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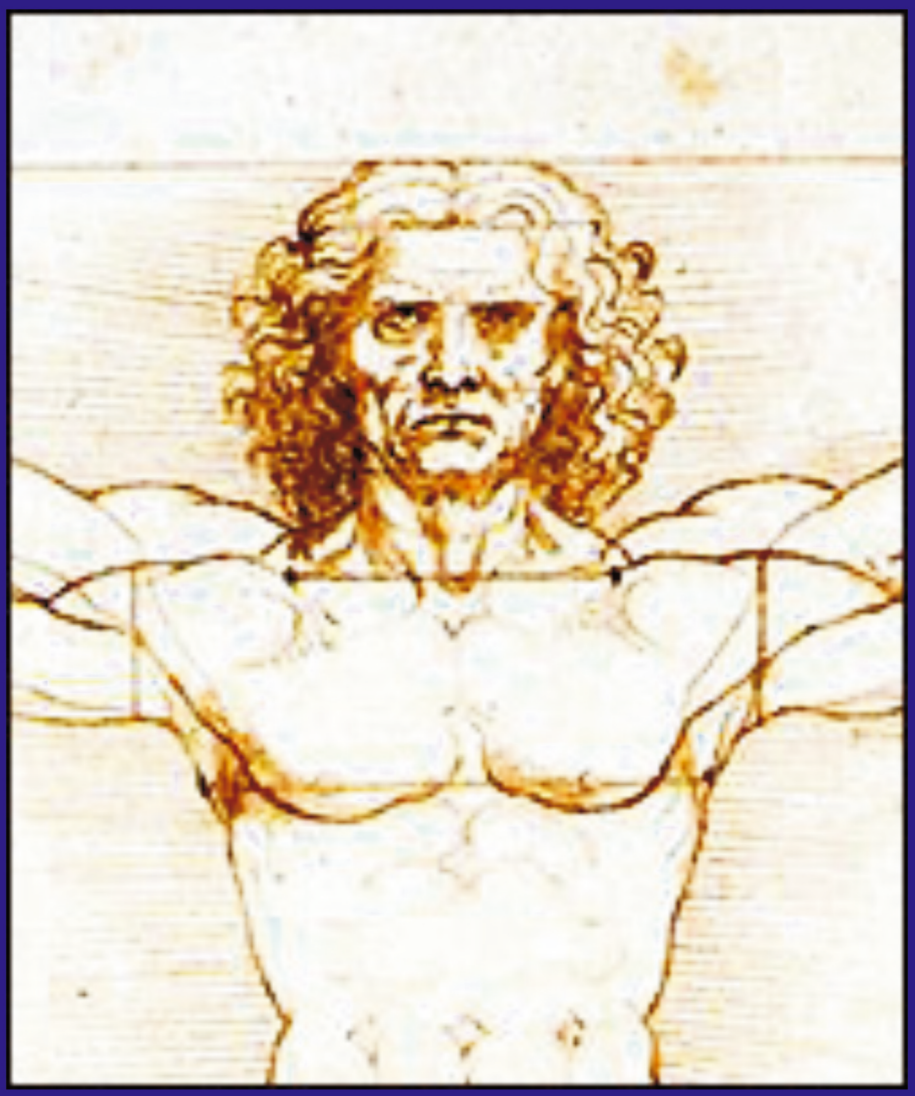

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Original article

ARE THERE ANY VARIATION IN NEUTROPHIL LYMPHOCYTE RATIO, MEAN PLATELET VOLUME AND PLATELET COUNT BETWEEN PAPILLARY THYROID CANCER AND BENIGN NODULAR THYROID DISEASES

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Abstract: **Objective:** Neutrophil lymphocyte ratio (N/L) and mean platelet (Plt) volume (MPV), the markers of systemic inflammatory response, has been investigated in many cancers, but data for the head and neck cancers and thyroid carcinoma are limited. It had been purposed to study N/L, MPV, and Plt levels in papillary thyroid carcinoma (PTC) as a diagnostic marker. **Material and Methods:** A total of 104 patients, had undergone ultrasonography guided fine needle aspiration (FNA) and thyroidectomy, for the indicated cases, between April 2010 and August 2013, were enrolled in the study. The laboratory tests, regarding N/L, MPV, and Plt, of the cases had been collected retrospectively. **Results:** No difference was found between PTC and benign nodular thyroid diseases (BNTD) in terms of age, gender, size of the nodule, N/L, MPV, and Plt ($p > 0.05$). **Conclusion:** The preoperative inflammatory hematological parameters, in terms of N/L, MPV, and Plt, may not be useful as a predictive diagnostic marker of the thyroid malignancy, PTC.

Key words: Thyroid neoplasms, Papillary thyroid cancer (PTC), Ultrasonography (US), Ultrasonography guided fine needle aspiration (US-g-FNA), Bethesda, Neutrophils, Lymphocytes, Neutrophil lymphocyte ratio, Mean platelet volume (MPV), Blood platelets.

INTRODUCTION

Thyroid cancer, the most common endocrine cancer, that has the dramatically increased incidence worldwide in terms of new diagnosis and mortality with the significant change in the papillary histotype (1-5). The shortage of the clically proven markers in the diagnosis of thyroid cancers like the other head and neck cancers still sustains the adversity in absolute and definitive preoperative diagnosis in the field of Neck-Endocrine Surgery. Many studies established the augmentation of neutrophil lymphocyte ratio (N/L) and mean platelet (Plt) volume (MPV), the markers of systemic inflammatory response, being related with the progression and survival of the certain types of cancers (6, 7).

In the present study, the laboratory tests of the patients that have thyroid nodules have been evaluated retrospectively and the relationship between papillary thyroid cancer (PTC) and the inflammatory hematological parameters including N/L, MPV, and Plt had been investigated.

MATERIAL AND METHODS

A retrospective analysis comprised of the patients that posses the nodular thyroid disease, who had undergone one-endocrine surgeon performed ultrasonography (US) guided fine needle aspiration (FNA) between April 2010 and August 2013. The documents were consisting the complete blood counts and US guided FNA (US-g-FNA) cytologies (FNACs) which had been reported according the guidance of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), a 6-diagnostic-category system which was constituted through multidisciplinary formulation, which was proposed at the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Art and Science Conference held in Bethesda, Maryland, 2007. TBSRTC is at present the most used and accepted reporting system

for reporting FNA cytology worlwide (8). The use of TBSRTC has also been endorsed by 2015 American Thyroid Association (ATA) management guidelines (9) as 2009 ATA guidelines (10) which is a revision of 2006 ATA guidelines (11). However, a special 2½-hour symposium entitled 'The Bethesda System for reporting thyroid cytopathology: past, present', future was moderated by Ali and Vielh at The 19th International Congress of Cytology (ICC) in Pacifico Yokohama, Japan, on 28 May–01 June, 2016 (12, 13). Pusztaszeri et al (14). Ali et al (12, 13) also discussed briefly the concensus of panel, recommendations, proposed modifications and updates for the second edition, TBSRTC II (12) by anticipating the second edition of TBSRTC, TBSRTC II, in early 2018.

As a result, cases were divided into two groups, benign nodular thyroid diseases (BNTD), diagnosed by the current TBSRTC I Class II as Group 1and PTC whose diagnoses also had been verified histopathologically as Group 2. They were taken into account if the age, gender, size of the tumor had ben correlated to the inflammatory hematological parameters regarding N/L, MPV, and Plt.

The Criteria for Incorporation into the Study

The screening outcome revealed the 104 cases in conformity with the criteria for being incorporated into the study. 95 cases with BNTD and 9 cases with PTC had been enrolled the present study between April 2010 and August 2013 by excluding the hematologic disorders, cardiac disorders, autoimmune diseases, inflammatory or infective diseases, endocrinologic diseases and diabetes, the patients with the elevated thyroid antibodies or impaired thyroid function tests, liver diseases, renal failure, recurrent disases, previous or accompanying other malignancies, as well as those who had medical records as to the usage of steroids, anticoagulants, and alcohol along with those with a medical history of hepatitis.

