i>	0.0096	Moderate
<i>E. coli</i>	0.0027	None	<i>E. coli</i> +	0.012	Moderate
<i>E. coli</i>	0.0017	None	<i>E.coli</i>	0.0097	Moderate
<i>E. coli</i>	0.0034	None	<i>E. coli</i>	0.0113	Moderate
<i>E. coli</i>	0.0031	None	<i>E. coli</i>	0.0096	Moderate
<i>S. agalactiae</i>	0.0019	None	<i>E. coli</i>	0.0099	Moderate
<i>E. coli</i>	0.0023	None	<i>E.coli</i>	0.0099	Moderate
<i>E. coli</i>	0.0056	Weak	<i>E.coli</i>	0.0137	Moderate
<i>E. coli</i>	0.0068	Weak	<i>Morganella</i>	0.0177	Moderate
<i>Enterococcus</i>	0.0049	Weak	<i>Kl. oxytoca</i>	0.0162	Moderate
<i>Kl. oxytoca</i>	0.0077	Weak	<i>E.coli</i>	0.0125	Moderate
<i>E.coli</i>	0.0071	Weak	<i>E.coli</i>	0.0143	Moderate
<i>E.coli</i>	0.0096	Moderate	<i>E.coli</i> +	0.010	Moderate
<i>E.coli</i>	0.0099	Moderate	<i>Enterococcus</i>	0.064	Strong
<i>E.coli</i>	0.0098	Moderate	<i>E.coli</i>	0.051	Strong
<i>E.coli</i> +	0.0100	Moderate	<i>E.coli</i>	0.057	Strong
<i>E.coli</i>	0.0121	Moderate	<i>E.coli</i>	0.042	Strong
<i>E.coli</i>	0.0117	Moderate	<i>E.coli</i>	0.044	Strong
<i>E.coli</i>	0.0103	Moderate	<i>E.coli</i> +	0.066	Strong
<i>E.coli</i>	0.021	Strong	<i>Kl.pneumoniae</i>	0.079	Strong
<i>E.coli</i>	0.030	Strong	<i>E.coli</i> +	0.052	Strong
<i>E.coli</i>	0.049	Strong	<i>P. mirabilis</i>	0.060	Strong

The biofilm producing strains isolated from patients with recurrent UTI had higher ODs than correlated groups of biofilm producers among the patients with first time infection.

According to the criteria for biofilm-forming ability, after 24-h incubation 45 strains were slime producers: 15 (37.5%) from the first-time symptomatic UTI and 30 (75%) from the recurrent UTI group of patients.

The percentage of different categories of biofilm producers observed among the two groups of patients, including the prevalence of the non-adherent isolates is given in Table 4.

Table 4 shows that the biofilm producers were more present in the urine samples of the 40 patients with a history of recurrent UTI as compared to the 40 urine samples collected from patients with first-time symptomatic UTI.

**Table 4.** The ability of biofilm production of the isolates from patients with first-time symptomatic UTI and with a history of recurrent UTI

Source of isolate	N° of isolates	Biofilm producing abilities				Over all biofilm producers
		None	Weak	Moderate	Strong	
Urine from patients with first-time symptomatic UTI	40	25 (62.5%)	7 (17.5%)	5 (12.5%)	3 (7.5%)	15 (37.5%)
Urine from patients with a history of recurrent UTI	40	10 (25%)	7 (17.5%)	13 (32.5%)	10 (25%)	30 (75%)

## DISCUSSION

Since biofilm formation is central to the pathogenesis of most recurrent and chronic infections (catheter associated UTI included) we conducted this study to examine the possibility of biofilms being associated with recurrent urinary tract infections in ambulatory patients as well.

In human studies, recurrent UTI rates in untreated individuals have been reported to range from about 25% to greater than 40%.

A growing number of studies indicate that many recurrent UTIs may in fact be relapses caused by the resurgence of intracellular bacterial reservoirs that can persist for many weeks to months within the urothelium [5, 16, 17, 18, 19]

Our results were based on two assays for assessment of biofilm formation: qualitative tube method and quantitative microtitre plate method.

The overall percentage of biofilm producers observed among all of the investigated strains was higher in the TCP method (56.3% vs. 48%) and the difference (in the dye binding) between different categories of biofilm producers was more evident by this method.

This led us to a conclusion that although TM can be recommended as a screening test to identify biofilm-producing isolates TCP method is more accurate technique which could serve as a reliable quantitative tool for determining biofilm producing abilities. These results are consistent with the results of Saxena et al [20].

Our findings had shown higher prevalence of biofilm producers among isolates from UTI patients with recurrent episodes as compared to the isolates from first time UTI infection leading to a presumption that the ability of bacteria to persist and grow on the uroepithelium might be a important factor in the recurrent nature of their UTI. The results presented here are in agreement with previous findings suggesting that long-lived UPEC reservoirs within the bladder consist primarily of small bacterial clusters or microcolonies that are bound by EPC and compartmentalized within the urothelium barrier [21, 22, 23].

Biofilm plaques attached on the uroepithelium are cause for number of complication among which promotion of resistant species and potential poor treatment outcome

This implies the need for further analyses with a larger study population which will provide us better inside in outdoor patients with recurrent UTI.

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## THE IMPACT OF INTRAOPERATIVE TARGETING OF THE CENTRAL VENOUS PRESSURE ON THE ONSET OF DIURESIS IN LIVING DONOR KIDNEY TRANSPLANTATION

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### ABSTRACT

**Introduction:** Early graft function is very important and can be achieved with an adequate intraoperative perfusion characteristics of the graft and urine output. The goal of this study was to examine the influence of targeting CVP on the onset of diuresis in kidney transplantation.

**Material and methods:** The patients were divided in 2 groups of thirty patients: group **A** receiving normal saline intraoperatively, targeting for CVP 15 mmHg until vascular clamps were off and group **B** receiving normal saline 10ml/kg/h. The hemodynamic changes were recorded as systolic, diastolic and mean arterial pressure in 4 times: T0 before the induction, T1 after induction, T2 before the clamping the vessels and T3 after unclamping. We also recorded the duration of surgery, the duration of cold and warm ischemia, and the amount of normal saline until the unclamping of the vessels, lactates at the end of the surgery and total urine output from unclamping the renal vessels to the end of the surgery in both groups. We were monitoring the administration of plasma expander, dopamine and furosemide (if higher than 40mg) and we were inspecting if any tissue edema occurred.

**Results:** There were no statistically significant differences in intraoperative hemodynamic parameters between both groups. The onset of diuresis in seconds was insignificantly longer in group B  $p > 0.05$  ( $p = 0.31$ ). The average value of postoperative levels of the lactate showed that in group B the level of the lactate were significantly higher for  $Z = -5.79$  and  $p < 0.001$  ( $p = 0.000$ ).

**Conclusion:** CVP as a guide for volume substitution is still highly recommended in kidney transplantation. The fact that in group B (the constant infusion group) we had 5 (16.7%) patients in whom we didn't achieved urine output at the end of the surgery and the level of lactate was higher in group B gives us the right to conclude that targeting higher CVP, promotes diuresis and better urine output at the end of the surgery.

**Key words:** target CVP, onset of diuresis, kidney transplantation

### INTRODUCTION

Kidney transplantation is the best choice for patients in the end stage renal disease (ESRD). Nowadays this is a routine intervention and with the progress in medicine it becomes very common in the whole world [1, 2]. Early graft function is very important for successful kidney transplantation. This can be achieved with adequate intraoperative perfusion characteristics of the graft and urine output. In the last few years, a multidisciplinary approach, together with the advances in the technical skills of the surgeons and anesthesiologists as well as significant improvements in the immunosuppressive drug therapy. This has led to ever-expanding selection criteria, making those patients eligible for transplantation who would have been excluded a few years ago [3, 4].

A lot of studies have examined specific values of the perioperative central venous pressure (CVP) that may reduce the risk of postoperative graft failure [5, 6, 7]. Previous trials have also examined several hydration regimens for kidney transplantation, using crystalloids, colloids, albumins in addition to mannitol or loop diuretics, to expand intravascular volume and promote diuresis.

Crystalloids are widely used but they mostly distribute to the interstitial space, while colloids remain in the vascular space. The most usual crystalloid used in kidney transplantation is normal saline, because of the absence of potassium which can lead to cardiac dysrhythmias.

According to several authors after infusion of 1000ml of normal saline, plasma volume is expanded by 180ml and the other 820 ml are extravasated in interstitial space [8].

Despite the well-known bias introduced by the use of right heart pressures (mostly CVP) to estimate preload status and to be guide for intraoperative fluid regimes, no effort has been made to change time-honored CVP monitoring. Central venous cannulation and monitoring is still recommended for all patients who are monitored for intravascular volume status. More precise techniques were developed for monitoring the preload (PiCCO, Pulsion, LiDCO) minimally invasive but still much more expensive [9].

It is well known that the most important intraoperative measure to improve immediate graft function is to maintain an adequate intravascular volume. Early graft malfunction has been associated with decreased graft survival and increased complications. This is a specific task of the anesthesiologist to maintain and optimize the hemodynamic status before kidney reperfusion [9, 10, 11]. Carlier et al. demonstrated that maximal hydration during anesthesia up to 100ml/kg/h and elevated right heart pressure (CVP) up to 10-17 mmHg, were associated with improved early graft function [10, 11, 12, 13, 14]. On the other side patients with ESRD have a narrow margin of safety with IV hydration and may oscillate between hypo and hypervolemia [15].

To our knowledge, no published studies have validated the relationship between time course of volume expansion and the period of renal ischemia and beside the recommendation for CVP values, we still don't have an answer for exact recommended value of CVP. Besides the great progress and improvement in kidney transplantation the risk of postoperative complications is still very high. 25% of the recipients are suffering from delay graft function [16]. This led to need of protocols regarding intraoperative management and hydration during the intraoperative period. The goal of this study was to examine the influence of targeting CVP of 15 mmHg on onset of diuresis and the urine output at the end of the kidney transplantation.

## METHODS

This study was designed as a prospective clinical study for a period of 2 years. After approval of the Ethical committee of the Medical Faculty in Skopje, we obtained an informed consent from 60 patients undergoing renal transplantation of living-related person at the Clinic of Urology in Skopje. The patients were divided in 2 groups: group **A** receiving normal saline intraoperatively, targeting for CVP 15 mmHg until vascular clamps were off and group **B** receiving normal saline 10ml/kg/h.

The exclusion criteria were: severe left ventricular impairment, cardiomyopathy with ejection fraction below 50%, problem with coagulation, excessive bleeding during the operation, resistant graft arterial spasm or any other surgical difficulty.

All transplantations in this study were performed by the same surgical team. All patients underwent full medical and surgical history, and routine laboratory investigations (i.e., blood Hb, plasma proteins, coagulation status, serum electrolytes, blood glucose, lactate, arterial blood gases, chest radiography, and echocardiography). All patients underwent preoperative hemodialysis 48 and 24 hours before renal transplant surgery.

Protocol for anesthesia: standard monitoring ECG in 5 leads, noninvasive blood pressure and pulse oximetry before the induction were recorded. Before the induction, an epidural catheter was inserted on level L2-L3 or L3-L4 and a test dose of bupivacaine 10 mg was given. We didn't use the epidural catheter until the end of the surgery. . At the end of the intervention we gave 100mcg fentanyl and 20 mg of bupivacaine in volume of 10 ml to avoid any interference with intraoperative hemodynamics. For induction we used remifentanyl in doses of 0,5mcg/kg and propofol 2mg/kg and the intubation was facilitated with atracurium 0,5mg/kg and maintaining of anesthesia was with remifentanyl 0,25mcg/kg and propofol 0.5-1mg/kg depending on the depth of anesthesia which was recorded with entropy electrodes. Patients were ventilated with mixed oxygen/air 50-50% with tidal volume of 7-9ml/kg and end-tidal CO<sub>2</sub> between 35-40mmHg (Datex-Ohmeda Avance S-5). After the induction, a central venous catheter aseptically was placed in the internal jugular vein and pressure was transduced and recorded. For measuring of the invasive arterial pressure, an arterial catheter was placed in radial artery and was recorded. The hemodynamic changes were recorded as systolic, diastolic and mean arterial pressure in 4 times. T<sub>0</sub> before the induction, T<sub>1</sub> after induction, T<sub>2</sub> before clamping the vessels and T<sub>3</sub> after unclamping. We also recorded the duration of surgery, duration of cold and warm ischemia, amount of normal saline until the unclamping the vessels, lactate at the end of the surgery and total urine output from unclamping the renal vessels to the end of the surgery in both groups. We were monitoring the administration of plasma expander, dopamine and furosemide ( if higher than 40mg) and we were inspecting if any tissue edema occurred. Kidney turgidity was evaluated by the surgical team who were unaware of the hydration regimen on 3 point scale: score I (soft graft), score II (turgid graft) ,score III (highly turgid)

### Statistical analysis

Statistical analysis was performed with SPSS (version 9.0 for Windows, SPSS, Chicago, IL). Continuous data are described as mean  $\pm$  SD and categorical variables are given as percentages. All data were tested for normality using the method of Kolmogorov-Smirnov. Intergroup differences in demographic, perioperative hemodynamic values, and laboratory values were compared using unpaired Student *t* test. Mann-Whitney *U* test was used for unpaired nonparametric data, including the volume of crystalloid infused, urine output, and the onset of diuresis. Percentages were compared by  $\chi^2$  contingency analysis. *P* <0.05 was considered to be significant. Mean group differences and their 95% confidence intervals were calculated to determine which of the specific variables differed between groups. If the 95% confidence interval includes 0, it indicates no significant difference between groups.

## RESULTS

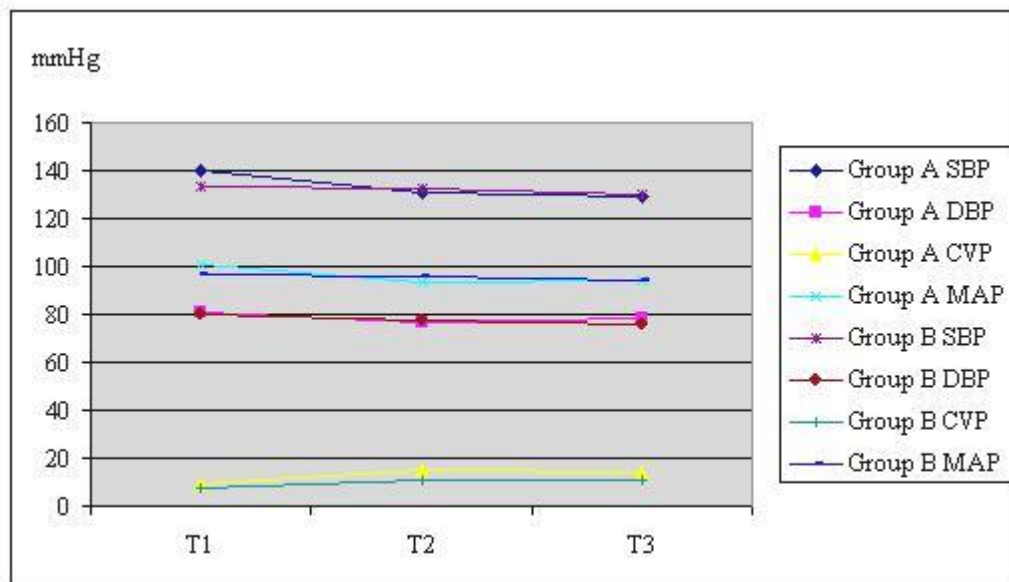
All the patients underwent for hemodialysis 48 and 24 hours before surgery. In group A 4 patients who had not required hemodialysis for their renal failure and 2 patients in group B. Mean arterial preoperative blood Hb and serum creatinine were similar in both groups. Average Hb in group A was  $116.73 \pm 19.07$  and for group B was  $112.93 \pm 17.19$ . Average creatinine for group A was  $632.63 \pm 187.00$  and for group B  $556.52 \pm 164.14$ .

**Table 1.** Demographic and operative data of both groups

	<b>Group A</b>	<b>Group B</b>
Age(years)	$37.87 \pm 9.32$	$41.47 \pm 10.25$
Sex F/M	15/15	17/13
Body weight kg	$74.17 \pm 10.92$	$70.83 \pm 11.83$
Duration of surgery(min)	$236.67 \pm 40.33$	$250.83 \pm 61.65$
Cold ischemia(min)	$210.10 \pm 33.98$	$221.43 \pm 35.62$
Warm ischemia( sec)	$170.30 \pm 39.34$	$184.20 \pm 38.13$
Months on hemodialysis	$12.17 \pm 13.32$	$17.95 \pm 31.71$
comorbidities		
1. none	11	16
2. hypertension	16	11
3. Hypertension and diabetes mellitus	3	3

Values are mean $\pm$ sd; group **A** is CVP 15 target group, group **B** constant infusion group

Figure 1 shows the systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MBP) and central venous pressure (CVP) in both groups during 3 times T1, T2 and T3. In T1, T2 and T3 time there were no statistical significant difference between both groups.



**Fig. 1.** Perioperative mean values of SBP, DBP, MBP and CVP in group A and group B.

Tables 2 and 3 show the amount of intravenous normal saline infused, the onset of diuresis, the urine output at the end of the surgery and lactate at the end of the surgery. The amount of IV fluids administrated up to the time of unclamping the vessels  $t=1.92$  and  $p>0.05$  ( $p=0.06$ ) insignificantly higher in group A than in group B (table 2).

**Table 2.** Amount of normal saline infused in both groups

parameter	Mean Gr A	Mean Gr B	t-value	df	p	Valid N	Valid N	Std.Dev. Gr. A	Std.Dev. Gr.B
Normal saline ml	2885.00	2580.00	1,92	58	0.06	30	30	666.33	559.96

**Table 3.** Onset of diuresis in both groups, urine output at the end of the surgery and lactate at the end of the surgery

Parameter	Rank Sum Gr. A	Rank Sum Gr. B	U	Z	p-level	Valid N Gr. A	Valid N Gr. B
Onset of diuresis (sec)	780.00	760.00	315.00	-1.01	0.31	30	25
Urine output	829.50	710.50	364.50	-0.18	0.86	30	25
lactate	523.50	1306.50	58.50	-5.79	<b>0.000</b>	30	30

The onset of diuresis in seconds was insignificantly longer in group B  $p > 0,05$  ( $p = 0,31$ ) (table 3). The average value of the amount of urine at the end of the surgery (table 3) showed that group B had insignificantly bigger amount of urine  $Z = 0,18$  and  $p > 0,05$  ( $p = 0,86$ ). But in this group, 5 patients didn't have diuresis until the end of the surgery. The average value of postoperative levels of the lactate showed that in group B, the level of the lactate were significantly higher for  $Z = -5.79$  and  $p < 0.001$  ( $p = 0.000$ )

**Table 4.** Kidney turgidity at the end of vascular anastomosis in both groups

	group	Turgor score			Вкупно
		I	II	III	
Count	group A	3	26	1	30
Row Percent		10.00%	86.67%	3.33%	
Count	group B	5	24	1	30
Row Percent		16.67%	80.00%	3.33%	
Count	All Grps	8	50	2	60

In table 4, the turgidity score in both groups is presented. 86.67% of the patients in group A had turgid graft and 80.00% in group B.

**Table 5.** Concomitant events and adjuvant medications used in both groups

	Group A(No 30)	Group B( No30)	% group A	% group B
Dopamine	0/30	4/30	0%	13,33%
Plasma expander	10/30	9/30	33,33%	30,00%
Furosemide >40mg	8/30	19/30	26,77%	63,33%
Visible tissue edema	3/30	3/30	10%	10%

The use and administration of dopamine (4 patients in group B only) and plasma expander, the administered dose of furosemide higher than 40 mg as well as the presence of visual tissue edema, appeared only in 10 % in both groups (presented in table 5).

## DISCUSSION

Many studies suggest that during kidney transplantation the systolic and diastolic pressure should be higher than 120/85 mm Hg. They also suggest that the MAP should be higher than 95mmHg and CVP above 10[14-16]. These values are favorable to ensure maximal filling pressure of the graft and its fast recovery. Intraoperative volume expansion is associated with increased renal blood flow and better immediate graft function [15, 16]. Early graft malfunction has been associated with decreased graft survival and increased recipient complications [17]. Carlier et al showed that maximal hydration during anesthesia up to 100ml/kg and 30ml/kg/h and CVP 10-17 were associated with improved early graft function [10].

Many of the clinical trials showed that that regimen targeting CVP before cross-clamp of the donor kidney provides a more favorable outcome [10, 15, 17]. They showed that high hydration regime provides more turgid graft and faster onset of diuresis. Our study shows that in intraoperative T1, T2, T3 time, there were no statistical differences in hemodynamic parameters between the two groups. Prolonged arterial hypotension can lead to graft hypoperfusion and after that to prolonged time for graft recovery and delay graft function [17, 18, 19, 20, 21]. In both groups we didn't have any episodes of hypotension and there was no need for vasopressors. The time of surgery, cold ischemia and warm ischemia were similar in both groups in table 3 there are presented adjuvant medications and concomitant events in both groups.

We used dopamine only in 4 patients (13.33%) in group B, but no patient in group A. We used furosemide in doses higher than 40 mg in group A in 8 patients or 26.77% but in group B 63.33 patients received higher dose of furosemide. 33.33 % of the patients in group A received plasma expander and 30% in group B. Visual tissue edema appeared only in 10 % in both groups (table 5). Our study didn't show any benefit from targeting CVP to 15 mmHg. We couldn't find any significant differences on intraoperative hemodynamic parameters, the onset of diuresis and urine output after the unclamping the vessels. However in the constant infusion group (group B), the dosage of furosemide was higher and the level of the lactate was higher. 5 patients in group B didn't have diuresis at the end of the surgery.

## CONCLUSION

This study shows that there isn't any statistical difference between the groups; however in group B we had 5 patients with no diuresis at the end of the surgery. In 63.33% patients in group B received larger amount of furosemide and in 30% dopamine to promote diuresis. Patients in group A had better graft turgidity.

This study has limitations. We only evaluated onset of the diuresis and have not considered whether there are long-term benefits. This study did not have sufficient power to determine a clinical superiority of targeting CVP. There is need for larger study to confirm if there is true benefit (improved long-term outcomes).

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## TISSUE EXPANSION RECONSTRUCTION OF THE SCALP WITH SECONDARY CUTIS VERTICIS GYRATA

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### ABSTRACT

Cutis verticis gyrata (CVG) is a descriptive term for a rare condition manifesting as convoluted folds and furrows formed from thickened skin of the scalp resembling cerebriform pattern. One form of secondary cutis verticis gyrata is the naevoid form in which a naevus causes hypertrophy of the skin.

We present a case of secondary cutis verticis gyrata associated with dermoepidermal papillomatous naevus, and we discuss the clinical aspects of diagnosis and as well as the surgical treatment using tissue expansion reconstruction of the scalp.

**Key words:** cutis verticis gyrata, dermoepidermal naevus, skin expansion

### INTRODUCTION

Cutis verticis gyrata (CVG) is a descriptive term for a condition manifesting as convoluted folds and furrows formed from thickened skin of the scalp resembling cerebriform pattern. It is a rare condition, and the lesions are mostly located on the parietal scalp, but can also manifest on other parts of the body [1-6]. Although Alibert first mentioned it, the condition was first described by Robert in 1848 and Unna introduced the term cutis verticis gyrata in 1907 [2]. Polan and Butterworth established the classification of cutis verticis gyrata in 1953, dividing cutis verticis gyrata into primary and secondary forms. In secondary forms of cutis verticis gyrata, hypertrophy of the skin is caused by an underlying disease [2].

One rare form of secondary cutis verticis gyrata is the naevoid form in which a dermal naevus causes hypertrophy of the skin. A cerebriform naevus resembling cutis verticis gyrata was first described by Hammond and Ransom in 1937 [2].

We present a case of secondary cutis verticis gyrata associated with dermoepidermal papillomatous naevus, and we discuss the clinical aspects of diagnosis and as well as the surgical treatment using tissue expansion reconstruction of the scalp.

### CASE REPORT

A 20-year-old male with progressive growth of parietal and occipital mass causing secondary deformity on the margins of the lesion described as cutis verticis gyrata (CVG) was admitted to our hospital (Figure 1). Physical examination revealed an extensive brown-yellowish-coloured lobulated, granulated lesion (15x11 cm) covered with crusts and with alopecia. The lesion's growth had caused folding of the surrounding tissue forming 10-15 skin folds, of 1.5 cm width, and 1 cm depth of furrows, predominantly in the occipital region. No other family members presented with similar lesions.

In the first stage of the planned two-stage procedure, the scalp was undermined in a subgaleal plane through occipital incisions on the right side (Figure 2). In order to avoid complications, based on the location and size of the lesion, the crescent shaped expander with capacity of 700 cc was chosen. Strict sterilization of the injection area was ensured to avoid infections as saline was injected into the expanders once per week. During the injection procedure, the blood supply of the scalp was closely monitored in order to avoid any blood supply problem. The expansion of the scalp was performed thoroughly. Six weeks later the hair from the expanded skin started to fall out and that was the reason to stop the filling of the expander. We continued with the second stage of the procedure which allowed expanded tissue advancement, excision of the lesion scalp, and covering of the defect (Figure 3). The expanded scalp flap was fully flattened and extended forward to the scalp defect site. The flap was sutured without tension (Figure 4). During the procedure we didn't excise the secondary formed folds around the lesion.

Histological examination showed stratified squamous epithelium with adnexa, which was partially papillomatous with profound keratosis. Nevus nest cells were present in the dermis, and in some of the sections in the epidermis. In the deep dermis, inflammatory infiltration forming granulomas with central cavities and sporadic foreign-body giant cells were found. Based on the histology, a diagnosis of dermoepidermal papillomatous naevus was made.

The follow-up period was 5 years. The skin was similar to the surrounding normal skin in terms of color and texture. The hair growth and sweat and sebaceous gland secretions were normal. The scar was fully concealed. In the six months following the second operation, flattening of the surrounding skin folds was noticed. The patient was completely satisfied with the outcome (Figure 5).



**Fig. 1.** Patient at admission, with progressive growth of lobulated parietal and occipital mass



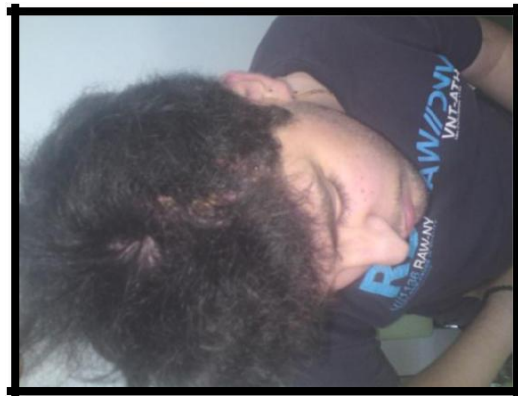
**Fig. 2.** Expander in place



**Fig. 3.** Excised lesion



**Fig. 4.** Covered defect after the second-stage operation



**Fig. 5.** The patient six months after the surgery

## DISCUSSION

The common methods used for correction of skin lesions include partial excision, skin grafting and tissue expansion. The most frequently used method for scalp reconstruction, including CVG correction, is tissue expansion [1, 3, 4, 7, 8, 9, 10, 11, 12, 13].

Correction of the scalp using tissue expansion is a multistage process. Not only is patient selection crucial, but individualized preoperative planning as well. The expectations of the patient and those of the surgeon should match. Patient acceptance of the weekly or biweekly injection processes and the progressive deformity caused by the expander is essential. Several parameters must be considered prior to expansion. Issues related to the insertion process are less controversial when compared with the details as to how this should be done. However, other issues are controversial.

The type of incision, paralesional or remote, is still under scrutiny. The orientation and the number of expanders have also been scrutinized. The size of the expander that should be used and the degree of the flap advancement are on the debate [4]. In our case, based on the location and size of the lesion, we used the crescent shaped expander with capacity of 700 cc.

Other treatment includes partial removal of the scalp followed by suture-tightening surgery and skin grafting. This method has the benefits of being a simple and short procedure that involves low cost. But, there are some disadvantages: the lesion cannot be removed completely, it is easy to relapse, and therefore, it may require multiple surgeries for a complete correction. Opposed to scalp-lesion excision, the advantages of skin grafting method are simple and short surgical procedure, complete removal of the lesion, and low cost. But it may cause loss of hair growth in skin graft area, scalp contracture causing the stretching deformation of eyelids, eyebrows, and ears, and unsatisfactory cosmetic outcome affecting the appearance and scar formation in the donor sites [3]. In the present study, we used skin expansion method for removing of the primary lesion, which led to flattening and correction of CVG.

CVG is a congenital disease with unclear genetic model [1, 2, 3, 5, 6]. Secondary CVG is associated with certain local or systemic diseases, such as acromegaly, cretinism, myxedema, leukemia, syphilis, or paraneoplastic syndrome. The pathogenesis of CVG is still unclear. Under normal conditions, fibrous membrane is found between healthy scalp and epicranial aponeurosis. However, when the scalp becomes thickened and relaxed due to the hyperplasia of connective tissue and sebaceous glands, limited by the fibrous membrane, part of the scalp cannot extend further, leading to the formation of convoluted folds and furrows resembling cerebriform pattern. The secondary CVG can be expected to be dismissed after the cure of the primary disease [3], as in our study where during the first six months after the second stage of the surgery, flattening of the skin folds surrounding the lesion was noticed.

One rare form of secondary cutis verticis gyrata is the naevoid form in which a dermal naevus causes hypertrophy of the skin. This condition is called cerebriform intradermal naevus (CIN) or pseudo or secondary cutis verticis gyrata. Clinically, CIN is characterized by a well demarcated cerebriform skin surface, usually on the parietal area of the scalp [2]. Histologically, many intradermal naevus cells are present in CIN. Sometimes secondary cutis verticis gyrata associated with intradermal naevus shows abnormalities of epithelial and mesenchymal structures, leading to inclusion in the spectrum of hamartomatous lesions, which may be congenital. CIN is usually congenital, but can also be acquired. CIN lesions may vary in size from 2 x 3 cm to 25 x 22.5 cm [2]. The diagnosis of CIN is based on clinical and histopathological investigations. Differential diagnosis of CIN includes primary cutis verticis gyrata, other forms of secondary cutis verticis gyrata, leukaemic infiltrates in the skin, cerebriform sebaceous naevus, pachydermoperiostosis, cicatricial alopecia, (perinaevoid) alopecia areata, aplasia cutis congenita, alopecia mucinosa, cerebriform epithelial-connective tissue hamartoma, persistent and repeated rubbing of the skin of the scalp with secondary thickening of the connective dermal tissue in mentally retarded subjects [2]. There have been two reports of malignant melanoma arising on a CIN lesion [2, 7].