Statistical Analysis

The statistical analysis were performed by using SPSS 23.0 computer program. The Fisher Exact Test was applied for gender parameter. The Mann Whitney U-tests were applied for MPV, N/L and size parameters due to the samples not being obtained from normal population according to Kolmogorov-Simirnov and Shapiro Wilk Normality tests. The Independent sample t-tests were used to detect difference among two groups for age and Plt parameters and p value less than 0.05 was considered as statistically significant.

RESULTS

9 (8.65%) out of 104 cases possesing thyroid nodules (male/female: 15/89, 10.41%/61.8%) had PTC, while 95 (91.35%) had BNTD. It had not been detected any statistically significant difference between the cases with BNTD, Group 1 and cases with PTC, Group 2 in terms of age, gender, size of the nodule, N/L, MPV, and Plt ($p > 0.05$) (Figure 1a-f). Therefore, according to the statistical test results, there was no difference between PTC and benign thyroid nodules for all the parameters (Table 1).

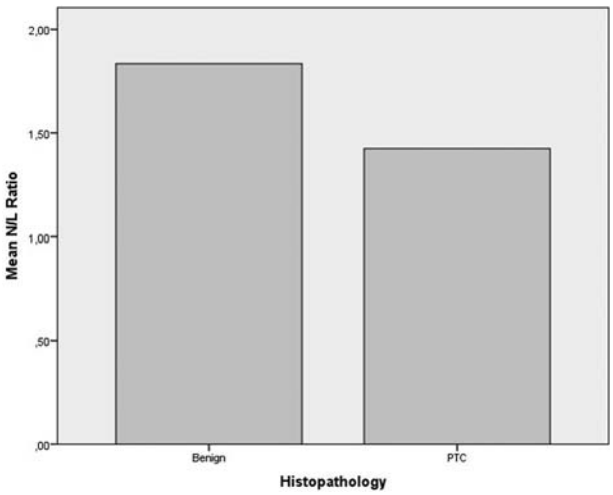

Figure 1a: *The median N/L from PTC and Control group*

Table 1 — *The comparison of demographic features and hematological paramaters between the patients with benign nodular thyroid disease and PTC*

Parameters	Benign	PTC	p Value
MPV, femtoliters, fL	191 ∓ 262	172 ∓ 234	0,470
Plt, $x10^9$/L)	271 ∓ 56	280 ∓ 66	0,649
N\L	1,8 ∓ 0,8	1,4 ∓ 0,4	0,051
Age, year	50 ∓ 12	53 ∓ 9	0,565
Size, mm	18 ∓ 9	19 ∓ 10	0,728
Gender, male/female	15/80	0/9	0,351

PTC, papillary thyroid carcinoma; MPV, mean platelet volume; Plt, platelet; N/L; neutrophil lymphocyte ratio; Size, size of the nodule

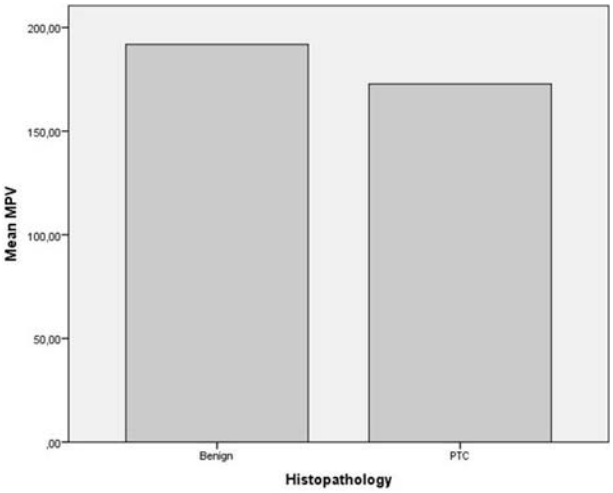

Figure 1b *— The median MPV from PTC and Control group*

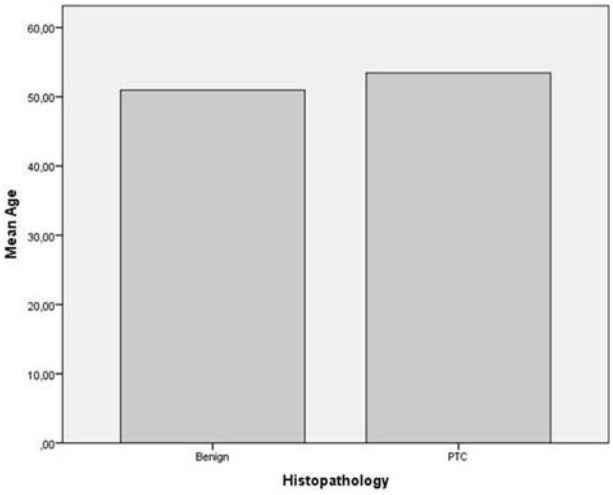

Figure 1d *— The median age from PTC and Control group*

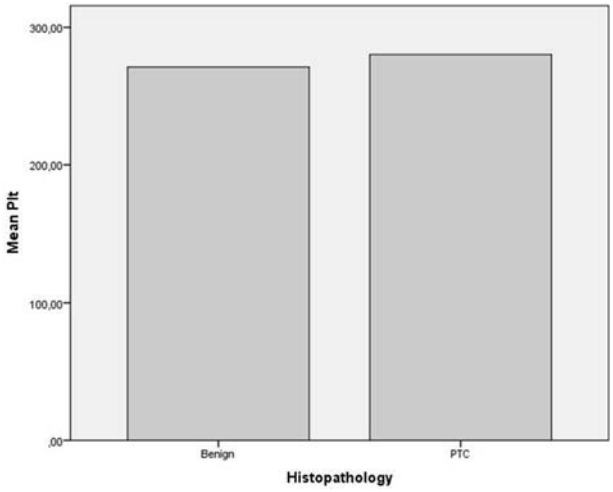

Figure 1c *— The median Plt from PTC and Control group*

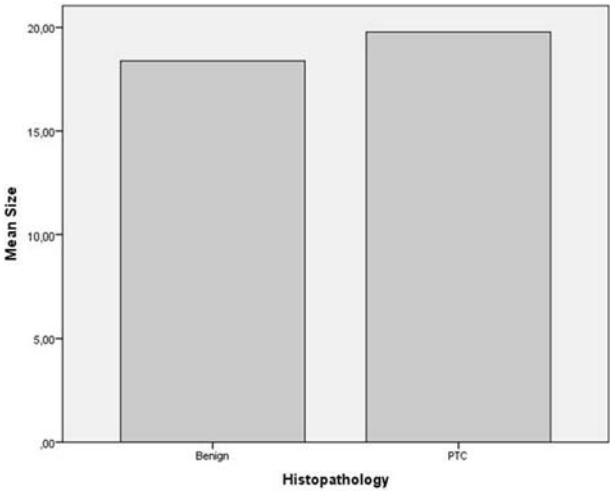

Figure 1e *— The median size of the nodule from PTC and Control group*

DISCUSSION

As a common clinical problem, the thyroid nodules, reveal the prevalance of approximately 5% in women and 1% in man living in iodine-sufficient areas of the world epidemiologically in palpation, whereas 19%-68% is the detection rate in high resolution US, with higher frequencies in women and elderly (9). The thyroid nodules are important clinically as long as eliminating the thyroid cancer comprising 7%-15% of the cases being based on age, sex, radiation exposure history to head and neck and thorax, particularly during first two decades, family history, and the other factors (15, 16).