In conclusion, the described expanding scalp flap method has good clinical effect and we recommend it as an effective method of treating larger areas of CVG.

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## MEANING OF THE URGENT GASTRODUODENAL ULCER IN THE CONTEMPORARY SURGERY

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### ABSTRACT

The acute, urgent complications by the peptic ulcer disease such as the bleedings and the perforations of the gastroduodenal ulcer are some of the most common urgent, life-threatening conditions with the gastroduodenal tract.

The goal of this study is to assess the meaning of this entity in the contemporary surgical practice.

This is a prospective-retrospective study which involves patients with urgent, life-threatening complications with the gastroduodenal ulcer who have been treated at the University Clinic for digestive Surgery and University Clinic of anesthesia, reanimation and intensive treatment in Skopje in the period from 01 January 2003 to 31 December 2015. The following variables were applied: type of complication, age, gender, localization of the ulcer lesion, Forrest classification on the seriousness of the bleeding, type of treatment and outcome.

In 531 (52.94%) of the cases were in the group of bleeding gastroduodenal ulcers. 337 (63.47%) were treated operatively, and 194 (36.53%) were treated with the conservative method. In 472 cases (47.06%) perforation was present. Of these, 456 (96.61%) were operated and 16 (3.39%) were treated conservatively. In total of 144 (14.36%) there was a lethal outcome. Of these, 88 (8.77%) were with bleeding ulcer and 56 (5.58%) with perforated ulcer.

Despite the enormous progress in the understanding and treatment of the PUD, the complications from this disease remain common and life-threatening, which is the reason why the research in direction of improved treatment, diagnostics and outcome remain very important. On the other hand, the overall mortality or the individual bleeding and perforation correlates with the results published in the studies that cover this problematics.

**Key words:** urgent, life-threatening, gastroduodenal ulcer.

### INTRODUCTION

The peptic ulcer disease (PUD) is an obstruction of the integrity of the mucosis in any part of the upper gastrointestinal tract with clearly defined malfunction caused by a local inflammatory area.

The peptic ulcer comes as a consequence of the exposure of the stomach and the duodenum to pepsin and stomach acid. It develops when the protective mechanisms, such as the mucus and the bicarbonats are overcome by the harmful affection of the pepsin and the gastric acid [1].

The word "peptic" comes from the Greek word "pepticos" which means digestion [2]. The main etiological factor for this disease is the bacteria *Helicobacter pylori* (*H. pylori*). More than half of the world population is infected with this bacteria, which makes the *H. pylori* the most common infective agens present in the human race [3]. The prevalence of the *H. pylori* is 80-90% in the developing countries and between 40 and 60% in the developed world.

Overall, there is a tendency for reducing the prevalence of the *H. pylori* in many areas of the world in the last years. This is due to the available treatment for eradication of the *H. pylori* and consequently, the reduced number of infections [4, 5].

Although *H. pylori* is present in the gastroduodenal mucosis in most of the population, only some 10 to 15% develop PUD [6]. The cases of PUD where no presence of *H. pylori* was verified are put in correlation with the use of non-steroid anti-inflammatory drugs (NSAID), and the assessments indicate that 15 to 35% of all ulcer complications are a result of their use [7, 8]. Synergic activity of both *H. pylori* and the NSAID is also possible [9]. Besides these two most common factors, other factors that contribute to the development of the PUD are: smoking, alcohol, age, certain hyperacid conditions or the so-called stress ulcers, infective and other diseases, use of corticosteroids, radiotherapy on the abdominal region etc [7, 10].

The cases of PUD without clear reason, such as infection with *H. pylori* or NSAID use or hypergastrinemia are called idiopathic peptic ulcer disease (IPUD) or idiopathic ulcers.

The development of the peptic ulcer moves from resultion without intervention to development of complications such as bleeding, perforation and gastric outlet obstruction, with potential for significant morbidity and mortality. The complications from the PUD are present in 10 to 20% of the patients [11].

From a clinical aspect, the urgent peptic ulcer attracts attention, which covers the bleedings and the perforations. The urgent peptic ulcer is an extraordinary serious condition which is directly life-threatening for the patient and is one of the most common urgent conditions in the gastrointestinal system.

Despite the enormous progress in the conservative treatment, the surgery remains the most important segment in the treatment of the urgent gastroduodenal ulcer.

Although the indications for the surgical treatment of this type of ulcer have not changed dramatically in the last few decades, the positions and the manner of their treatment have.

## **MATERIALS AND METHODS**

This is a prospective-retrospective study that covers 1003 patients with urgent complications of the gastroduodenal ulcer, which include perforations and bleedings, treated at the University Clinic for Digestive Surgery in Skopje and the University Clinic of anesthesia, reanimation and intensive treatment in Skopje in the period from 01 January 2003 to 31 December 2015.

The data for 2011 were gathered from the patients files, and the following variables were applied: age, gender, localization of the ulcer lesion, type of complication, Forrest classification of the bleeding, treatment and outcome. From 2012 to 2015 the same variables were monitored prospectively and the obtained data were recorded in a pre-prepared questionnaires.

With regard to the age, the patients were divided in five groups: up to 20 years of age, 21 to 40, 41 to 60, 61 to 80 and 80+. With regard to the localization of the ulcers, they were predominantly divided on: stomach ulcers and duodenal ulcers. With the stomach ulcers, we identified: cardia, corpus, antrum and pylorus, and with the duodenum, the horizontal part, i.e. bulbus and the descendent part, i.e. D2. The patients with bleeding ulcer were grouped according to the Forrest classification for determining the localization and the level of bleeding. With regard to the treatment, the patients were divided depending on the type of operation, as well as those who were treated conservatively. With regard to the outcome, the patients were divided on those who were cured by life-threatening complication of the peptic ulcer and those with lethal outcome.

Target of this work was: 1. The target group; 2. A group that covers the cases from 2003 to 2010; and 3. A group that covers the cases from 2011 to 2015. The results from the cases in the period 2003-2010 were compared with the results obtained in the period 2011-2015.

The database was created with an application of specific computer programmes. The numerical serials were analysed through measures with central tendency and with measures of data dispersion. The attributive statistical series were analysed by determining the coefficient of relations, proportions, rates and by determining the statistical significance among the detected differences. The statistical significance of the differences between the attributive series will be tested by using the Difference Test. For CI (confidence interval) as a precision mark we took  $p < 0.05$ . The results are presented in tables.

## **RESULTS**

A total of 1003 patients with urgent complications with the gastroduodenal ulcer were covered with the research, of whom 727 patients (72.5%) were male, and 276 (27.5%) were female.

The ratio that is registered according to the Difference test between the two genders is statistically significant for  $p < 0.05$  ( $p = 0.0000$ ). The correlations between male and female subjects was 2.63:1.

In the period 2003-2010 there are average  $83.8 \pm 14.0$ , minimum 68 and maximum 106 patients annually. In the period since 2011-15 years there have been an average of  $66.4 \pm 9.9$  minimum 51 and maximum 76 patients annually.

In 2005, largest number of cases of complicated ulcers were treated (106). The bleedings are among the most common complications, present in 531 cases, i.e. in 52.9% of the cases, followed by perforations present in 472 i.e. 47.1% of the cases.

The ratio that is registered according to the Difference test between the two types of complications – perforation and bleeding, is statistically significant for  $p < 0.05$  ( $p = 0.094$ ). The correlations between the bleeding ulcers versus perforations is 1.13:1 with advantage at the side of the bleeding ulcers (Table 1.). Out of the 671 cases in the period 2003-2010, 385 cases or 57.4% were with a bleeding ulcer, and 286 cases or 42.6% were with perforated ulcer. In the period from 2011 to 2015, out of 332 cases, 146 or 44% were with a bleeding ulcer, and 186 or 56% of the patients had perforated ulcer.

Most present age group was the one between 41 and 60 years of age (415) and the group from 61 to 80 years of age (390) i.e. 80.3% of the patients in the analysed period were at the age between 41 and 80 (Table 2.).

More common were the complications with the duodenal ulcers, 583 (58.1%), compared with the stomach ulcers 420 (41.9%), and most present localizations were on the bulbus of the duodenum (547-54,5%) and on stomach corpus (228-22,7%) (Table 3.).

Out of 531 cases with a bleeding ulcer, 370 were diagnosed with an endoscope (69.7%), most of whom, 133 or 25.1% had a visible bleeding vessel, i.e. with FIIA finding from the Forrest classification (Table 4.).

Most of the patients with bleeding ulcers were operated (337 – 63.5%), and 194 (36.5%) were treated conservatively. In 193 patients (36.4%), the local hemostasis was the dominant method (Table 5.)

When it comes to the perforations, we should note that dominant operative technique was the sutura on the perforated opening following the method of R Graham, in 435 (92.2%) cases (Table 6.).

The overall mortality in the study carried out on 1003 patients was 144 patients or 14.36%, where bleeding was cause of death in 88 cases or 8.77%, and perforations in 56 cases or 5.58%.

The ratio difference that is registered with the Difference test between the mortality caused by the bleeding ulcers and mortality caused by perforated ulcers is statistically significant for  $p < 0.05$  ( $p = 0.0056$ )

The mortality caused by the bleeding ulcers is 88 out of 531 cases or 16.57%, and with the perforations, the mortality is 56 cases out of 472, or 11.86% (Table 7.)

The ratio difference that is registered with the Difference test between the mortality caused by the bleeding ulcers versus the mortality caused by the perforated ulcers is statistically significant for  $p < 0.05$  ( $p = 0.0343$ )

## DISCUSSION

The PUD is a serious health problem worldwide. Four million people suffer from this disease worldwide every year [12, 13]. Assessments indicate that in the US the expenses related with this disease, due to the absence from work, hospitalization and medical care (without the expenses for medicines) reach the amount of 5,65 billion dollar annually [14]. In the US, the presence of duodenal ulcers and the non-complicated gastric ulcers has been decreasing in the last three to four decades, while the presence of complicated ulcers and the hospitalization remains on the same level. The hospitalization rate with PUD is around 30 out of 100,000 cases [15].

In their study, Lanas and co report on a significantly reduced number of hospitalized patients due to bleeding or perforation of peptic ulcer in the period from 1996 to 2005 [16]. Similar epidemiologic changes have been published also in the study of Paimela and co, which reports on reduced number of hospitalization for urgent surgery due to PUD in Finland [17].

The bleeding is more common complication than the perforation when it comes to the PUD [18]. The percentage of patients that were surgically treated due to bleeding gastroduodenal ulcer, despite the progress of the conservative method, is 10% to 20% from all patients due to upper digestive bleeding [19]. Perforation was present in 2-10% of all PUD patients [19, 20]. More than two-thirds of the patients with acute ulcer bleeding were older than 60 years of age and more than one-fourth were more than 80 [21].

Although in the last two decades there is a reduced incidence with peptic ulcer among men and increase among the women, generally, the PUD is more present among the men. Ulcers at the front wall of the duodenum cause perforations most often (60%), followed by antral (20%) and gastric ulcers at the small curve (20%) [22].

Mortality due to perforation is between 10 and 40% [19, 20]. In this study, male dominate over the female patients with 2,63:1. From the results in this study, there is a tendency of decreasing the incidence with the urgent peptic ulcer.

The total number of patients from 2003 to 2010 was 671 patients, and in the period from 2011 to 2015 there were 332 patients. The incidence or urgent complications due to PUD has decreased from 84 average at annual level to 66 in the last five years. In this study, the bleeding ulcers are present with 531 cases, i.e. 52.9% of the patients, while perforations are present with 472 or 47.1% of the patients and the correlation is 1.13:1. The results from the study indicate reduced incidence with the bleeding ulcers and increased incidence with the perforated ulcers in the last five years. Out of 671 cases in the period from 2003 to 2010, 385 cases, or 57.4% were with bleeding ulcer, and 286 cases or 42.6% with perforated ulcer. In the period from 2011 to 2015, out of 332 cases, 146, or 44% were with bleeding ulcer, and 186 or 56% with perforated ulcer. Most present age group in this study is the one from 41 to 60 years of age with 415 cases or 41.4% and the one from 61 to 80 years of age with 390 cases or 38.9%, i.e. the age from 40 to 80 is present with 80.3% of the cases. There is a slight increase in the participation of the age group from 61 to 80, from 37.9% in the period 2003-2010 on 40.1% in the period 2011-2015, as well as a slight decrease of the participation of the age group from 41 to 60, from 42.6% in the period 2003-2010 to 38.9% in the period 2011-2015.

In the study, the duodenal ulcer was more present with 583 cases or 58.1% compared with the stomach ulcer with 420 cases or 41.9% and their correlation is 1.39:1. Most common localisations were at the bulbous of the duodenum present in 547 cases or 54.5%, and at the corpus of the stomach present in 228 cases or 22.7%.

The results show reduced presence of cases with corporal peptic ulcer, which participated with 23.1% in the period 2003-2010, while in the period 2011-2015 there were 18.7% cases with corporal peptic ulcers. Contrary to this, the presence of ulcers with antral localization and the ulcers located at the bulbous of the duodenum has increased. In the period 2003-2010 the antral ulcers were present in 7.8% of the cases while in the period 2011-2015 this percentage increased to 15.1%. The ulcers located at the bulbous of the duodenum were present in 53.7% of the cases in the period 2003-2010, while in the period 2011-2015 this percentage increased to 59.6%. Most of the patients with bleeding ulcer, 133 or 25%, had an FIIA diagnosis according to the Forrest classification. The results show reduced number of non-diagnosed cases, which from 37.7% in the period 2003-2010 had decreased to 11% in the period 2011-2015. At the same time, there is an increased percentage of cases with FIA, FIB and FIIA, which in the period 2003-2010 was 16.4%, 7% and 22.6% consecutively, and in the period 2011-2015 these percentages reached 26%, 21.9% and 31.5% consecutively.



Most of the patients with bleeding ulcers were operated, 337 or 63.5%, while 194 or 36.5% were treated conservatively. Dominant operation technique was a local hemostasis in 193 or 36.3% of the cases. From the radical operation methods, most used was the resection method following the Billroth II, with 112 or 21.1% of the cases. The use of other radical methods in this study is minor.

There is a visible trend for increased application of the local hemostasis in the last five years, applied on one-half of the cases. In the period 2003-2010, it was applied in 31.2% of the patients, and in the period 2011-2015 its participation reached 50.00%. At the same time, the conservative treatment was reduced, from 42.1% in the period 2003-2010 to 21.9% in the period 2011-2015. The use of the resection method following Billroth II is constant in both periods and marks 21% and 21.2% consecutively.

When it comes to the perforations, we should note that the dominant operation technique was the sutura at the perforation following the method of R. Graham used in 435 i.e. 92.2% of the patients. In the last five years, no cases were treated conservatively, and the sutura following the R. Graham method was applied in 89.5% of the cases in the period 2003-2010, and in 96.2% of the cases in the period 2011-2015.

The overall mortality in the study is 144 out of 1003 patients, or 14.36%, where bleedings are a cause in 88 cases or 8.77%, and perforations in 56 cases or 5.58%. The mortality in the bleeding ulcers, 531 cases is 16.57% and in perforations, 472 cases is 11.86%.

There is no significant difference in the overall mortality in the period 2003-2010 and 2011-2015, which was 14.61% and 13.86% consecutively. There is however a significant difference in the cause for mortality in the two periods. In the period 2003-2010, the bleeding was the cause in 69.39%, while in the period 2011-2015, the perforations were cause for mortality in 56.52% of the cases.

### CONCLUSION

The results from the study indicate decrease of the incidence of the urgent peptic ulcer, probably as a result of the new approaches in the diagnostics and in the treatment of the patients.

The perforation in the last five years, unlike previously, is more common cause for urgent peptic ulcer compared with the bleeding, which together with the reduced percentage of conservatively treated patients in the same period indicates increased admission of these patients in internist gastroenterology hospitals as a result of the progress of the intervention endoscopy and the application of the inhibitors with proton pump.

The age group from 61 to 80 is most present in the last five years, unlike in the previous period when the age group from 41 to 60 was most present, which is probably due to the increased use of NSAID and aspirins in this age group.

The mortality in the study of 14.36% is in correlation with the reports of other authors. The bleedings were cause of death in 8.77% of the cases and the perforations in 5.58% of the cases.

Despite the progress in the diagnostics and in the therapy, the mortality is pretty high, which is in context of the fact that the patients with peptic ulcer are older persons facing other comorbid factors. Other reasons for this poor outcome include the condition of shock, sepsis, delayed operative treatment.

**Table 1. Overview of type of complications**

	<b>Perforations</b>	<b>%</b>	<b>Bleeding</b>	<b>%</b>	<b>Total</b>
<b>2003</b>	<b>30</b>	32.61	<b>62</b>	67.39	<b>92</b>
<b>2004</b>	<b>28</b>	32.94	<b>57</b>	67.06	<b>85</b>
<b>2005</b>	<b>37</b>	34.91	<b>69</b>	65.09	<b>106</b>
<b>2006</b>	<b>32</b>	44.44	<b>40</b>	55.56	<b>72</b>
<b>2007</b>	<b>34</b>	44.16	<b>43</b>	55.84	<b>77</b>
<b>2008</b>	<b>46</b>	46.46	<b>53</b>	53.54	<b>99</b>
<b>2009</b>	<b>40</b>	55.56	<b>32</b>	44.44	<b>72</b>
<b>2010</b>	<b>39</b>	57.35	<b>29</b>	42.65	<b>68</b>
<b>2011</b>	<b>45</b>	60.81	<b>29</b>	39.19	<b>74</b>
<b>2012</b>	<b>49</b>	64.47	<b>27</b>	35.53	<b>76</b>
<b>2013</b>	<b>23</b>	45.10	<b>28</b>	54.90	<b>51</b>
<b>2014</b>	<b>39</b>	58.21	<b>28</b>	41.79	<b>67</b>
<b>2015</b>	<b>30</b>	46.88	<b>34</b>	53.13	<b>64</b>
<b>Total</b>	<b>472</b>	47.06	<b>531</b>	52.94	<b>1003</b>

Period 2003 - 2010 compared with period 2011 - 2015						
	Perforations	%	Bleeding	%	Ttl.	
2003	30		62		92	
2004	28		57		85	
2005	37		69		106	
2006	32		40		72	
2007	34		43		77	
2008	46		53		99	
2009	40		32		72	
2010	39		29		68	
	286	42.62	385	57.38	671	66.90
2011	45		29		74	
2012	49		27		76	
2013	23		28		51	
2014	39		28		67	
2015	30		34		64	
Total	186	56.02	146	43.98	332	33.10
	472	47.06	531	52.94	1003	

Table 2. Overview of patients according to age group

	Up to 20	%	21-40	%	41-60	%	61-80	%	> 80	%	Total
2003	1	1.09	12	13.04	52	56.52	21	22.83	6	6.52	92
2004	0	0.00	18	21.18	35	41.18	23	27.06	9	10.59	85
2005	5	4.72	9	8.49	49	46.23	42	39.62	1	0.94	106
2006	0	0.00	11	15.28	30	41.67	23	31.94	8	11.11	72
2007	2	2.60	12	15.58	21	27.27	38	49.35	4	5.19	77
2008	1	1.01	7	7.07	44	44.44	43	43.43	4	4.04	99
2009	1	1.39	6	8.33	35	48.61	28	38.89	2	2.78	72
2010	1	1.47	7	10.29	20	29.41	36	52.94	4	5.88	68
2011	0	0.00	8	10.81	30	40.54	31	41.89	5	6.76	74
2012	0	0.00	9	11.84	36	47.37	27	35.53	4	5.26	76
2013	0	0.00	8	15.69	17	33.33	23	45.10	3	5.88	51
2014	0	0.00	9	13.43	25	37.31	26	38.81	7	10.45	67
2015	2	3.13	9	14.06	21	32.81	29	45.31	3	4.69	64
Total	13	1.30	125	12.46	415	41.38	390	38.88	60	5.98	1003
Period 2003 - 2010 compared with period 2011 - 2015											
	Up to 20	%	21-40	%	41-60	%	61-80	%	> 80	%	Total
2003	1		12		52		21		6		92
2004	0		18		35		23		9		85
2005	5		9		49		42		1		106
2006	0		11		30		23		8		72
2007	2		12		21		38		4		77
2008	1		7		44		43		4		99
2009	1		6		35		28		2		72
2010	1		7		20		36		4		68
	11	1.64	82	12.22	286	42.62	254	37.85	38	5.66	671
2011	0		8		30		31		5		74
2012	0		9		36		27		4		76
2013	0		8		17		23		3		51
2014	0		9		25		26		7		67
2015	2		9		21		29		3		64
Total	2	0.60	43	12.95	129	38.86	136	40.96	22	6.63	332

**Table 3. Overview of patients according to ulcer localization**

	cardia	%	corpus	%	antrum	%	pilorus	%	bulbus	%	D2	%	Total
2003	2	2.17	32	34.78	8	8.70	6	6.52	38	41.30	6	6.52	92
2004	4	4.71	21	24.71	8	9.41	9	10.59	41	48.24	2	2.35	85
2005	0	0.00	34	32.08	3	2.83	8	7.55	58	54.72	3	2.83	106
2006	6	8.33	18	25.00	4	5.56	5	6.94	36	50.00	3	4.17	72
2007	4	5.19	15	19.48	6	7.79	5	6.49	40	51.95	7	9.09	77
2008	3	3.03	19	19.19	7	7.07	10	10.10	53	53.54	7	7.07	99
2009	1	1.39	16	22.22	3	4.17	5	6.94	46	63.89	1	1.39	72
2010	0	0.00	11	16.18	14	20.59	6	8.82	37	54.41	0	0.00	68
2011	0	0.00	9	12.16	16	21.62	6	8.11	42	56.76	1	1.35	74
2012	0	0.00	11	14.47	11	14.47	7	9.21	45	59.21	2	2.63	76
2013	0	0.00	12	23.53	8	15.69	0	0.00	28	54.90	3	5.88	51
2014	0	0.00	13	19.40	6	8.96	2	2.99	45	67.16	1	1.49	67
2015	0	0.00	17	26.56	9	14.06	0	0.00	38	59.38	0	0.00	64
Total	20	1.99	228	22.73	103	10.27	69	6.88	547	54.54	36	3.59	1003
			420	41.87						583	58.13		
<b>Period 2003 - 2010 compared with period 2011 - 2015</b>													
	cardia	%	corpus	%	antrum	%	pilorus	%	Bulbus	%	D2	%	Total
2004	4		21		8		9		41		2		85
2005	0		34		3		8		58		3		106
2006	6		18		4		5		36		3		72
2007	4		15		6		5		40		7		77
2008	3		19		7		10		53		7		99
2009	1		16		3		5		46		1		72
2010	0		11		14		6		37		0		68
	18	3.11	134	23.14	45	7.77	48	8.29	311	53.71	23	3.97	579
2011	0		9		16		6		42		1		74
2012	0		11		11		7		45		2		76
2013	0		12		8		0		28		3		51
2014	0		13		6		2		45		1		67
2015	0		17		9		0		38		0		64
Total	0	0	62	18.67	50	15.06	15	4.52	198	59.64	7	2.11	332

Table 4. Overview of patients according to the Forrest classification of bleeding ulcers

	F Ia	%	F Ib	%	F IIa	%	F IIb	%	F IIc	%	F III	%	Without diagnosis	%	Total
2003	7	11.29	4	6.45	13	20.97	2	3.23	3	4.84	3	4.84	30	48.39	62
2004	10	17.54	3	5.26	6	10.53	6	10.53	3	5.26	2	3.51	27	47.37	57
2005	7	10.14	3	4.35	16	23.19	1	1.45	3	4.35	2	2.90	37	53.62	69
2006	7	17.50	3	7.50	10	25.00	2	5.00	6	15.00	2	5.00	10	25.00	40
2007	6	13.95	1	2.33	9	20.93	5	11.63	2	4.65	8	18.60	12	27.91	43
2008	12	22.64	4	7.55	15	28.30	3	5.66	1	1.89	3	5.66	15	28.30	53
2009	6	18.75	6	18.75	10	31.25	2	6.25	0	0.00	1	3.13	7	21.88	32
2010	8	27.59	3	10.34	8	27.59	1	3.45	0	0.00	2	6.90	7	24.14	29
2011	7	24.14	5	17.24	8	27.59	0	0.00	0	0.00	1	3.45	8	27.59	29
2012	4	14.81	6	22.22	10	37.04	2	7.41	0	0.00	1	3.70	4	14.81	27
2013	8	28.57	9	32.14	8	28.57	0	0.00	0	0.00	1	3.57	2	7.14	28
2014	9	32.14	6	21.43	9	32.14	3	10.71	0	0.00	0	0.00	1	3.57	28
2015	10	29.41	6	17.65	11	32.35	4	11.76	0	0.00	2	5.88	1	2.94	34
Total	101	19.02	59	11.11	133	25.05	31	5.84	18	3.39	28	5.27	161	30.32	531

Period 2003 - 2010 compared with period 2011 - 2015

	F Ia	%	F Ib	%	F IIa	%	F IIb	%	F IIc	%	F III	%	Without diagnosis	%	Total
2003	7		4		13		2		3		3		30		62
2004	10		3		6		6		3		2		27		57
2005	7		3		16		1		3		2		37		69
2006	7		3		10		2		6		2		10		40
2007	6		1		9		5		2		8		12		43
2008	12		4		15		3		1		3		15		53
2009	6		6		10		2		0		1		7		32
2010	8		3		8		1		0		2		7		29
	63	16.36	27	7.01	87	22.60	22	5.71	18	4.68	23	5.97	145	37.66	385
2011															
2012	7		5		8		0		0		1		8		29
2013	4		6		10		2		0		1		4		27
2014	8		9		8		0		0		1		2		28
2015	9		6		9		3		0		0		1		28
	10		6		11		4		0		2		1		34
Total	38	26.03	32	21.92	46	31.51	9	6.16	0	0	5	3.42	16	10.96	146

**Table 5. Overview of treatment of bleeding ulcers**

Loc. Hem.	%	BI	%	B.II.	%	HI	%	T.G.	%	Sub.G.	%	Wh	%	Cons.	%	Total
2003	17	27.42	1	1.61	17.74	1	1.61	0	0.00	0	0.00	0	0.00	32	51.61	62
2004	19	33.33	1	1.75	24.56	0	0.00	0	0.00	0	0.00	0	0.00	23	40.35	57
2005	11	15.94	3	4.35	26.09	0	0.00	0	0.00	0	0.00	0	0.00	37	53.62	69
2006	16	40.00	1	2.50	20.00	0	0.00	1	2.50	0	0.00	0	0.00	14	35.00	40
2007	20	46.51	1	2.33	16.28	0	0.00	0	0.00	0	0.00	0	0.00	15	34.88	43
2008	14	26.42	5	9.43	24.53	0	0.00	0	0.00	0	0.00	0	0.00	21	39.62	53
2009	14	43.75	2	6.25	15.63	0	0.00	0	0.00	0	0.00	0	0.00	11	34.38	32
2010	9	31.03	1	3.45	17.24	0	0.00	0	0.00	5	17.24	0	0.00	9	31.03	29
2011	10	34.48	0	0.00	37.93	0	0.00	0	0.00	1	3.45	1	3.45	6	20.69	29
2012	12	44.44	0	0.00	14.81	1	3.70	0	0.00	2	7.41	0	0.00	8	29.63	27
2013	20	71.43	0	0.00	10.71	0	0.00	0	0.00	0	0.00	0	0.00	5	17.86	28
2014	11	39.29	0	0.00	32.14	0	0.00	1	3.57	1	3.57	0	0.00	6	21.43	28
2015	20	58.82	0	0.00	11.76	0	0.00	1	2.94	2	5.88	0	0.00	7	20.59	34
Total	193	36.35	15	2.82	21.09	2	0.38	3	0.56	11	2.07	1	0.19	194	36.53	
																337
																63.47

**Period 2003 – 2010 compared with period 2011 – 2015**

Loc. Hem.	%	BI	%	B.II.	%	HI	%	T.G.	%	Sub.G.	%	Wh	%	Cons.	%	Total
2003	17	1	0	11	21.04	1	0.26	1	0.26	5	1.30	0	0.00	32	42.08	62
2004	19	1	0	14	21.04	0	0.00	0	0.00	0	0.00	0	0.00	23	36.53	57
2005	11	3	0	18	21.04	0	0.00	0	0.00	0	0.00	0	0.00	37	57.86	69
2006	16	1	0	8	21.04	0	0.00	1	1.56	0	0.00	0	0.00	14	21.43	40
2007	20	1	0	7	21.04	0	0.00	0	0.00	0	0.00	0	0.00	15	21.43	43
2008	14	5	0	13	21.04	0	0.00	0	0.00	0	0.00	0	0.00	21	31.03	53
2009	14	2	0	5	21.04	0	0.00	0	0.00	0	0.00	0	0.00	11	15.94	32
2010	9	1	0	5	21.04	0	0.00	0	0.00	5	17.24	0	0.00	9	31.03	29
Total	120	15	3.90	81	21.04	1	0.26	1	0.26	5	1.30	0	0.00	162	42.08	385
2011	10	0	0.00	11	21.23	0	0.00	0	0.00	1	0.68	1	0.68	6	21.92	29
2012	12	0	0.00	4	21.23	1	0.68	0	0.00	2	1.37	0	0.00	8	21.92	27
2013	20	0	0.00	3	21.23	0	0.00	0	0.00	0	0.00	0	0.00	5	15.94	28
2014	11	0	0.00	9	21.23	0	0.00	1	0.92	1	0.92	0	0.00	6	21.92	28
2015	20	0	0.00	4	21.23	0	0.00	1	0.92	2	1.84	0	0.00	7	21.92	34
Total	73	0	0.00	31	21.23	1	0.68	2	1.37	6	4.11	1	0.68	32	21.92	146