Differentiated thyroid cancer (DTC), consisting PTC, follicular thyroid carcinoma (FTC), and Hurthle cell carcinoma (HCC), constitutes vast majority, > 90%, of the thyroid cancers (17). In the United States, the yearly incidence of thyroid cancer has nearly tripled from 4.9 per 100,000 in 1975 to 14.3 per 100,000 in 2009 and virtually the entire change has been attributed to an increase in the incidence of papillary thyroid cancer (18, 19). One study estimates PTC will being

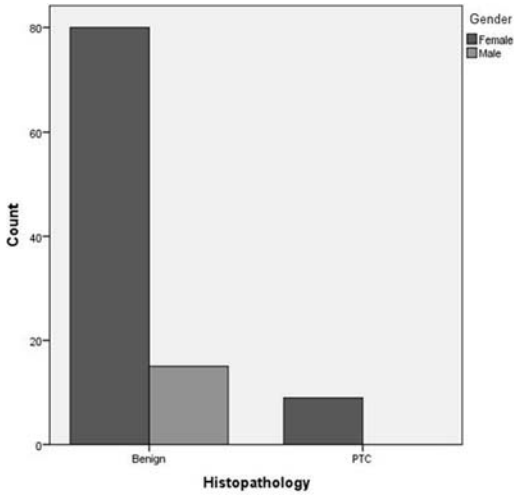

Figure 1f *— The numerical value of gender from PTC and Control group*

become the third most common cancer in women at a cost of $19–21 billion in the United States (20).

N/L, known as marker of systemic inflammatory response, have been associated with progression and survival in most kind of cancers (6, 7). Chang et al (21) found N/L, Hb, and Plt count beneficial for predicting long-term mortality in cases with nasopharyngeal carcinoma. N/L estimated as a negative indicator for oral cancer (22), breast cancer (23), and pancreatic adenocarcinoma (24). Feng et al (25) reported in a pilot study the elevated levels of N/L in cases with papillary thyroid microcarcinoma (PTmC) and PTC. Hower, N/L was not statistically different the patients with BNTD and PTC, in the present study. Similiar to the present study, Liu et al (26) reported a metanalysis on December 2016 to be able to clarify the undecided association between N/L and DTC. They conducted a systematic meta-analysis based on 7 prospective cohort studies published between 2013 and 2015, to investigate a potential association between N/L and DTC comprising 7349 patients. It was not detected any significant difference in N/R between the patients with benign nodules and PTC aged < 45 years and those aged ≥ 45 years, similar to our study.

Larger platelets are more metabolically and enzymatically active than the smaller ones. MPV reflects platelet activity indicating being an important biological variable (26). In a Turkish study, MPV was suggested as a possible biomarker in the diagnosis of PTC and estimator for therapeutic effectiveness in PTC in terms of its attenuated postoperative levels (27). However, we haven't detected significant difference between the groups, BNTD and PTC, in terms of MCV and Plt.

CONCLUSION

The present study lasted approximately three and a half years. However, a retrospective design, a relatively low sample count, not analyzing postoperative values of hematologic parameters and not comparing them with the preoperative ones were the limitations of the present study.

In conclusion, preoperative N/L, MPV, and Plt levels may not be useful as a predictive diagnostic marker of thyroid malignancy, PTC, in contrast to the related investigation. However, further studies with larger groups in multidicipliner and multicentric studies may reveal the different results in the future.

Conflict of interest

No any conflict of interest relevant to this article was declared.

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It has not been used any funding for the present work. DS had contributed in constituting the notion and hypothesis, intellectual planning and management of the study, collecting the data, performing the statistical analysis, writing the whole manuscript, its linguistic and academical revisions. IS had contributed in examining the patients and performing US-guided-FNA for each indicated thyroid nodule, collecting the data, academical revision of the manuscript. All the authors finally approved the submitted and proof versions without any conflict of interest.

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Abreviations

N/L — Neutrophil lymphocyte ratio
MPV — Mean platelet volume
Plt — Platelet
PTC — Papillary thyroid cancer
BNTD — Benign nodular thyroid diseases
DTC — Differentiated thyroid cancer
FTC — Follicular thyroid carcinoma
HCC — Hurthle cell carcinoma
US — Ultrasonography
FNA — Fine needle aspiration
US-g-FNA — US guided FNA
FNAC — FNA cytology
TBSRT — The Bethesda System for Reporting Thyroid Cytopathology
ATA — American Thyroid Association

Sažetak

DA LI POSTOJE VARIJACIJE U ODNOSU NEUTROFILA I LIMFOCITA, SREDNJEG VOLUMENA TROMBOCITA I BROJA TROMBOCITA IZMEĐU PAPILARNOG TIROIDNOG KARCINOMA I BENIGNOG NODULARNOG POREMEĆAJA ŠTITNE ŽLEZDE?

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Uvod: Odnos neutrofila i limfocita (N/L) i srednjeg volumena trombocita (MPV), markeri sistemskog inflamatornog odgovora, istraživani su u mnogim karcinomima, ali podaci o karcinomima glave i vrata i tiroidnom karcinomu su ograničeni. Cilj ove studije bio je da se izuči povezanost N/L, MPV, Plt niova u papilarnom karcinomu tireoidne žlezde (PTC) kao dijagnostičkog markera.

Materijal i metode: Ukupno 104 pacijenta koja su bila podvrgnuta ultrasonografski vođenoj biopsiji pomoću tanke igle (FNA) i tireoidektomiji za slučajeve kod kojih je to indikovano uključeni su u studiju u periodu između aprila 2010. i avgusta 2013. godine. Podaci o laboratorijskim analizama, koje uključuju N/L odnos, MPV, Plt bili su sakupljani retrospektivno.

Rezultati: Nije postojala statistički značajna razika između PTC i benignog nodularnog poremećaja štitaste žlezde u pogledu godina, pola, veličine nodula, N/L, MPV i Plt ($p > 0.05$).

Zaključak: Preoperativni inflamatorni hematološki parametri, kao što su N/L, MPV i Plt nisu upotrebljivi kao prediktivni dijagnostički markeri tireoidnog maligniteta, PTC.

Ključne reči: tireoidna neoplazma, papilarni tireoidni karcinom (PTC), ultrasonografija, ultrasonografski vođena biopsija tankom iglom, bethesda, neutrofili, limfociti, odnos neutrofila i limfocita, srednja vrednost volumena trombocita, trombociti.

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Original article

PATTERNS OF SUPERIOR ARTICULAR FACET AND MORPHOMETRIC STUDY OF NEPALESE DRY CALCANEI

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Abstract: **Introduction:** The three important articulating facets in the superior aspect of the calcaneum are the anterior, middle and posterior articulating facet. Descriptions of the posterior talar facet on the dorsum of the calcaneus are similar. However, there are differences when facet for the head of the talus on the calcaneus is considered. Four types (pattern I, II, III, IV) of calcaneus having different talar facets are reported in the literature.

Objective: This study aims to describe the calcaneal bone by measuring its dimensions and determining the variations of talar articulating facet.

Materials and methods: Overall 142 calcanei (68 right, 74 left) with unidentified gender, were assessed. Vernier calipers and Goniometry were used.

Results: In this study Type I calcaneus (56.34 %) was the most prevalent type with Type II calcaneus (42.25 %) as the second most common type followed by Type IV (1.41 %) as the third frequently found pattern of calcaneus.

Conclusion: Type I calcaneus was the most frequent type in the Nepalese showing similarity to the results of the studies performed in Spanish, American, African and various Indian population. Bohler's angle of the right and left calcanei was 34.92° ± 8.09° and 35.4° ± 7.30° respectively. Development of database of calcaneal measurements in various populations is recommended.

Key words: Calcanei, Talar articular facets, Nepalese.

INTRODUCTION

Calcaneus is the longest, largest and one of the major weight bearing tarsal bones forming the talocalcaneal joint with the talus. This joint is also termed as subtalar joint where eversion and inversion of the foot takes place (1). There are three facets for synovial joints between the talus and calcaneus, anterior, middle and posterior talar facet with variations seen in the arrangement of these facets as described in this study. Calcaneal fractures are the most commonly encountered tarsal fractures mostly involving the intra-articular subtalar joint (2). The majority of bony coalition commonly involves the middle talar facet of the talocalcaneal joint, also a common cause of painful flatfoot (3). Morphometric values of calcanei are essential for the science of anatomy, treatment and diagnosis procedures on orthopedic surgery, kinesiology, physical treatment and rehabilitation sessions (4). Structural dissimilarity of the calcanei has an impact on the fixed and kinetic dynamics of the foot. The relationship of talus and the calcaneus should be thoroughly considered during the treatment of talocalcaneal coalition, congenital club foot, subtalar instability, cases of severe pronation, valgus deformities, designing subtalar implants and others (5, 6, 7). Bohler's angle is commonly evaluated via radiography during calcaneal fractures for proper diagnosis and treatment. There is a significant loss or decrease of this angle in a severe case of heel fracture (8, 9, 10).