Table 6. Overview of treatment of perforations

	Str	%	BI	%	BP	%	Sub. G.	%	Petz.	%	Cons.	%	Total
2003	26	86.67	1	3.33	1	3.33	0	0.00	0	0.00	2	6.67	30
2004	26	92.86	0	0.00	1	3.57	0	0.00	0	0.00	1	3.57	28
2005	34	91.89	0	0.00	0	0.00	0	0.00	0	0.00	3	8.11	37
2006	28	87.50	0	0.00	1	3.13	0	0.00	0	0.00	3	9.38	32
2007	31	91.18	1	2.94	0	0.00	0	0.00	0	0.00	2	5.88	34
2008	39	84.78	0	0.00	3	6.52	0	0.00	0	0.00	4	8.70	46
2009	36	90.00	1	2.50	2	5.00	0	0.00	0	0.00	1	2.50	40
2010	36	92.31	0	0.00	3	7.69	0	0.00	0	0.00	0	0.00	39
2011	44	97.78	0	0.00	0	0.00	0	0.00	1	2.22	0	0.00	45
2012	48	97.96	0	0.00	1	2.04	0	0.00	0	0.00	0	0.00	49
2013	23	100.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	23
2014	37	94.87	0	0.00	0	0.00	1	2.56	1	2.56	0	0.00	39
2015	27	90.00	0	0.00	1	3.33	1	3.33	1	3.33	0	0.00	30
Total	435	92.16	3	0.64	13	2.75	2	0.42	3	0.64	16	3.39	472

Period 2003 - 2010 compared with period 2011 - 2015

	Str	%	BI	%	BP	%	Sub. G.	%	Petz.	%	Cons.	%	Ttl.
2003	26		1		1		0		0		2		30
2004	26		0		1		0		0		1		28
2005	34		0		0		0		0		3		37
2006	28		0		1		0		0		3		32
2007	31		1		0		0		0		2		34
2008	39		0		3		0		0		4		46
2009	36		1		2		0		0		1		40
2010	36		0		3		0		0		0		39
2011	256	89.51	3	1.05	11	3.85	0	0.00	0	0.00	16	5.59	286
2012	44		0		0		0		1		0		45
2013	48		0		1		0		0		0		49
2014	23		0		0		0		0		0		23
2015	37		0		0		1		1		0		39
2015	27		0		1		1		1		0		30
Total	179	96.24	0	0.00	2	1.08	2	1.08	3	1.61	0	0.00	186

### Abbreviations:

- \*PUD– Peptic Ulcer disease
- \*NSAID - Non-steroid anti-inflammatory drugs
- \*IPUD– Idiopathic Peptic Ulcer Disease \*Perf.  
– Perforations
- \*D2 – Descendent part of the duodenum
- \*F – Forrest – Endoscopic classification of the type, localisation and prognosis of the bleeding from upper gastrointestinal tract
- \*Loc. Hem. – Local hemostasis
- \*B I – Billroth I gastrectomy
- \*B II – Billroth II gastrectomy
- \*H I – Harkins I
- \*T.G. – Total gastrectomy
- \*SubT.G. – Subtotal gastrectomy
- \*Wh. - Whipple procedure
- \*Petz. – Closure of the perforation with a tube Petzer
- \*Cons. – Conservative treatment
- \*Ttl. – Total

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## ANEURYSM OF THE ANTERIOR COMMUNICATING ARTERY

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### ABSTRACT

Aneurysms represent local pathological enlargement of the brain blood vessels that occur in 5% of the population. Intracranial aneurysms in 30 to 37% of the population are localized on the anterior communicating artery. Rupture of aneurysms of the anterior communicating artery lead to subarachnoid hemorrhage characterized by a high rate of morbidity and mortality. There are a number of open issues that are debated in the scientific community for aneurysms the anterior communicating artery. The purpose of this paper was to analyze clinical features, diagnostic and therapeutic modalities of aneurysms of the anterior communicating artery. All patients in this study were treated operatively and aneurysm was excluded from circulation by placing permanent clip to the neck of the aneurysm. Morphological analysis and topographical characteristics of the aneurysms of the anterior communicating artery is very important to decide the treatment of the aneurysm. Use of microneurosurgical clipping is an effective method for the treatment of aneurysms of the anterior communicating artery.

**Key words:** anterior communicating artery, aneurysm, treatment

### INTRODUCTION

Intracranial aneurysms are focal dilatations of intracranial arteries, usually at their branching points, that occur in 5% of the population. Most intracranial aneurysms remain asymptomatic and never rupture. When an intracranial aneurysms ruptures, arterial bleeding typically causes a subarachnoid hemorrhage [1]. Intracranial aneurysm rupture with resultant subarachnoid hemorrhage is a serious and often deadly phenomenon with an incidence that affects as many as 30,000 individuals each year in the United States [2].

As indicated in several series, anterior communicating artery (ACoM) aneurysms account for 30 to 37% of all intracranial aneurysms, are more prone to rupture, and demonstrate the highest incidence of postoperative morbidity among anterior circulation aneurysms [3].

Currently, the treatment of aneurysms is immensely controversial. At present day, both endovascular coiling and microneurosurgical clipping techniques represent viable treatment modalities [4]. However, the strengths and limitations of the two techniques suggest a complementary relationship; factors including aneurysm morphology and presence of mass effect related to hemorrhage may drive treatment selection [2].

The aim of this study is through the presentation of clinical features, diagnostic and therapeutic modalities of the aneurysms of the ACoM.

### MATERIAL AND METHODS

The study population enrolled 43 patients referred to the University Clinic of Neurosurgery in Skopje, R. Macedonia during a 1-year period. This study included 55.8% females and 44.1% males, ranging in age from 43 to 76 years; mean age 53.2 years. Patients were referred for treatment based on signs and symptoms suggestive of intracranial aneurysms and all patients had undergone surgery at the University Clinic of Neurosurgery. Patient medical records were analyzed for relevant demographic and clinical information. Patient data on risk factors commonly associated with aneurysm development or aneurysm rupture were collected, including smoking status, family history, presence of multiple aneurysms, history of hypertension. All patients underwent a routine physical examination at arrival to our hospital. The preoperative clinical state was expressed according to the Hunt and Hess score and Glasgow Coma Score. Clinical features at onset were obtained by interview of patient/family and review of medical records. A computed tomography scan and CT-angiography or digital subtraction angiography was obtained shortly after arrival. In our institution, all patients in this series underwent conventional surgical treatment of the aneurysms with direct clipping. All procedures were performed with the patient under general anesthesia.

### RESULTS

The commonest projection of the aneurysm of the ACoM was superior, followed by anterior projection.

Multiple aneurysms were present in 13 patients (30.23%). Multiple aneurysms more often occur in female patients than in male patients.

The dimension of the aneurysms was measured during CTA examination with SYNGO software. The diameter of the aneurysms was in range between 3 to 16 mm, and the mean value of the aneurysm neck was 3.6 mm. In our group 37 aneurysms (86.04%) were small and 6 aneurysms (13.95%) were medium according to the size.

According to the health habits of the patients in this group 32.1% were alcohol drinkers and 46.5% were cigarette smokers. In this group 67.44% of the patients have hypertension and were on therapy for the treatment of the hypertension and 6.97% of the patients have diabetes mellitus.

All patients in this group presented with SAH and were admitted during the acute phase of SAH. Patients were graded according to the Hunt and Hess scale and 18.6% of the patients were admitted with Hunt and Hess Grade I, 20.93% of the patients with Hunt and Hess Grade II, 27.90% with Hunt and Hess Grade III, 18.60% with Hunt and Hess Grade IV and 13.95% with Hunt and Hess Grade V.

After the discharge all patients in this group were followed up clinically between 3 to 6 months after the surgical treatment and all patients experienced good recoveries, they improved at least one grade on modified Rankin scale score.

## DISCUSSION

Aneurysms and their risks, diagnosis, and management are controversial topics at the beginning of the 21st century [5]. Currently, AComA aneurysms are diagnosed incidentally during investigation for unrelated symptoms or in association with other symptomatic aneurysms in patients with multiple aneurysms. When cerebral aneurysms are considered by location, the AComA aneurysms represent 39% of all intracranial aneurysms. They are among the most difficult lesions to manage surgically [4].

The true AComA aneurysm arises from AComA and is defined further by the projection of its dome in an anterior, superior, posterior, or inferior direction. In Yasargil's experience with AComA aneurysms, the superiorly and anteriorly projecting aneurysms were the most common (34% and 23%, respectively), while posteriorly and inferiorly projecting aneurysms were the least common (14% and 13%, respectively). Some aneurysms (approximately 16%) have mixed projection or multiple lobes [5, 6].

Despite the fact generally intracranial aneurysms are asymptomatic up to their rupture, they can have an unspecific symptom as frequent headache resistant to medical treatment or they can be disclosed by nerve palsy or compression effect to nervous structures [7].

Aneurysm rupture is the most common presentation of patients with AComA aneurysms, with the classic headache characterized by its sudden onset and severity. Patients can present in much worse neurologic condition, with obtundation or coma depending on the extent of hemorrhage and presence or absence of hydrocephalus. AComA aneurysms are notoriously small, often rupturing at sizes smaller than those that would be considered a threshold for treatment. Therefore, advance symptoms are uncommon. When large or giant, AComA aneurysms can produce symptoms from mass effect on the optic apparatus (visual field deficits), hypothalamus (endocrine dysfunction), hydrocephalus (obstruction of the foramen of Monro), or frontal lobes (cognitive dysfunction, memory impairment, and seizure) [1, 2, 5].

According to the size aneurysms are divided in several groups: small aneurysms with the diameter less than 7 mm, medium aneurysm with the diameter between 7–14 mm, large aneurysms with the diameter from 15 to 24 mm and giant aneurysms bigger than 25 mm [1]. According to the morphology, AComA aneurysm can be saccular, fusiform, blister-like or extremely dysmorphic [1].

AComA was the vessel segment most commonly bearing a ruptured aneurysm, followed by the PComA and MCA bifurcation aneurysm. The occurrence of SAH secondary to the rupture of aneurysms was more frequent in the AComA and in the PComA than in the MCA bifurcation aneurysm. [8].

The majority of intracranial aneurysms do not rupture over time, but the risk is size dependent. In the International study of unruptured intracranial aneurysms, the 5-year cumulative risk of rupture was negligible for those measuring <7 mm. Whereas the risk was 2.6% and 14.5% for those sized 7–12 mm, located in the anterior and posterior circulation, respectively [9, 10, 11]. Large and giant aneurysms were associated with a very high risk of rupture [12].

The location of the aneurysm is also known to be an important risk factor for rupture of the aneurysms. The aneurysms most prone to rupture are located in the anterior communicating and posterior communicating arteries [12]. Middle cerebral artery aneurysms had the lowest rupture rate [1].

The mean size of ruptured aneurysms at the AComA were smaller than ruptured aneurysms located at other sites, but this difference was not statistically significant. However, of ruptured aneurysms smaller than 7 mm in diameter, aneurysms located at the AComA were most frequent, and this was statistically significant [10]. The optimal management of AComA aneurysms remains a challenge. Endovascular options are limited in this area, and surgical management is often required. They are the most complex aneurysms of the anterior circulation due to the angioarchitecture and flow dynamics of the AComA region, frequent anatomical variations, deep interhemispheric location, and danger of severing the perforators with ensuing neurologic deficits.

### **Surgical approach to the aneurysms**

The surgical treatment of AComA aneurysms started in 1936, Tonnis was the first to directly operated an AComA aneurysm. He used an intrahemispheric approach to expose an AComA aneurysm and pack it with muscle. In 1950, Elvidge and Feindel reported two cases in which they used a transfrontal approach to obliterate AComA aneurysms. The subfrontal approach described by Hamby and Falconer subsequently became the approach used most often for the treatment of AComA aneurysms, probably because the majority of neurosurgeons were already using it to access suprasellar lesions; however, premature rupture continued to affect outcome adversely. To avoid premature aneurysmal rupture, Kempe and Vander Ark described resection of the gyrus rectus in combination with the subfrontal approach to improve exposure. This approach allowed the fundus of the aneurysm to be left undisturbed while the aneurysm neck was exposed. Resection of the gyrus rectus in combination with the PT transsylvian approach was popularized by Yasargil and became the standard for the treatment for exposure of AComA aneurysms. This approach permits the aneurysm to be viewed in the same axis as the sylvian fissure, thereby improving the ability to dissect and apply clips while minimizing brain retraction [4, 5, 11].

Difficulties with surgical exposure, combined with the complex vascular anatomy of the AComA, result in a higher risk of postoperative complications compared with other anterior circulation sites. The difficulty of the surgical exposure varies with the orientation of the aneurysm and location of the AComA complex, being greatest for those aneurysms that point superiorly and higher within the interhemispheric fissure. In such cases, retraction may provide inadequate exposure. To overcome this problem, the gyrus rectus can be resected [4].

Being aware of the technical difficulties and potential morbidity of surgical adjuncts, many surgeons have proposed different approaches in attempts to decrease the surgical complication rates. There are four standard techniques (frontoorbitozygomatic, interhemispheric, transorbital and pterional) for treatment of AComA aneurysms [11]. Because of the anatomic limitations, these approaches chiefly included resection of the roof and lateral wall of the orbit, in efforts to provide surgeons with an unhindered approach to the AComA complex [3].

Moreover, AComA aneurysms are associated with the highest postoperative morbidity rates, primarily in terms of neuropsychological deficits, among all anterior circulation aneurysms [4]. Le Roux et al. reported that 5 to 25% of the cases of morbidity or death after SAH could be attributed to surgical complications. Complication rates were highest for AComA aneurysms in the anterior circulation and basilar bifurcation aneurysms in the posterior circulation. Parenchymal resection, which is sometimes required for exposure of AComA aneurysms with the classic pterional approach, was a negative factor affecting the outcomes of poor-grade patients with SAH [3].

In the study conducted by Hashemi et al. all the surgical mortality was 10%. French and colleagues reported a rate of surgical mortality of 4%, Hook and Norlen reported 7% mortality and Pool reported 7% mortality in his study [11, 12]. The results of our survey are similar to the majority of the surveys done in previous studies.

The limitations traditionally associated with AComA surgery, especially in the presence of acute SAH, include limited exposure and suboptimal observation of the AComA complex. The problem with the pterional approach is the axis of access to the AComA, which lies in the interhemispheric fissure, 5 to 10 mm above the cranial base; this approach usually requires gyrus rectus resection, extensive dissection of the sylvian fissure, and brain retraction. These necessary actions, which may be harmful to the brain, may be associated with increased surgical morbidity rates [3].

Andaluz et al. advocated an OPT approach for the treatment of AComA aneurysms. Using frameless stereotaxy, the angles of exposure and surgical field provided via the PT and OPT approaches were quantified. It was concluded that the OPT approach increases the angles of approach compared with the PT approach and might avoid resection of the gyrus rectus, although the OZ approach was not evaluated. Furthermore, the area of exposure was not quantified, and the relative effects of resecting the gyrus rectus were not examined [3].