With the means of facet variation and bone dimension, this study attempts to describe the calcaneus bone of Nepalese race.

MATERIALS AND METHODS

A total of 142 dried calcanei (68 right, 74 left) without major defects and unidentified gender were assessed. All the bones were classified with Type I, II and IV identified as the predominant finding of our study. Pattern of articular facet on the superior aspect of the calcaneus was classified as follows:

Type I: Anterior and middle fused and posterior separate. (Figure 1)

Type II: Anterior, middle, and posterior facets separate. (Figure 2)

Type III: Anterior facet absent and other two present.

Type IV: Anterior, middle and posterior facet fused. (Figure 3)

Following measurements on the calcaneus were performed using Vernier Calipers:

a) Maximum anterior posterior length: optimum anterior and optimum posterior extension of the calcaneus (Figure 4a)

b) Maximum transverse diameter: optimum medial and lateral extensions of the calcaneus (Figure 4b)

c) Maximum vertical length: optimum extension of superior margin of posterior facet to the base of the calcaneus (Figure 4c)

Boehler's angle: Fixing the calcaneus in anterior posterior axis, the angles were measured by setting up the arms of the goniometry at following points: (Figure 5)

I. Superior edge of anterior process to superior edge of posterior facet.

Figure 1 *— Type I articular facet on the superior aspect of the calcaneus*

Figure 2 *— Type II articular facet on the superior aspect of the calcaneus*

Figure 3 *— Type IV articular facet on the superior aspect of the calcaneus*

Figure 4(a) *— Measuring maximum anterior posterior length of the calcaneus*

Figure 4 (b) *— Measuring maximum transverse diameter of the calcaneus*

II. Superior edge of tuberosity to superior edge of posterior facet.

SPSS software for windows was used for statistical analysis. Results are expressed in mean ± SD (standard deviation).

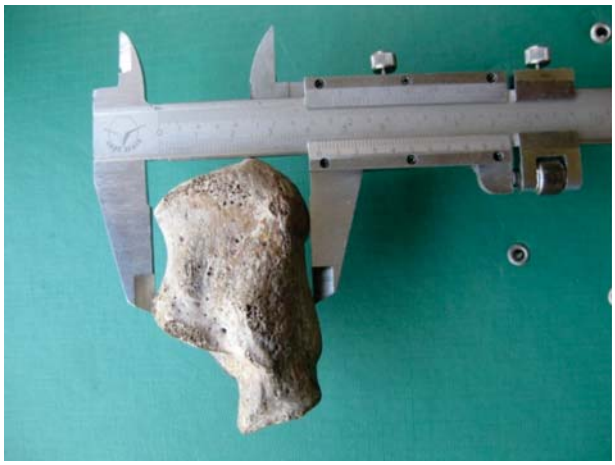

Figure 4 (c) *— Measuring maximum vertical length of the calcaneus*

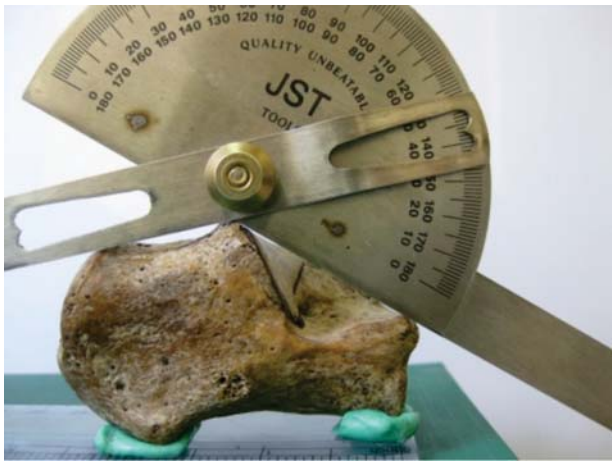

Figure 5 *— Measuring the Boehler's angle*

RESULTS

The talar articular facets in 142 dry calcanei were classified into four different types with three types being identified in this study (Table 1) and the same compared to that of other studies (Table 2). Type I (56.34%) was recognized as the most prevalent type (Figure 1), followed by Type II (42.25%), Figure 2 and Type IV (1.41%) pattern (Figure 3). None of the observed calcanei showed Type III configuration.

Table 1. *Classification of talar articulating facet of calcanei and its percentage*

Pattern of articular facet	Side (n)		Total (n = 142)
	Right (68)	Left (74)	
Type I	46 (57.5%)	34 (42.5%)	80 (56.34%)
Type II	23 (38.33%)	37 (61.67%)	60 (42.25%)
Type III	0 (0%)	0 (0%)	0 (0%)
Type IV	0 (0%)	2 (100%)	2 (1.41%)

Table 2. *Comparison of pattern of talar articulating facet between Nepalese and that reported by other investigators*

Study	Year	Country	n (sample size)	I%	II%	III%	IV%
Gupta *et al.*[14]	1977	India	401	66.8	25.9	5.2	1.9
Campos and Pellico[15]	1986	Spain	176	53.4	46.5	0	0
El-Eishi[11]	1974	Egypt	200	49	40	11	0
Bunning and Barnett[5,13]	1963, 1965	British	194	32.9	67	0	0
Bunning and Barnett[5,13]	1963, 1965	Africans	492	63.4	37.7	0	1
Uygur *et al.*[4]	2009	Turkey	221	58	39.3	0	0
Verhagen FD[12]	1993	Americans	191	54.4	26.7	18.85	0
Nepalese (Present study)	2017	Nepal	142	56.34	42.25	0	1.41

Table 3. *Morphometric measurements of the calcaneus*

Measurements	Right calcaneus, mean ± SD (mm), n = 68	Left calcaneus, mean ± SD (mm), n = 74	p value	Total, mean ± SD (mm), n = 142
Anterior posterior length	70.22 ± 7.1	70.47 ± 8.79	0.96	70.35 ± 7.64
Transverse length	38.36 ± 4.17	38.77 ± 3.87	0.87	38.58 ± 3.81
Vertical height	44.48 ± 5.32	43.83 ± 7.87	0.88	44.13 ± 6.51

Table 4. *Boehler's angle estimation*

Boehler's angle	Right (n = 68)	Left (n = 74)	p-value
	34.92° ± 8.09°	35.4° ± 7.30°	0.92

Morphometric measurements and their findings are shown in Table 3. Boehler's angle in the right and left calcanei are shown in Table 4.

DISCUSSION

The common pattern of the articular facets on the superior surface of the calcaneus for the head of the talus in our study is Type I (56.34%) and II (42.25%) as shown in Table 1. From Table 2 it is clear that the outcome of our study is consistent with the studies done by different authors previously. The prevalence of Type III pattern of calcanei was observed to a greater degree in Egyptians in an article by EI-Eishi (11) and Americans in a study by Verhagen FD (12) implying that the facets could be genetically determined as stated by Bunning and Barnett (13). A relatively small sample of Type IV patterned facet was common to the Africans (5), Indians (14) and our study. This finding may possibly be used as a racial characteristic. Additionally, Table 2 reveals, that in the Americans (12), Africans (5, 13) and Indians (14) the percentage of Type II is almost about half of Type I, whereas Spanish (15) and Egyptian (11) population has equal preponderance of Type I and Type II facet. Interestingly in the British (5, 13), Type II facets are almost twice as frequent as Type I, explaining another probable racial attribute. Geographical region, human habits like squatting, use of shoes and genetic factors may be the predisposing cause to the variations observed in the facets, with Type I more common in females (13).

The configuration of talar articulating facet also plays a key role in the stability of the subtalar joint is consistent with Bruckner's hypothesis that the joints with two facet configuration are comparatively more stable (16). This stability also depends on the height of the longitudinal arch, which is usually referred to as a cavus foot (16, 17). Computerized tomography scans show that the flat foot (planus foot) has no anterior sustentaculum tali facet (18). These findings suggests that the population with continuous facet and medial only facet pattern of the sustentaculum tali may be at a greater risk for subtalar joint instability than those with two facet type pattern (12). Furthermore, study by Chavan et al. suggests that leggedness, right or left could also be the contributing factor to the development of talar articulating patterns seen in human calcanei (19).

Calcaneal fracture accounts for 33% of foot fractures with 100% association to the posterior talocalcaneal facet in intra-articular fractures (20). The evaluation of vertical length of calcaneus may be a supportive criterion of calcaneus fractures (21). In our study the height, transverse and anterior-posterior length of right and left calcaneus was insignificant when compared to each other (Table 3). The given dimensions may provide a landmark for postoperative assessment of status of fractured calcanei.

Decompression fractures particularly alters Boehler's angle. Preserving normal Boehler's angle postoperatively demonstrates surgical success. Study by Khoshhal et al. in the Saudi population found the mean Boehler's angle to be 31.21° not related to age, gender, or side of body (9). Similarly in the study by Uygur et al. the Boehler's angles of right and left calcanei were found as mean 30.8° ± 4.9° and 30.09° ± 5°, respectively with left Boehler's angle correlating with the left vertical length of the calcaneus (4). The mean Bohler's angle of the right and left calcanei estimated in our study was somewhat greater than these studies with the similarity that Boehler's angle did not relate to the sides of calcanei (Table 4). When Boehler's angles of congenital clubfoot were compared to the normal side by Kalenderer et al. no differences were noted between them (22). The mean Boehler's angle in their study measured 35.2° which was close to that of our study.

Bohler's angle has a significant prognostic value in terms of predicting morbidity of calcaneal fractures. There was much poorer two year outcome regardless of treatment of fractures with a markedly diminished Bohler's angle (8). Also, significant correlation between preoperative Böhler's angle and the injury severity of displaced intra-articular calcaneal fractures was observed with only the postoperative Böhler's angle parameters found to have a significant correlation with functional recovery (23). Due to the lack of studies in Boehler's angle involving different population group, development of database for reference purpose, prognosis and treatment especially during postoperative angle measurements could be recommended.

CONCLUSION

Proper management (internal and external fixation and surgical procedures) of various conditions of the foot like deformities, fractures, arthritis etc demands the understanding of the knowledge of size and shape and relationship of the talus and calcaneus with each other and other bones of the foot. The dimensions of the calcaneus are evaluated. Type I calcaneus was determined as the most frequent type in the Nepalese showing similarity to the results of the studies performed in Spanish, American, African and various Indian

population. Bohler's angle of the right and left calcanei was 34.92° ± 8.09° and 35.4° ± 7.30° respectively. Development of database of calcaneal measurements in various populations is recommended.

The study was performed in:

1. Tribuvan University Teaching Hospital, Department of Anatomy, Maharajgunj, Kathmandu, Nepal

2. Chitwan Medical College, Bharatpur-10, Chitwan, Nepal

3. Birat Medical College and Teaching Hospital, Tankisinwari, Biratnagar, Nepal

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DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

Licensing

Sažetak

VRSTE GORNJE ZGLOBNE POVRŠINE I MORFOMETRIJSKA ANALIZA PETNE KOSTI KOD NEPALACA

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Uvod: Tri najbitnije zglobne površine u gornjem delu kalkaneusa su prednja, srednja i zadnja artikularna površina. Izgled zadnje talarne površine i zadnje strane kalkaneusa je slična. Međutim, postoje razlike kada se posmatra zglobna površina kalkaneusa koja je predviđena da se zglobljava sa glavom talusa. Postoje četiri tipa kalkaneusa sa različitim talarnim površinama koja se navode u literaturi.

Cilj: Cilja ovog rada bio je da se opiše kalkaneus merenjem dimenzija i određivanjem varijacija talusne zglobne površine.

Materijal i metode: Ukupno 142 kalkaneusa (68 desnih, 74 levih) pacijenata kojima nije određivan pol su bili uključeni u studiju. Vernierov caliper i goniometrija su bili korišćeni.

Rezultati: Prva vrsta (Tip I) kalkaneusa (56,34%) pokazala se kao najčešća sa najvišom stopom prevalence zajedno sa drugom vrstom (Tip II) petne kosti (42,25%), koja je drugom mestu po učestalosti. Treća po učestalosti vrsta kalkaneusa je tip IV(1,41%).

Zaključak: Tip I kalkaneusa je najčešći tip kod Nepalaca koji pokazuje sličnost sa rezultatima studija vršenim u španskoj, američkoj, afričkoj i različitim indijskim populacijama. Bolerov ugao desne i leve petne kosti bio je 34.92° ± 8.09° i 35.4° ± 7.30° respektivno. Preporučili bismo razvoj baze podataka za merenje parametara petne kosti u različitim populacijama.

Ključne reči: kalkaneus, talarna zglobna površina, Nepalci.

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THE IMPORTANCE OF ANTHROPOMETRIC PAREMETERS IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

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Abstract: **Introduction:** The concept of subclinical thyroid disease appeared in the 1980s when sensitive procedures for the measurement of the thyroid-stimulating hormone in the serum were introduced. Subclinical hypothyroidism is defined by the finding of elevated serum TSH concentrations with normal thyroid hormone levels. The incidence of subclinical hypothyroidism with increased cardiovascular risk has not yet been fully clarified.

The aim of the study was to identify anthropometric parameters that may indicate an increased cardiometabolic risk in patients with subclinical hypothyroidism.

Method: The study will include 140 patients aged 18-65, with 105 patients with subclinical hypothyroidism and a control group of 35 healthy, normally nourished subjects without subclinical hypothyroidism. A program of research will be carried out in all patients and it will include: detailed anamnesis and physical examination, anthropometric measurements (weight measurements, body height, waist circumference, hip circumference, body weight mass measurement by the bioelectrical impedance analysis method (%BFP), calculation of: body mass index (BMI), waist-to-hip circumference ratio (WC/HC), waist-to-height ratio (WC/Ht) and laboratory testing (FT3, FT4, TSH).

Results: Examinees with subclinical hypothyroidism had statistically significantly elevated mean TSH values (6.87 + 1.34 mIU/ml) compared to TSH euthyroid examinees (1.9 + .88 mIU/ml). The mean age of subjects with subclinical hypothyroidism was 44.15 ± 11.23 years (MA = 43 years), and in subjects without subclinical hypothyroidism, 33.80 ± 10.60 years (MA = 33 years). In relation to the control group (euthyroid patients), patients with subclinical form of hypothyroidism had higher average mean values and statistically significantly higher incidence of elevated values: BMI (T test = 7.465, $p < 0.0001$; $\chi^2 = 35.977$, $p < 0.0001$), %BFP (T test = 8.594, $p < 0.0001$; $\chi^2 = 44.956$, $p < 0.0001$), WC (T test = 6.262, $p < 0.0001$; $\chi^2 = 48.865$, $p < 0.0001$), and WC/Ht ratio (T test = 7.372, $p < 0.0001$; $\chi^2 = 39.175$, $p < 0.0001$). The WC/HC ratio in the group with subclinical hypothyroidism was higher than in the group without subclinical hypothyroidism, but not statistically significant (T test = -0.946, p = ns; $\chi^2 = 0.622$, $p = 0$).

Conclusion: In the subclinical form of hypothyroidism, changes in the degree of nutrition and body weight can already be recorded, which, among other things, contributes to the development of increased cardiometabolic risk.

Key words: subclinical hypothyroidism, anthropometric parameters, cardiometaolic risk

INTRODUCTION

Subclinical thyroid dysfunction or “mild” thyroid disease is a common disorder, mainly in middle-aged and elderly people (1).

Subclinical hypothyroidism (SH) is defined by the finding of elevated serum TSH concentrations with the normal values of thyroid hormones (2, 3).

Subclinical thyroid disease attracts attention and researchers reaffirm the need for the analysis of the possible meaning of this condition.