### **CONCLUSION**

Each aneurysm is a unique combination of geometry, size, location and relationship with its surrounding vasculature. Based on both the current literature and our experience surgical clipping represents treatment of choice for the aneurysms of the anterior communicating artery. However, the treating physicians should consider all treatment options before the treatment decision, and the treatment modality should be made individually for each patient in a multidisciplinary fashion.

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## EVALUATION OF THE PHYSICAL TREATMENT AND REHABILITATION RESULTS IN PATIENTS WITH PERTROCHANTERIC FEMORAL FRACTURES

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### ABSTRACT

The increase in the average life span has made treatment of upper femoral fractures a major problem of modern surgery. Trochanteric fractures occur in population older than 65 years where osteoporosis, loss of bone mass, is characteristic. Non-surgical treatment methods are accompanied by a high mortality rate and do not offer satisfactory anatomical and functional results. Post-surgical physical therapy and rehabilitation are of great importance if the goal is a faster and more efficient recovery of the patient. This paper aims to demonstrate the results of physical therapy and rehabilitation at operatively treated pertrochanteric femoral fractures with dynamic hip screw (DHS); to compare the efficiency of both methods by using physical agents: magnetic therapy – low-frequency field and interferential currents.

**Method:** This paper represents a prospective randomized pilot study of 16 inpatients with operatively treated pertrochanteric femoral fractures with dynamic hip screw, DHS, at the Institute of Physical Medicine and Rehabilitation in Skopje. The patients were divided in two cohorts according to the treatment they received. The first cohort was treated with kinesitherapy and magnetic therapy, and the second cohort was treated with kinesitherapy and interferential currents. All patients were female, over 65 years of age. They were categorized according to several variables, such as: occupation, hand-side and manner of fracture occurrence, comorbidities, ability to walk on admission and discharge from the Institute, as well as the extent of hip joint and knee movement.

**Results:** The results were statistically processed using appropriate statistical methods. With respect to the objective variable of the extent of movement in the affected hip and the knee the following mean values were obtained: straight knee flexion  $p = 0.027$  on admission,  $p=0.25$  on discharge; bent knee flexion  $p=0.07$  on admission,  $p=0.058$  on discharge; extension  $p=0.25$  on admission,  $p=0.7$  on discharge; abduction  $p=0.04$  on admission and  $p=0.058$  on discharge; adduction  $p=0.09$  on admission,  $p=0.09$  on discharge; internal rotation  $p=0.024$  on admission,  $p=0.07$  on discharge; external rotation  $p=0.5$  on admission,  $p=0.67$  on discharge; knee flexion  $p=0.19$  on admission,  $p=0.2$  on discharge; and extension  $p=0.067$  on admission,  $p=0.96$  on discharge. A statistical significance in the extent of hip and knee movements between the two cohorts was not present in all the values.

**Conclusion:** The combination of physical agents and exercise in patients with operatively treated pertrochanteric femoral fractures with dynamic hip screw, DHS, stimulates osteogenesis, reduces pain, improves physical activity and the health-related quality of life. The results of this study are preliminary and they provide an initial insight into the efficiency of physical procedures and exercise in patients with. Due to the small sample the efficiency of these interventions should be further investigated.

**Key words:** pertrochanteric fracture, magnetic therapy, interferential currents, kinesitherapy

### INTRODUCTION

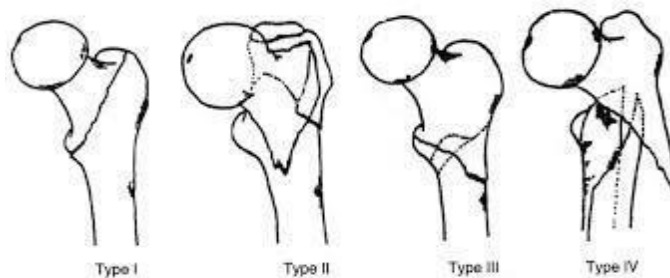
With the increase of the average life span, addressing upper femoral fractures has become a major problem of modern surgery. Pertrochanteric fractures are approximately four times more frequent than femoral neck fractures and they mostly occur in patients older than 65. This portion of the affected population is also suffering from osteoporosis. Women are more susceptible to these types of fractures. Since patients are often elderly individuals, 2/3 of them have other comorbidities, such as: vascular, respiratory, endocrine, and other diseases. The injury complicates the existing states which results in a higher mortality rate.

After Kyle's classification pertrochanteric femoral fractures are divided into four groups:

Kyle Classification of Intertrochanteric Femoral Fractures		
Type	Stability	Description
I	Stable	2-part, no comminution
II		3-part, minimal comminution
III	Unstable	4-part, large posteromedial comminuted area
IV		subtrochanteric extension, highly unstable

**Fig. 1.** Kyle's classification of pertrochanteric femoral fractures

Following this classification, stable (I and Type II) is operated with the fixation of the femur with DHS (dynamic hip screw), while unstable pertrochanteric fractures (III and type IV) resolved with the fixation of the femur with the PFN (proximal femur nail)



**Fig. 2.** Schematic representation of Kyle's classification of pertrochanteric fractures

Non-surgical treatment methods are accompanied by a high mortality rate and do not provide satisfactory anatomical and functional results. The surgical treatment offers a significant reduction in mortality rate compared to the non-surgical treatment methods with a reduced degree of complications and satisfactory functional results.

Surgical treatment with dynamic implants is a method of choice when it comes to fixation of pertrochanteric fractures. The dynamic implants enable dynamization and compression of the fracture in the axis of the neck and the femoral diaphysis. This reduces the incidence of mechanical complications, and at the same time allows for an efficient fracture healing, early activation, and mobilization of the injured limb [1]

Physical therapy and rehabilitation play a major role in the postoperative period and they stimulate osteogenesis, i.e. callus creation, they also improve the muscle trophics, establish the function of the affected joint, and enable the patient to return to their prefracture functional state faster and more efficiently which in turn improves mobility and health-related quality of life. The physical therapy consists of kinesitherapy and physical agents [2].

Physical agents that stimulate osteogenesis are magnetic therapy (low-frequency pulsed electromagnetic field - PEMF) and electrotherapy (interferential currents IF with a constant frequency of 100Xs). There is a limited number of studies on the efficiency of physical procedures as treatment methods for stimulating osteogenesis in patients with femoral fractures [2].

There was a prospective randomized clinical study on 90 patients with wrist fractures treated with conventional methods, divided in three cohorts: the first cohort was treated with a low-frequency pulsed electromagnetic field, the second cohort was treated with interferential currents, and the third cohort was treated with both physical therapy methods. Best results, considering all the variables, were obtained in the third cohort [2].

Multiple studies show the role of kinesitherapy in osteogenesis stimulation, improved strength, muscle flexibility and coordination, improved posture, balance, and thereby improved functional status, reduced pain, and prevention of falls and risks of future fractures.

In a randomized controlled trial of proximal femoral fracture patients, 40 patients were treated with high-intensity quadriceps training and 40 patients were treated with standard physiotherapy alone. The training group exercised twice weekly, with six sets of 12 repetitions of knee extension (both legs), progressing up to 80% of their one-repetition maximum. The results after six weeks (at the end of the intervention) were better in the training group and at sixteen weeks significant benefits were maintained for the same group. It can be concluded that a progressive high-intensity quadriceps training in elderly proximal femoral fracture patients increased leg power and reduced disability [3].

However, there is a lack of randomized controlled trials on physical therapy protocols; the number of studies investigating specific types of exercise especially in femoral fracture patients is also limited.

### **OBJECTIVE**

To demonstrate the results from physical therapy and rehabilitation in DHS surgically treated pertrochanteric femoral fracture patients. To compare the efficiency of both methods by using physical agents: low-frequency pulsed electromagnetic field – magnetic therapy and interferential currents.

### **HYPOTHESIS**

Petrochanteric femoral fractures are serious lesions whose functional outcome is independent in a certain number of patients. Surgical treatment of these fractures is the best alternative, but it depends on the type of applied fixation, for the final results are not always satisfactory. Therefore, results will be analyzed in order to obtain a more objective assessment of the positive and negative aspects of the chosen treatment method. The evaluation should clearly point to the advantages of a certain method as a rational and logical approach in the pertrochanteric fracture treatment. Osteogenesis stimulation, muscle mass improvement, returning to prefracture functional state, will all result in an improved physical functioning that improves the quality of life in pertrochanteric fracture patients.

### **MATERIAL AND METHODS**

A randomized prospective clinical pilot study including 16 female patients which were monitored and treated postoperatively at the Institute of Physical Medicine and Rehabilitation in Skopje in a period of 4 weeks. All the patients had a DHS surgical treatment of their pertrochanteric femoral fractures.

Eligibility criteria were: female patients with surgically treated pertrochanteric fractures; female patients with a DHS surgical treatment and female patients older than 65.

Ineligibility criteria were: female patients with femoral neck fractures; female patients with pertrochanteric fracture treated with a surgical method other than DHS; female patients with pathological femoral fractures and female patients younger than 65

The patients were divided in two cohorts:

1. First cohort consisted of a total of 8 patients treated with kinesitherapy (exercise) and magnetic therapy
2. Second cohort consisted of a total of 8 patients treated with kinesitherapy (exercise) and interferential currents

The osteogenesis stimulation was conducted with physical therapy such as: magnetic therapy, low-frequency pulsed electromagnetic field with 8mT 25Hz intensity in a period of 20 minutes/15 treatments and interferential currents with a constant frequency of 100Hz in a period of 20 minutes/15 treatments.

Kinesitherapy consisted of a progressive exercise program for the lower extremities: strengthening of the quadriceps in both the injured and the healthy leg, strengthening the hamstrings, starting with isometric followed by isotonic exercise, exercise such as assisted walking or walking with an assistive device. The exercises were performed in a supine position with the help of a physiotherapist. Isometric exercises were initiated on the second day after surgery, and the process of verticalization of patients commenced 5-7 days post-surgery; assisted in the beginning, depending on the patient condition – with a walker or crutches.

The physiotherapist instructed the patient to properly perform each individual movement during the entire rehabilitation period and encouraged them to cooperate.

The physical therapy and the general health condition of the patients were monitored by a physical medicine and rehabilitation specialist. Patients were advised on the role and importance of exercise in the pathogenesis of their condition. This perpetuated the patients' will to cooperate and was necessary in order to keep the patients exercising once they were home.

At the beginning of the study data such as age, occupation, hand-side of the fracture, smoking status, comorbidities, manner of fracture occurrence, manner of walking on admission and discharge, range of movements in the treated hip and the knee of the fractured leg on admission and on discharge, were collected.

The assessment of the range of movements was performed with a protractor and a measuring tape in supine position on both lower extremities on admission and on discharge. Results were recorded on special forms.

### STATISTICAL ANALYSIS

A data-base in SPSS for Windows was created for the statistical data processing. Category variables are presented with absolute and relative numbers.

The continuous variables are presented with mean values (median), minimal and maximal values of 25 and 75 percentiles.

The significance of the difference was tested using a Mann-Whitney U Test. Significance level of  $p < 0.05$  was considered statistically significant.

### RESULTS

The pilot study results showed that there was no difference regarding the occupation variable in both cohorts. In the first group (exercise + MT) 6 (75%) patients were retired, while 2 (25%) patients were housewives. In the second cohort (exercise + IF) 7 (87.5%) patients were retired, and 1 (12.5%) patient was a housewife.

The hand-side of the fracture variable was equally distributed in both cohorts, 4 (50%) patients had a right hand-side fracture and 4 (50%) patients had a left hand-side fracture.

The smoking status was not a significant risk factor in fracture occurrence, because patients in both cohorts were predominantly nonsmokers: 7 (87.5%) nonsmokers and 1 (12.5%) smoker in the first cohort; 6 (75%) nonsmokers and 2 (25%) smokers in the second cohort.

With respect to comorbidities characteristic of the elderly, there were: 8 and 7 patients with hypertension in the first and second cohort, respectively; one patient in each cohort had an established osteoporosis with densitometry; 1 and 2 patients in the first and second cohort, respectively, have had previous surgical treatments. Three and 2 patients in the first and second cohort, respectively, have had previous fractures (treated surgically or conventionally). Two patients in the first cohort had a cerebrovascular insult as the underlying condition with the femoral fracture as a consequence. There were no such patients in the second cohort. One patient in the first and 2 patients in the second cohort had diabetes mellitus.

The mechanics of fracture occurrence was the same in all the patients – falling. Seven (87.5%) patients in the first cohort and 5 (62.5%) patients in the second cohort fell from standing; 1 (12.5%) patient in the first cohort and 2 (25%) patients in the second cohort slipped on a wet floor; while only 1 (12.5%) patient fell from an armchair.

The functional status of the patients on admission was as follows: in the first cohort 5 (62.5%) patients used a walker and 3 (37.5%) patients used crutches; while in the second cohort 5 (62.5%) patients used a walker, 2 (25%) patients used crutches, and 1 (12.5%) patient couldn't walk.

On discharge 4 (50%) and 5 (62.5%) patients of the first and second cohort, respectively, used a walker, while 4 (50%) and 3 (37.5%) patients from the first and second cohort, respectively, used crutches.

**Table 1.** Range of hip movement on admission and on discharge

Movement	Cohort	min-max	25%	Median	75%	p-value
Straight knee flexion / admission	exercise+MT	50 - 80	70	77.5	80	p=0.027
	exercise+IF	0 - 80	15	55	67.5	Z=2.2
Straight knee flexion / discharge	exercise+MT	75 - 85	77.5	80	80	p=0.25
	exercise+IF	0 - 85	22.5	65	80	Z=1.15
Bent knee flexion / admission	exercise+MT	60 - 100	85	90	95	p=0.07
	exercise+IF	0 - 100	47.5	70	85	Z=1.78
Bent knee flexion / discharge	exercise+MT	90 - 110	95	100	100	p=0.058
	exercise+IF	0 - 100	55	80	97.5	Z=1.89
Extension / admission	exercise+MT	-5 - 10	0	0	5	p=0.25
	exercise+IF	-5 - 10	-5	0	0	Z=1.15
Extension / discharge	exercise+MT	0 - 15	0	0	7.5	p=0.7
	exercise+IF	-5 - 10	0	0	7.5	Z=0.37
Abduction / admission	exercise+MT	10 - 40	20	22.5	40	p=0.04
	exercise+IF	5 - 25	10	15	20	Z=2.05



<b>Abduction / discharge</b>	exercise+ <b>MT</b>	20 - 40	22.5	25	40	p=0.058
	exercise+ <b>IF</b>	10 - 30	15	20	25	Z=1.89
<b>Adduction / admission</b>	exercise+ <b>MT</b>	5 - 30	10	15	30	p=0.09
	exercise+ <b>IF</b>	0 - 15	7.5	10	12.5	Z=1.68
<b>Adduction / discharge</b>	exercise+ <b>MT</b>	10 - 30	12.5	20	30	p=0.09
	exercise+ <b>IF</b>	5 - 25	10	10	20	Z=1.68
<b>Internal rotation / admission</b>	exercise+ <b>MT</b>	10 - 35	15	17.5	20	p=0.024
	exercise+ <b>IF</b>	0 - 20	10	10	12.5	Z=2.26
<b>Internal rotation / discharge</b>	exercise+ <b>MT</b>	15 - 40	15	17.5	22.5	p=0.07
	exercise+ <b>IF</b>	0 - 30	10	15	15	Z=1.78
<b>External rotation / admission</b>	exercise+ <b>MT</b>	5 - 30	10	10	10	p=0.5
	exercise+ <b>IF</b>	5 - 30	10	10	15	Z=0.6
<b>External rotation / discharge</b>	exercise+ <b>MT</b>	10 - 35	10	10	15	p=0.67
	exercise+ <b>IF</b>	5 - 30	10	15	15	Z=0.42

The mean values for bent knee flexion, which implies a greater range of movements, were 90 and 70, for the first and second cohort, respectively, with  $p=0.07$  and  $Z=1.78$ . Mean values on discharge were 100 and 80 in the first and second cohort, respectively, with  $p=0.058$  and  $Z=1.89$ .