There are still controversial opinions about defining, clinical significance, the need for rapid diagnosis and the treatment of sub-clinical thyroid dysfunction (4). It is still an open question whether subclinical thyroid dysfunction can lead to fatal consequences for the

cardiovascular system by increasing the risk of mortality (2, 3, 5-10).

Cardiometabolic risk presents a comprehensive risk of developing type 2 diabetes and cardiovascular disease as a result of multiple risk factors. The central type of obesity, dyslipidemia, glycosidic tolerance and hypertension disorder are its main characteristics (11, 12).

In this study we proceeded from the assumption that changes in the size and distribution of body weight, which among other things contribute to the development of increased cardiometabolic risk, can be recorded in the subclinical form of hypothyroidism.

The authors assume that the effect of levothyroxine therapy in these patients would be to reduce mortality from cardiovascular diseases (1, 13-20).

AIM OF THE STUDY

The aim of this study is to identify anthropometric parameters that may indicate an increased cardiometabolic risk in patients with subclinical hypothyroidism: BMI, body fat percentage, distribution of body weight (waist circumference, waist-to-hip ratio, waist-to height ratio).

MATERIALS AND METHOD

The study included 140 patients aged 18-65, out of whom 105 patients had subclinical hypothyroidism and 35 patients were the euthyroid controls.

The study was carried out according to the following protocol:

1. Obtaining history data. History data were obtained by means of structured history questionnaire.

2. Physical examination.

3. Anthropometric measurements. The patients were examined in fasting state (not taking food 12 to 14h prior to testing).

a) Measurement of body weight was performed by medical decimal scales with moving weights, with the precision of 0.1 kg.

b) Body height was measured with Martin's anthropometer with the precision of 0.1 cm.

c) Measurement of waist circumference was performed in the standing position at the level of the median distance between the costal arch and the anterior superior iliac spine.

d) BMI was obtained as the quotient of body weight (kg) and body height (m2).

e) Measurement of the body fat mass was performed using the bioelectric impedance analysis procedure. Patients were recommended not to eat or drink anything at least four hours before measurement, to avoid physical activity 12 hours before measurement, not to take alcohol for 48 hours before measurement, not to take diuretics seven days before measurement, and to empty their urinary bladder 30 minutes before measurement. The body fat mass measurement was performed with Tanita Body Composition Analyzer BC-418 MA III (Tanita Corporation, MADE IN P.R.C.2004).

Technical characteristics of the appliance: Max 136 kg, delta = 0.1 kg,% Body fat increments: 0.5%

4. Laboratory tests: TSH and FT4 were determined by immunochemical method -chemiluminescent procedure including chemiluminescent substrate. The method was automated (IMMULITE® DPC). Reference values: TSH: 0.27-4.20 mIU/ml; FT4: 10-22 pmol/L. Variation coefficient: fT4: 6.20%, TSH: 5.50%. FT3 hormone was measured by enzyme-linked fluorescence assay (ELFA) using miniature VIDAS immunochemical analyzer. Reference values were 4.00-8.30 pmol/L. Variation coefficient: 5.30 %.

The study included patients who met all inclusion and had none of exclusion criteria.

Inclusion criteria were as follows:

1. Patients aged 18 to 65.

Exclusion criteria:

1. Patients with diagnosed diabetes mellitus.

2. Use of medicaments that may interfere with studied parameters (glucocorticoids, iodine preparations, amiodarone, diuretics, lithium, cytostatics, antidepressants, estrogens, androgens).

3. Chronic diseases that may have effect on studied parameters (systemic autoimmune diseases, malignant diseases, chronic renal failure, liver insufficiency, acute coronary syndrome and stroke within the last 6 months).

4. Recent use of radioactive iodine, thyroid surgery and external neck radiation.

5. Pregnancy and breast feeding.

Forming study group: Criterion for patients to be enrolled in the subclinical hypothyroidism group and in the controls was TSH > 4.2 IU/mL and TSH ≤ 4.2UI/mL.

Recommendations by the International Diabetes Federation (IDF) of April 2005 were taken for the definition of abdominal obesity. IDF recommends that the waist circumference threshold for abdominal obesity should be > = 94 cm in men and > = 80 cm in women of European descent.

Before starting the statistical analysis, laboratory reports with the results of the patients' analyses were anonymized and all of them were granted identification numbers (for the protection of patient privacy, while patient data were only known to investigators). Electronic data base was created using the SPSS version 20.0. Mean, standard deviation (SD), median, minimum and maximum as well as normal distribution of all studied continuous variables (normal distribution of

values within the group was analyzed using Kolmogorov-Smirnov test) were determined. To compare the mean values of the continuous variables, we used repeated-measure unifactorial ANOVA and the dependent sample T-test in normal distribution, or alternatively, Mann-Whitney U-test (non-parametric test, alternative to T-test), and Wilcoxon matched pairs test for the outcomes not following normal distribution, as well as χ^2 test for the comparison of frequency of categorical (dichotomous) variables. $P < 0.05$ was statistically significant, with a 95% confidence interval.

RESULTS

The study included 140 patients aged 18-65, out of whom 105 patients had subclinical hypothyroidism and 35 patients were the euthyroid controls.

Testing the normality of the series (Skewness test), as well as determining the coefficient of variation (> 30%), it was shown that the mean TSH value of patients in the group with SH has a mean value which is statistically significantly higher than in patients without SH (Table 1).

The average age of patients with SH was 44.15 ± 11.23 years (MA = 43 years), and for patients without SH it was 33.80 ± 10.60 years (MA = 33 years). The mean age of 105 patients from the experimental group was statistically significantly higher than the mean age in 35 patients from the group without SH (analyzed using ANOVA test, $p < 0.0001$. (Table 2).

Testing the normality of the series (Skewness test), as well as determining the coefficient of variation (> 30%), proved that the following series of parameters that were monitored have a normal distribution (Table 3).

Table 1. *Parameters of thyroid status in relation to the presence of SH*

	With SH			Without SH			Variant analysis		Stud. T test/U test	
	Number	Mean value	SD	Number	Mean value	SD	F	sig.	T test /U test	sig
FT3 pmol/L	105	4.98	0.86	35	4.71	0.64	2.851	0.094	1.688	0.094
FT4: pmol/L	105	14.45	2.37	35	14.94	2.38	1.118	0.292	-1.057	0.292
TSH:m IU/ml*	105	6.87	1.34	35	1.9	0.88	419.612	0.0001***	630.00	0.0001***

FT3-free triodothyronine; FT4 - free thyroxine; TSH: thyroid stimulating hormone

Table 2. *Mean age in relation to groups and T test*

	With SH			Without SH		
	Number	Median	Skewness	Number	Median	Skewness
Age	105	43.00	0.09	35	33.00	0.49
	number	Mean value	SD	Number	Mean value	SD
Age	105	44.15	11.23	35	33.80	10.60
	Variant analysis					
Age	$F = 22.91$, $p < 0.0001$***					
	Stud. T test					
Age	T, $p < 0.0001$***					

SH: subclinical hypothyroidism

Table 3. *Testing the distribution normality, median by group*

	With SH			Without SH		
	Number	Median	Skewness	Number	Median	Skewness
WC:cm	105	90.00	0.34	35	77.00	0.19
HC:cm	105	102.00	0.73	35	89.00	-0.33
WC/HC	105	0.88	0.19	35	0.88	0.18
Ht:cm	105	166.00	0.57	35	170.00	1.11
WC/Ht	105	0.54	0.31	35	0.45	-0.13
BWT:kg	105	80.60	0.48	35	63.80	0.47
BMI	105	28.41	0.32	35	22.97	-0.95
%BFP	105	38.50	-0.46	35	25.50	-0.16

WC(waist circumference); HC(hip circumference); WC/HC (waist-to-hip ratio); Ht (body height); WC/Ht (waist-to-height ratio); BWT(body weight); BMI (Body Mass Index); %BFT (% body fat percentage).

Table 4. *Descriptive statistics of anthropometric parameters in relation to groups*

	With SH			Without SH			Variant analysis		Stud. T test	
	Number	Mean value	SD	Number	Mean value	SD	F	sig.	T test	Sig.
WC:cm	105	90.88	11.53	35	77.66	8.24	39.217	0.0001***	6.262	0.0001***
HC:cm	105	103.62	11	35	87.49	6.64	66.987	0.0001***	8.185	0.0001***
WC/HC	105	0.88	0,06	35	0.89	0.06	0.895	0.346	-0.946	0.346
Ht:cm	105	166.47	7.74	35	171.14	8.99	8.817	0.004**	-2.969	0.004**
WC/Ht	105	0.55	0.07	35	0.45	0.04	54.353	0.0001***	7.372	0.0001***
BWT:kg	105	80.18	14.26	35	65.81	10.42	30,136	0.0001***	5.490	0.0001***
BMI	105	28.89	5.02	35	22.35	2.11	55,719	0.0001***	7.465	0.0001***
%BFP	105	37.26	7.73	35	24.56	7.07	73,856	0.0001***	8.594	0.0001***

WC(waist circumference); HC(hip circumference); WC/HC (waist-to-hip ratio); Ht (body height); WC/Ht (waist-to-height ratio); BWT(body weight); BMI (Body Mass Index); %BFT (% body fat percentage).

Table 5. *Distribution of selected parameters in relation to reference values and in relation to groups*

		With SH		Without SH		χ^2
		Number	%	Number	%	sign
WC	Normal	19	18.1%	29	82.9%	48.865
	Elevated	86	81.9%	6	17.1%	0.0001***
WC/HC	Normal	43	41.0%	17	48.6%	0.622
	Elevated	62	59.0%	18	51.4%	0.430/ns
WC/Ht	Normal up to 0.5	25	23.8%	30	85.7%	39.175
	Elevated > 0.5	80	76.2%	5	14.3%	0.0001***
BMI	do 25	23	21.9%	35	100.0%	65.977
	> 25	82	78.1%	0	0.0%	0.0001***
%BFP	Normal	28	26.7%	32	91.4%	44.956
	Elevated	77	73.3%	3	8.6%	0.0001***

WC (waist circumference); HC (hip circumference); WC/HC (waist-to-hip ratio); Ht (body height); WC/Ht (waist-to-height ratio); BWT(body weight); BMI (Body Mass Index); %BFT (% body fat percentage).

Table 6. *Testing the differences of the selected parameters by groups*

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig.	Monte Carlo Sig	Kruskal Wallis Test	Sig.	Kolmo gorov-Smir. Z	Sig.
Age	925.50	1555.50	-4.39	**0.000**	0.00	19.29	**0.000**	1.95	**0.001**
WC:cm	669.00	1299.00	-5.63	**0.000**	0.00	31.66	**0.000**	2.49	**0.000**
HC:cm	331.00	961.00	-7.26	**0.000**	0.00	52.63	**0.000**	3.46	**0.000**
WC/HC	1655.50	7220.50	-0.88	**0.380**	0.39	0.77	**0.380**	0.68	**0.739**
Ht:cm	1292.50	6857.50	-2.63	**0.009**	0.01	6.90	**0.009**	1.27	**0.080**
WC/Ht	430.00	1060.00	-6.77	**0.000**	0.00	45.88	**0.000**	3.32	**0.000**
BWT:kg	782.50	1412.50	-5.08	**0.000**	0.00	25.78	**0.000**	2.44	**0.000**
BMI	402.00	1032.00	-6,91	**0.000**	0.00	47.72	**0.000**	4.00	**0.000**
%BFP	447.50	1077.50	-6.69	**0.000**	0.00	44.77	**0.000**	3.17	**0.000**
fT3 pmol/L	1449.00	2079.00	-1.87	**0.062**	0.06	3.50	**0.062**	1.42	**0.036**
fT4: pmol/L	1619.00	7184.00	-1.05	**0.293**	0.31	1.11	**0.293**	0.68	**0.739**
TSH:mIU/ml	0.00	630.00	-8.84	**0.000**	0.00	78.19	**0.000**	5.12	**0.000**

WC (waist circumference); HC (hip circumference); WC/HC (waist-to-hip ratio); Ht (body height); WC/Ht (waist-to-height ratio); BWT (body weight); BMI (Body Mass Index); %BFT (% body fat percentage); FT3-free triodothyronine; FT4 - free thyroxine; TSH: thyroid stimulating hormone.

Table 4 lists descriptive statistics of anthropometric parameters in relation to the groups, and the distribution of selected parameters in relation to the reference values and in relation to the groups is shown in Table 5.

Table 6 shows the results of testing of the tested parameters in the experimental group in relation to the control group with nonparametric tests.

In relation to the control group (euthyroid patients), patients with subclinical hypothyroidism had higher mean values and statistically significantly higher incidence of elevated values: BMI, % BFP, WC, and WC/Ht ratio ($p < 0.0001$). The WC/HC ratio in the subclinical hypothyroid group was higher than in the group without subclinical hypothyroidism, but not statistically significant (T test = -0.946, p = ns; $\chi^2 = 0.622$, $p = 0$).

DISCUSSION

In this study we found that in patients with SH, in relation to the control group of normally nourished persons without a thyroid gland function disorder, there are changes in the anthropometric parameters, especially in the degree of nutrition, as well as an increase in body weight, which among other things contributes to the development of increased cardiometabolic risk.

The prevalence of subclinical hypothyroidism in adult population is 4 to 8.5% (1, 21). The prevalence increases with age, and in women over 60 years of age it is 20% (1, 21). Annually, 2 to 5% of patients who have had subclinical hypothyroidism develop clinically expressed hypothyroidism.

The causes of subclinical hypothyroidism may be endogenous (chronic autoimmune thyroiditis, subacute thyroiditis, postpartum thyroiditis), or exogenous (tiroidectomy, radioactive iodine treatment, antithyroid drugs, inadequate thyroid hormone replacement) (3, 22).

The presence of hypothyroidism symptoms in patients with subclinical hypothyroidism remains controversial. Based on clinical symptoms, it is difficult to distinguish between a euthyroid person and a person with subclinical hypothyroidism. Many symptoms are non-specific and are related to the severity of the disease, the duration of the disease, the individual sensitivity of peripheral target organs to the deficit of thyroid hormones (4, 23, 24).

In their study (15), Kong and associates showed that women with subclinical hypothyroidism complained of fatigue (83%) and weight gain (80%). 50% of women had an elevated level of anxiety (25).

A more recent review of the clinical consequences of thyroid function variations within the normal reference range documented that even modest elevations of TSH might have substantial health outcomes, including cardiovascular mortality (26). The results of meta-analyses of Yang et al. demonstrated that SH was significantly associated with a higher risk of MetS (27).

Metabolic syndrome (MetS) can be defined in different ways, but the central type of obesity, dyslipidemia, glycosidic disorder and hypertension disorder are its main characteristics. These criteria are consistent with the data obtained from the INTERHEART study, which showed that dyslipidemia, hypertension, abdominal obesity and diabetes are among the nine most significant risk factors that account for 90% of the population risk for myocardial infarction (28).

In 2005, IDF and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) (29-31) tried to agree on the criteria of the clinical definition of MetS. However, their recommendations differ in terms of waist circumference.

IDF recommends that the threshold for waist circumference in abdominal obesity should be > = 94 cm in men and > = 80 cm in women of European descent; AHA/NHLBI recommend values of > = 102 cm for men and > = 88 cm for women.

In our study of 105 patients in the SH group, the waist circumference was 90.88 ± 11.53 cm, and in the group without SH the waist circumference was statistically significantly lower, and it was 77.66 ± 8.24 cm ($p < 0.0001$). In the group with SH there were 19 patients (18.1%) with WC within the reference values, while 86 (81.9%) of the patients had elevated values of waist circumference. In the group without SH there were 29 patients (82.9%) with WC within the reference values, while 6 (17.1%) of the patients had elevated values of waist circumference ($p < 0.0001$).

The average value of HC in patients with SH was 103.62 ± 11 cm, and in patients without SH it was 87.49 ± 6.64 cm ($p < 0.0001$).