With respect to the extension of the operated hip, the mean value on admission was 0 for both cohorts, with  $p=0.25$  and  $Z=1.15$ . On discharge the mean value was 0 for both cohorts, with  $p=0.7$  and  $Z=0.37$ .

In abduction on admission mean value in the first cohort was 22.5 and 15 in the second cohort, with  $p=0.04$  and  $Z=2.05$ . On discharge the mean value in the first cohort was 20, and 15 in the second cohort,  $p=0.09$  and  $Z=1.68$ .

Adduction of the operated hip on admission had a mean value of 15 and 10 in the first and second cohort, respectively, while on discharge the mean value was 20 and 10 for the first and second cohort, respectively, and  $p=0.09$  and  $Z=1.68$ .

The table also shows values for internal and external rotation of the operated hip. Mean values on admission for internal rotation were 17.5 and 10 in the first and second cohort, respectively, with  $p=0.024$  and  $Z=2.26$ ; and on discharge the mean values were 17.5 and 15 in the first and second cohort, respectively, with  $p=0.07$  and  $Z=1.78$ . Mean values on admission for external rotation were 10 for both cohorts, with  $p=0.5$  and  $Z=0.6$ ; and on discharge 10 and 15 for the first and second cohort, respectively, with  $p=0.67$  and  $Z=0.42$ .

Considering the above there is no significant difference in values between the two cohorts on admission and on discharge, except for a small significance in the straight knee flexion values on admission.

**Table 2.** Operated leg knee values on admission and on discharge

<b>Movement</b>	<b>Cohort</b>	<b>min-max</b>	<b>25%</b>	<b>Median</b>	<b>75%</b>	<b>p-value</b>
<b>Knee flexion / admission</b>	exercise+ <b>MT</b>	90 - 120	95	107.5	117.5	p=0.19
	exercise+ <b>IF</b>	30 - 120	90	97.5	102.5	Z=1.31
<b>Knee flexion / discharge</b>	exercise+ <b>MT</b>	100 - 120	100	110	117.5	p=0.2
	exercise+ <b>IF</b>	40 - 120	97.5	100	110	Z=1.26
<b>Knee extension / admission</b>	exercise+ <b>MT</b>	-10 - 0	0	0	0	p=0.67
	exercise+ <b>IF</b>	-10 - 0	-5	0	0	Z=0.42
<b>Knee extension / discharge</b>	exercise+ <b>MT</b>	-5 - 0	0	0	0	p=0.96
	exercise+ <b>IF</b>	-10 - 0	0	0	0	Z=0.06

Table 2 shows operated leg knee flexion values on admission with a mean of 107.5 and 97.5 for the first and second cohort, respectively, and  $p=0.19$  and  $Z=1.31$ ; the mean values on discharge were 110 and 100 for the first and second cohort, respectively, with  $p=0.2$  and  $Z=1.26$ .

Mean values of 0 were recorded in both cohorts regarding knee extension on admission with  $p=0.67$  and  $Z=0.42$ ; while the mean value on discharge was 0 for both cohorts with  $p=0.96$  and  $Z=0.06$ .

The results show an insignificant difference between the two cohorts with respect to mean values on admission vs. discharge.

**Table 3.** Individual knee and hip movement values

Movement	Cohort	Admission				Discharge			
		°	min. (N/%)	°	max. N/%	°	min	°	max
Straight knee flexion	exercise+MT	0	0	80	4(50%)	0	0	85	1/12.5%
	exercise+IF		1/12.5%		1/12.5%				1/12.5%
Bent knee flexion	exercise+MT	0	0	100	1/12.5%		0	110	1/12.5%
	exercise+IF		1/12.5%		1/12.5%				1/12.5%
Extension	exercise+MT	-5	1/12.5%	10	1/12.5%	-5	0	15	1/12.5%
	exercise+IF		3/37.5%		1/12.5%				1/12.5%
Abduction	exercise+MT	5	0	40	3/37.5%	10	0	40	3/37.5%
	exercise+IF		1/12.5%		0				1/12.5%
Adduction	exercise+MT	0	0	30	3/37.5%	5	0	30	3/37.5%
	exercise+IF		1/12.5%		0				1/12.5%
Internal rotation	exercise+MT	0	0	35	1/12.5%	0	0	40	1/12.5%
	exercise+IF		1/12.5%		0				1/12.5%
External rotation	exercise+MT	5	1/12.5%	30	1/12.5%	5	0	35	1/12.5%
	exercise+IF		1/12.5%		1/12.5%				1/12.5%
Knee flexion	exercise+MT	30	0	120	2/25%	40	0	120	2/25%
	exercise+IF		1/12.5%		1/12.5%				1/12.5%
Knee extension	exercise+MT	-	1/12.5%	0	7/87.5%	-	0	0	7/87.5%
	exercise+IF	10	2/25%		6/75%				1/12.5%

Table 3 shows that there were no patients with a minimum movement of 0 degrees on admission in the first cohort, while in the second cohort there was 1 (12.5%) such patient. A maximum movement of 80 degrees was recorded in 4 (50%) patients in the first cohort as opposed to only 1 (12.5%) such patient in the second cohort. There was an improvement in the range of movement on discharge, and there was 1 (12.5%) patient in each cohort with a maximum movement range of 85 degrees.

There was also an improvement in the bent knee flexion variable with 0 patients with a minimum movement of 0 degrees in the first cohort and 1 (12.5%) such patient in the second cohort on admission, while a maximum movement range of 100 degrees was recorded in 1 (12.5%) patient in each cohort. On discharge there was an improvement regarding maximum movement range of 110 degrees in 1 (12.5%) patient in the first cohort.

There was a 10 degrees improvement in the extension variable. In the first and second cohort, respectively, there were 1 (12.5%) and 3 (37.5%) patients with a minimum of -5 degrees on admission. On discharge there were 0 and 1 (12.5%) patients, respectively, from the first and second cohort with a minimum of -5 degrees. There were 1 and 0 patients in the first and second cohort, respectively, with a maximum flexion of 15 degrees.

With respect to the abduction and the adduction the difference was not significant except in the minimum movements, so only the minimum values were increased – the 5 degrees abduction on admission rose to 10 degrees on discharge, and a 0 degrees adduction on admission turned to a 5 degrees adduction on discharge in only 1 (12.5%) patient per cohort.

In the internal and external rotation there was an improvement in the maximum movements on admission and on discharge.

The table clearly shows improvement in knee movements such as flexion and extension, with respect to individual values of the minimum and maximum movements in all patients on admission and on discharge.

## **DISCUSSION**

The global ageing of the population increases the risk of fractures. Osteoporosis is one of the major causes, with compression fractures being most prevalent, followed by femoral and wrist fractures. The fractures of the proximal femur have become more common and along with femoral neck fractures represent the most common types of femoral fractures [4]. Their treatment is predominantly surgical with implantation of osteosynthetic material.

There are many studies comparing the two methods but it is confirmed that the DHS fixation of pertrochanteric fractures provides much better results in relation to Gamma nail treatment, both in terms of postoperative complications, re-operation rate, and the ability to walk independently 6 months following surgery [5].

Proximal fracture of the femur is the main cause of morbidity and mortality in the elderly. Its global incidence should increase from 1.7 million people in 1990 to about 6.3 million in 2050. Mortality is estimated at 24% up to 12 months after the hip fracture. Moreover, a significant number of these patients do not return to the prefracture functional state. A year after surgery, less than 50% of the survivors can walk unassisted and only 40% can perform every day activities independently [6].

With reduced muscle strength these individuals tend to present a decrease in the postoperative walking capacity, which makes them vulnerable to further falls and to the risk of sustaining a contralateral hip fracture. The odds of a new fracture are six to twenty times higher than the initial fracture within the first year of recovery [7].

Knowing this, the goal of physical therapy in the postoperative treatment of patients with a proximal femoral fracture is to increase muscle strength, and to improve walking safety and efficiency, thus enabling the elderly patient to become more independent.

To ensure a safe start for physical therapy it is extremely important for the professional to know the type of fracture, as well as the material used for surgical fixation. These data will interfere in the conduct, which includes walking time, weight bearing on the limb, and restrictions in some movements.

It is of crucial importance, regardless of the type of fracture and material used for fixation, for the patients to walk as early as possible to avoid respiratory complications and other complications inherent to immobility, but this is sometimes not possible due to the patient's general state of health. In a study conducted in a hospital ward where the patients were divided in two cohorts, one for early walking and the other for late walking, the professionals found evidence that cardiovascular stability is one of the main determinants of success of early walking after hip fracture surgery and this early gait was determinant for an increase of the subjects' functionality [8].

It is estimated that in 12 months following a hip fracture, the patient presents a loss of 6% of the lean body mass. A study conducted with 90 elderly individuals tested a 6-month intensive rehabilitation program compared with a control group that performed exercises of lower intensity and besides increasing the muscle strength of the patients from the intervention group, the program also increased gait speed, balance, and ADL performance [7].

Another similar study resulted in an increase in gait speed in the group of higher exercise intensity, yet only in patients with cognitive deficit. This shows that besides the physical benefits, strength exercises can also produce advantages in the psychosocial area, which is often altered in the elderly individual who was sustained a fracture and that can be one of the causes of low physical function in the post-trauma period [9].

Another study indicated that in 83% of the participants the fractured leg appeared weaker. This deficit of strength and asymmetric muscle power can complicate the transfer of weight during the stance phase of gait where only one leg is sustaining the body weight, generating a mainly lateral imbalance, where the highest rate of falls is reported [10].

Pain, a factor of crucial importance that can influence the treatment, should also be taken into account. This can delay recovery, and the high level of pain in the postoperative period has been associated with a longer hospitalization time, reduced adhesion to physiotherapy treatment protocols, and reduced walking capacity up to three days after the procedure. In a study with Transcutaneous Electrical Nerve Stimulation (TENS), pain decreased and functionality improved significantly [11].

Studies have demonstrated that patients with a hip fracture, who have taken part in some type of physical therapy, tend to recover their physical function and quality of life faster than the control group. As seen above, there are various plausible categories and techniques of physical therapy in the treatment of a patient with this type of fracture. Rehabilitation can be done at home or in a clinic, with the use of manual techniques, strengthening, proprioception, gait or ADL training, motor stimulation apparatuses and analgesia, among others. There is a high rate of therapy abandonment by elderly patients, due the intensity of the exercises that sometimes become intolerable or demotivating; the limited mobility, whether caused by physical or cognitive factors, and other comorbidities also end up interfering in the treatment frequency [3].

The difficult follow-up of elderly patients, cited by various articles, hinders research in this area, as it reduces the sample number, thus impairing the reliability of the study.

The literature does not feature a specific and detailed physical therapy treatment for elderly patients in the postoperative period of proximal femoral fractures. There is a tendency for strengthening exercises to be the key to the functional improvement of these patients. The evidence shows that physical therapy tends to accelerate the recovery of elderly patients, but their return to prefracture functional state is not yet guaranteed.

### CONCLUSION

Data presented are merely the preliminary results of this paper and they have not demonstrated significant differences between the two cohorts. There is, however, a marked improvement in the results related to hip and knee values in the operated limb as a result of the physical therapy and rehabilitation treatments. Kinesitherapy produces results and there is a need of further investigation. These results, although preliminary, point to the importance of physical therapy in the postoperative period and its impact on the HRQoL, indicating this type of therapy as a more efficient manner of restoring patient's condition as it was prior to the fracture.

In our country, and in general, there are but a few papers assessing the HRQoL in the postoperative period in trauma and orthopedic patients. This is why we need to continue research and work on this issue.

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## OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH OVERWEIGHT AND OBESITY

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### ABSTRACT

Overweight and obesity is more common in the population, and represents a risk factor for obstructive sleep apnea (OSA).

The aim of the study was to obtain data on the occurrence of obstructive sleep apnea in Macedonia since there are no official statistics related to this issue and to examine its association with overweight and obesity.

The study included 200 patients with minimum positive 2 of 3 OSA symptoms that included snoring, witnessed apnea and daytime sleepiness. Body mass index (BMI) was calculated and patients were divided into groups according to BMI. After that all patients underwent polysomnography (PSG). After PSG all patients were divided into groups according to severity of OSA based on respiratory disturbance index (RDI). All patients with RDI over 5 were diagnosed with OSA.

According to BMI, 21 patients were with normal weight, 99 patients were overweight and 80 patients were obese. According to severity of OSA, 17 were with mild OSA with RDI between 5-15, 44 with moderate OSA with RDI between 15-30, and 80 patients were with severe OSA with RDI>30. Comparing the groups we came to the conclusion that with the increase of BMI, RDI was increasing too. Appearance of severe OSA showed a clinically significant difference in obese patients compared to normal and overweight patients. On the other hand, there was no significant difference in the severity of OSA in overweight patients. OSA was rarely seen in patients with normal weight.

Gaining weight increases the risk of OSA. BMI is perhaps simple but important predictor of OSA development, especially the severe form.

**Keywords:** BMI, RDI, obesity

### INTRODUCTION

Obstructive sleep apnea (OSA) is a common chronic disorder affecting about 2–4% of the adult population, with the highest prevalence reported among middle-aged men [1]. Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial and complete airway obstructions during sleep with repetitive apneas and hypopneas [2]. The obstructive events (apneas or hypopneas) cause a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened [3]. OSA is often closely associated with other conditions which are recognized causes of morbidity and mortality such as obesity, metabolic syndrome, atherosclerosis, systemic inflammation, insulin resistance and type 2 diabetes mellitus [4, 5]. It has been reported that untreated OSA may shorten the lifespan of patients by up to 20 years [6]. Risk factors include snoring, male gender, middle age, menopause in women, obesity and a variety of craniofacial and oropharyngeal features such as a large neck circumference, retro- or micrognathia, nasal obstruction, enlarged tonsils/adenoids, macroglossia and low-lying soft palate [7]. On the other hand, modern society is currently faced with a serious global obesity epidemic. Recent estimates suggest that 60% of the adult population in industrialized countries is overweight ( $BMI \geq 25 \text{ kg/m}^2$ ) and at least 30% is obese ( $BMI \geq 30 \text{ kg/m}^2$ ) [8]. Obesity is a potent risk factor for the development and progression of sleep apnea. There is a consistent relationship between obesity and OSA, with a body mass index ( $BMI \geq 30 \text{ kg/m}^2$ ) having been reported in 60-90% of OSA patients. As the prevalence of obesity increases, there is likely to be a parallel increase in the prevalence of OSA. The prevalence of OSA in the adult population is estimated to be about 25%, rising to 45% in obese individuals [9].

The aim of the study was to obtain data on the occurrence of obstructive sleep apnea in Macedonia since there are no official statistics related to this issue and to examine its association with overweight and obesity.

### METHODS

The study included 200 patients and was conducted at the University Clinic of Pulmology and Allergy in Skopje. Inclusion criteria were positive 2 of 3 clinical symptoms for OSA. The symptoms were snoring, witnessed apnea and daytime sleepiness. Body mass index (BMI) was calculated and patients were divided into groups according to BMI. Patients with BMI from 18.5 to 25 were normal weight patients. Patients with BMI 25>30 were overweight, and with BMI>30 were obese patients. All patients underwent polysomnography. In this study we used polysomnograph Respirationix, model Alice 5.

All results from polysomnography were scored manually according to standard criteria. Apnea, hypoapnea and arousals were also identified according to standard criteria and summarized in the form of a respiratory disturbance index (RDI). All patients with RDI below 5 were diagnosed as negative, patients with RDI 5>15 were diagnosed as having mild OSA, patients with RDI 15>30 as moderate OSA, and patients with RDI>30 were diagnosed as severe OSA.

**RESULTS**

The study included 200 patients of whom 51 were females with an average age of 49 ± 9 years and 149 were men with an average age of 47 ± 9 years. There were no significant clinical differences in age groups with BMI and RDI, but there was a difference in the occurrence of OSA in men versus women. A total of 109 (73.2%) male patients were diagnosed with OSA, and 31 (62.8%) of female patients. According to BMI, patients were divided into 5 groups (Table 1). There were no patients with BMI <18.5, 21 patients were with normal BMI, while 99 (49.5%) patients were overweight and 80 (40%) patients were obese.

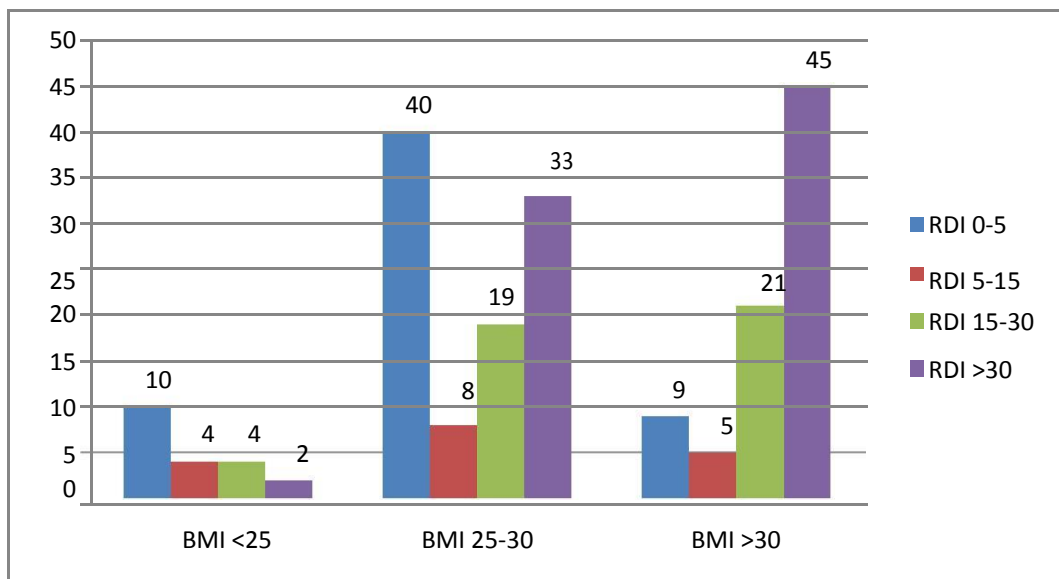
**Table 1.** Patients stratified by BMI

BMI (Kg/m <sup>2</sup> )	Number of patients
<18.5	0 (0%)
18.5-24.99	21 (10.5%)
25-29.99	99 (49.5%)
30-34.99	56 (28%)
35-39.99	20 (10%)
40>	4 (2%)

According to RDI, 59 (29.5%) patients were RDI < 5, or negative patients. 141 patient were diagnosed with OSA, of whom 17 (8.5 %) patients were RDI 5> 15, 44 (22%) patients were RDI 15 > 30, 80 (40%) patients were with RDI > 30 (Table 2).

**Table 2.** Patients stratified by RDI

RDI 0>5	59 (29.5%)
RDI 5>15	17 (8.5%)
RDI 15>30	44 (22%)
RDI >30	80 (40%)



**Fig. 1.** Diagnosis of OSA in relation to BMI

Patients with BMI <25 had the lowest chance to be OSA positive. The emergence of severe OSA significantly increases with increasing BMI. In overweight patients there was no significant difference in the occurrence of OSA.

**Table 3.** Comparison between RDI groups according to BMI

Groups	RDI	BMI
		X ± SD
1	1-4.99	27.44 ± 2.98 <sup>a, b</sup>
2	5-14.99	28.05 ± 3.70 <sup>c</sup>
3	15-29.99	29.64 ± 4.12 <sup>a, d</sup>
4	> 30	31.92 ± 4.23 <sup>b, c, d</sup>

(a), p=0.022; (b), p=0.000; (c), p=0.001; (d), p=0.009

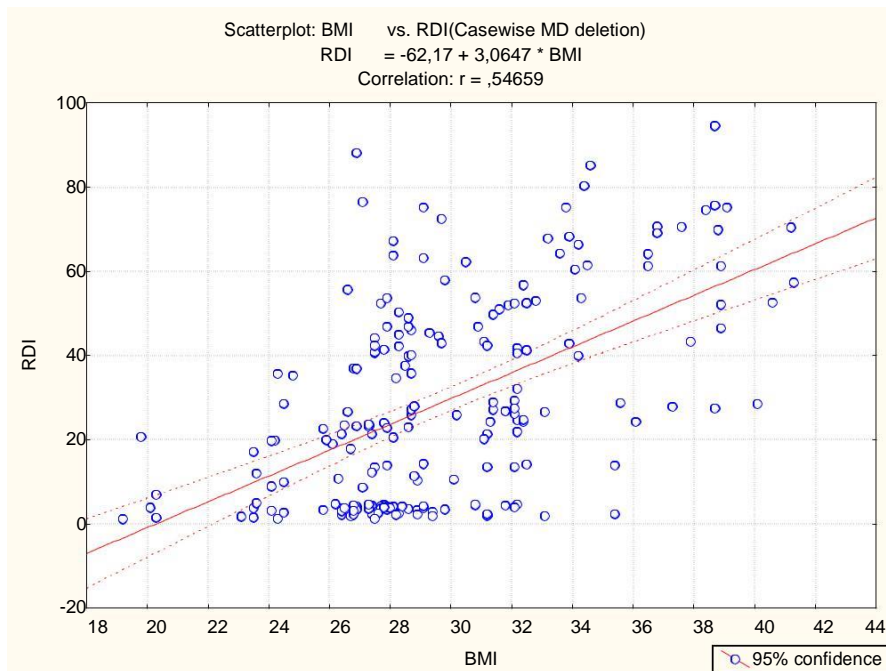
Patients who were OSA negative, had statistically significant lower BMI compared to patients with moderate and severe OSA. Patients with mild and moderate OSA had statistically significant lower BMI compared to those with severe OSA.

**Table 4.** Comparison between BMI groups according to RDI

Groups	BMI	RDI
		X ± SD
1	18.5-24.9	11.38 ± 11.26 <sup>a, c</sup>
2	25-29.9	23.15 ± 21.74 <sup>b, d</sup>
3	30-34.9	36.07 ± 21.97 <sup>a, b</sup>
4	35-40	48.50 ± 8.63 <sup>c, d</sup>
5	> 40	44.50 ± 3.90

(a), p=0.002; (b), p=0.012; (c), p=0.000; (d), p=0.000

There was no significant difference in RDI among patients with normal weight and overweight. But with BMI increasing, we found parallel RDI increase. Patients with normal weight and overweight had a significantly smaller RDI compared to obese patients. Statistical comparison with patients with BMI>40 was not made, because the number of patients in that group was very small.



**Fig. 2.** Correlation between BMI and RDI

Correlation was found between BMI and RDI (r = 0.546, p = 0.000). With the increase of BMI there was a detectable increase in RDI.

## DISCUSSION

Several risk factors, including obesity, male sex, age, and heritable factors, have been associated with an increased prevalence of obstructive sleep apnea in the general population [1]. OSA is primarily regarded as a male disorder. In our study 149 patients were male and 109 (73.2%) were OSA positive. 51 patients were female, and 32 (62.8%) of them were OSA positive. Also, in our study we male patients predominated, which is in agreement with the, as well as a higher percentage of female positive OSA patients. Our results were similar to those reported by Franklin KA et al, who concluded that OSA occurred in 50% of females aged 20–70 yrs [10]. However, the number of female patients in our study was small. The average age of female patients was  $49 \pm 9$  years and the average age of male patients was  $47 \pm 9$  years.

We found no significant statistical age difference in patients with different BMI and RDI. Obesity is one of the strongest sleep apnea risk factors [11, 12, 13, 14]. Furthermore, recent estimates suggest that 60% of the adult population in industrialized countries is overweight ( $BMI \geq 25 \text{ kg/m}^2$ ) and at least 30% is obese ( $BMI \geq 30 \text{ kg/m}^2$ ) [8]. In our study we got even greater percentage of patients with obesity compared to global estimates. From 200 patients who came to our clinic with suspicion of OSA, only 10.5% had normal BMI. A high percentage of 49.5% of all patients were overweight ( $BMI \geq 25 \text{ kg/m}^2$ ), and 40% of patients were obese with  $BMI \geq 30 \text{ kg/m}^2$ . Seventy percents of patients who were referred to the Clinic were diagnosed with OSA.

Half of the normal weight patients were negative for OSA. This frequency of OSA in normal weight patients was significantly lower than in overweight and obese subjects. This is consistent with findings reported in the literature, since obesity is the principal risk factor for OSA [15, 16, 17]. In the overweight group, 40% did not have OSA, and most of the diagnosed positive patients had severe OSA. The best prevalence estimates of OSA in the general population are derived from six large studies conducted worldwide.

These studies suggest that approximately 25% of adults with a BMI between  $25 \text{ kg/m}^2$  and  $28 \text{ kg/m}^2$  have at least mild OSA [1, 15, 18, 19, 20, 21]. In our study only 8% of overweight patients had mild OSA, but because we included patients with clinical symptoms of OSA, 52% of patients had moderate to severe OSA. Nevertheless, we found no clinically significant differences in patients with normal weight and overweight patients who were negative or had mild OSA. But there was a significant difference in the severe form of OSA.

There might be other factors for occurrence of severe OSA in normal and overweight patients. Namyslowski et al. observed no significant relationship between BMI and sleep study parameters (RDI, apnea index, hypopnea index and desaturation index) in overweight patients [22]. Similar results have been presented by Pillar who observed a significant correlation between BMI and AHI in the large population of patients referred to sleep laboratory. This correlation was moderate and weakened when the group was restricted to cases with only overweight patients [23]. In the obese group most patients were with severe OSA, with significant differences in severity of OSA in the groups with normal and overweight patients. This implies that as BMI increases, the severity of OSA also increases, being most severe in the more obese patients.

This data is consistent with a large number of other studies in the literature. In the study by Namyslowski et al. which compared sleep parameters between overweight and obese patients, a significant relationship was found between the increase in BMI and sleep parameters in obese subjects only, but not in overweight patients [22]. On the other hand, Akita et al. observed no significant correlation between BMI and either AHI or desaturation rate in obese patients. There was only a tendency for the increase of AHI together with the increase in BMI [24]. Vgontzas found in a group of 250 obese men and women that only 50% of men and 8.5% of women had AHI more than 30 during the night.

There was no difference in mean BMI in the group with and without apnea [25]. In severe obesity ( $BMI > 40 \text{ kg/m}^2$ ), the prevalence of sleep apnea was estimated to vary between 40 and 90% [26, 27, 28, 29, 30]. In our study there were 4 patients with  $BMI > 40$  and all 4 patients were diagnosed with severe OSA, but they did not have very high RDI as some patients with lower BMI. Probably severe obesity leads to OSA, but maybe severe obesity does not play such a big role in the severity of OSA. However, our study included a small number of patients and for obtaining better results we need a larger sample.

## CONCLUSION

Obesity is a potent risk factor for the development and progression of sleep apnea. Gaining weight increases the risk of OSA. BMI is perhaps simple but important predictor of OSA in the group of obese patients. There seems to be no correlation between overweight patients and RDI.



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**ANABOLICS ABUSE AND CARDIOMYOPATHY IN A BODYBUILDER: A CASE REPORT**

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Medical Faculty, University —Ss. Cyril and Methodius of Skopje—, Macedonia

**Background:** The abuse of anabolic steroids is an important issue in the bodybuilding community. Their adverse effects, including cardiovascular and hepatic toxicity are expected to rise in the following years.

**Case presentation:** A 39 years old male bodybuilder with a three year history of anabolic steroid abuse was admitted to the Intensive-Care Unit. The patient used massive doses of methandrostenolone, stanozolol and oxymetholone orally and nandrolone decanoate, testosterone enanthate and trenbolone enanthate intramuscularly. The patient experienced malaise, fatigue and decreased exercise tolerance three weeks prior to admission. His condition deteriorated and he subsequently developed anorexia and exercise induced breathlessness. On admission the blood pressure was 90/60 mmHg and the heart rate 100 bpm. The patient had generalized jaundice and an enlarged tender liver, but no signs of hepatic encephalopathy or chronic liver disease. Auscultation showed clear lung fields, but distant heart sounds. Total bilirubin, AST and ALT levels were dramatically increased. Free testosterone and delta 4-androstenedione concentrations were elevated. Acetaminophen was undetectable. The chest X-ray revealed cardiomegaly without evident pulmonary congestion. The echocardiography showed a dilated cardiomyopathy with an ejection fraction of 35%. A diagnosis of severe toxic cardiomyopathy associated with anabolic steroids abuse was made after ruling out other causes for non-ischemic dilated cardiomyopathy. ACE inhibitors, ARBs, beta-blockers, spironolactone and antiarrhythmic drugs were given. Serial echocardiograms showed partial left ventricular function improvement. A rapid fall in serum transaminases was observed after treating the cardiomyopathy which is typical for ischemic liver injuries. The patient was discharged in a good condition after 18 days of hospitalization with an advice for permanent anabolic steroid discontinuation.

**Conclusion:** Anabolic steroid abuse is an important potential cause of dilated cardiomyopathy. Unrecognized cardiomyopathy can produce severe ischemic liver injury. Physicians should be trained to recognize the signs and symptoms of anabolic steroid abuse and act promptly.

**Key words:** anabolic steroids, cardiomyopathy, bodybuilder, liver failure

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V v	V v	O o	O o
G g	G g	P p	P p
D d	D d	R r	R r
\	G g	S s	S s
E e	E e	T t	T t
@ ‘	Zh zh	] }	K k
Z z	Z z	U u	U u
Y y	Dz dz	F f	F f
I i	I I	H h	Kh kh
J j	J j	C c	Ts ts
K k	K k	^ ~	Ch ch
L l	L l	X x	Dzh dzh
Q q	Lj Lj	[ {	Sh sh
M m	M m		

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