The relationship between hip and waist is an index that easily distinguishes two types of obesity from each other, not equally significant in terms of presenting the potential risk of morbidity. If this ratio was higher than 0.9 in women and 1.0 in men, obesity is abdominal (32). When analyzing the WC/HC ratio in the group with SH there were 43 patients (41%) with WC/HC within the reference values, while 62 (59%) patients had elevated WC/HC values. In the group without SH there were 17 patients (48.6%) with WC/HC within the reference values, while 18 (51.4%) of the patients had elevated WC/HC values ($p = 0.430$).

The relationship between waist and height is a better indicator of heart disease and diabetes than a body mass index, according to a new study recently presented by Dr Margaret Ashwell (32-37).

In our study, the average value of the WC/Ht ratio of patients with SH was 0.55 ± 0.07, and for patients

without SH it was 0.45 ± 0.04 ($p < 0.0001$). In the SH group there were 25 patients (23.8%) with WC/Ht within the reference values, while 80 (76.2%) of patients had elevated WC/Ht values. In the group without SH there were 30 patients (85.7%) with WC/Ht within the reference values, while 5 (14.3%) of the patients had elevated WC/Ht values ($p < 0.0001$).

According to the criteria of the World Health Organization, the BMI values between 18.5 and 24.9 kg/m^2 corresponded to normal nutrition (38). The values given by IDF correspond to the BMI of about 25 kg/m^2.

The results of this study give an average BMI value in patients with SH of 28.89 ± 5.02 kg/m^2 and in patients without SH the BMI is 22.35 ± 2.11 kg/m^2 ($p < 0.0001$).

When analyzing the BMI in the group with SH, 23 BMI values (21.9%) were within the reference values up to 25, while 82 (59%) of patients had BMI values above 25. In the group without SH there were 35 patients (100%) with BMI within the reference values ($p < 0.0001$).

Fat tissue plays an important role in MetS pathogenesis, promoting inflammation, hypertension, and dyslipidemia, which all contribute to the development of T2DM, atherosclerosis, and thrombosis. Body weight increment in patients with subclinical hypothyroidism may also contribute to the development of insulin resistance (39-41), which, in addition to the earlier understanding of the causes of increased cardiovascular risk, may have implications in explaining these etiopathogenetic relationships. The role of obesity in the onset of MetS can be seen from the correlation between the rise in the prevalence of MS and obesity in the United States and other countries (42-44).

In our study, the percentage of average fat mass body fat (% BFT) was statistically significantly higher in patients with SH (37.26) compared to patients without SH (24.56) ($p < 0.0001$). In the SH group, 28 patients (26.7%) were with BFP in reference values, while 77 (73.3%) patients had elevated% BFP values. In the group without SH there were 32 (91.4%) patients with% BFP within the reference values, while 3 (8.6%) patients had elevated %BFP values.

In **conclusion**, we can say that the results of this study suggest that patients with subclinical hypothyroidism have changes in anthropometric parameters, especially in the degree of nutrition, as well as in the increase in body weight, and on the whole, represent a category of people with elevated cardiovascular risk. Timely and precise identification of these parameters in patients with subclinical hypothyroidism opens the possibility of specific therapeutic intervention directed against the reduction of cardiovascular risk.

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests

Abbreviations

SH — subclinical hypothyroidism
TSH — thyroid stimulating hormone
FT3 — free triodothyronine
FT4 — free thyroxine
WC — waist circumference
HC — hip circumference
WC/HC — waist-to-hip ratio
Ht — body height
WC/Ht — waist-to-height ratio
BWT — body weight
BMI — Body Mass Index
%BFT — % body fat percentage

Licensing

Sažetak

ZNAČAJ ANTROPOMETRIJSKIH PARAMETARA KOD BOLESNIKA SA SUBKLINIČKOM HIPOTIREOZOM

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Uvod: Koncept o subkliničkoj tiroidnoj bolesti pojavio se osamdesetih godina prošlog veka kada su uvedeni osetljivi postupci za merenje tireostimulišućeg hormona u serumu.

Subklinička hipotireoza definiše se nalazom povišene koncentracije TSH u serumu uz normalne vrednosti tireoidnih hormona. Udrženost subkliničke hipotireoze sa povećanim kardiovaskularnim rizikom još uvek nije u potpunosti razjašnjen.

Cilj ispitivanja predstavlja identifikaciju antropometriskih parametara koji mogu ukazati na povećan kardiometabolički rizik kod bolesnika sa subkliničkom hipotireozom.

Metod: Istraživanjem će biti obuhvaćeno 140 bolesnika uzrasta 18-65 godina i to 105 bolesnika sa subkliničkom hipotireozom i kontrolna grupa od 35 zdrava, normalno uhranjena ispitanika bez subkliničke hipotireoze. Kod svih ispitanika biće sproveden program istraživanja koji uključuje: detaljnu anamnezu i fizikalni pregled, antropometriska merenja (merenje telesne mase, telesne visine, obima struka, obima kukova, merenje masne mase tela postupkom bioelektrične impedansne analize (%BFT). Izračunavanje: indeksa telesne mase (ITM), odnosa obima struk/kuk (OS/OK), odnosa obima struk/telesna visina (OS/TV) i laboratoriska ispitivanja (FT3, FT4, TSH).

Rezultati: Ispitanici sa subkliničkom hipotireozom imali su statistučki značajno povišene prosečne vrednosti TSH (6.87 ± 1.34 mIU/ml) u odnosu na eutiroidne ispitanike TSH (1.9 ± 0.88 mIU/ml). Prosečna starost ispitanika sa subkliničkom hipotireozom bila je 44,15 ± 11,23 godina (Md = 43 god.), a kod ispitanika bez subkliničke hipotireoze bila je 33,80 ± 10,60 godina (Md = 33 god.). U odnosu na kontrolnu grupu (eutiroidni pacijenti), ispitanici sa subkliničkom formom hipotireoze imali su više prosečne srednje vrednosti i statistički značajno veću učestalost povišenih vrednosti: ITM (T test = 7,465, $p < 0,0001$; $\chi^2 = 35,977$, $p < 0,0001$), %BFT (T test = 8,594, $p < 0,0001$; $\chi^2 = 44,956$, $p < 0,0001$), OS (T test = 6,262, $p < 0,0001$; $\chi^2 = 48,865$, $p < 0,0001$), i odnosa OS/TV (Ttest = 7,372, $p < 0,0001$; $\chi^2 = 39,175$, $p < 0,0001$). Odnos OS/OK u grupi sa subkliničkom hipotireozom bio je viši nego u grupi bez subkliničke hipotireoze, ali ne i statistički značajno (T test = -0,946, p = ns; $\chi^2 = 0,622$, p = 0).

Zaključak: Već u subkliničkoj formi hipotireoze mogu se evidentirati promene u stepemu uhranjenosti i veličini masne mase tela, koja između ostalog, doprinosi nastanku povećanog kardiometaboličkog rizika.

Ključne reči: subklinička hipotireoza, antropometriski parametri, kardiometabolički rizik.

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COMPARASION OF THE RESULTS OF CORNEAL TOPOGRAPHY FINDINGS IN FUCHS ENDOTHELIAL DYSTROPHY AND PSEUDOPHAKIC BULLOUS KERATOPATHY

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Abstract: **Background:** Comparison of Fuchs endothelial dystrophy and pseudophakic bullous keratopathy with the help of Scheimpflug camera combined with a Placido disk corneal topographer.

Material and methods: 34 eyes of 34 patients pseudophakic bullous keratopathy (PBK) and 32 eyes of 20 patient Fuchs endothelial dystrophy (FED) have been examined by **Scheimpflug camera combined** with a **Placido disk** corneal topographer. Anterior chamber depth (ACD), anterior chamber volume (ACV), iridocorneal angle (ICA), central corneal thickness (CCT) and LogMAR best corrected visual acuity (BCVA) were compared in terms. Except for corneal edema, diseases of the eye that can impair vision (cataracts, glaucoma, retinal disease) were excluded.

Results: The average age of patients in group PBK and FED were found 64.9 ± 13.9 and 66.06 ± 10.5 respectively. ACD, ACV, ICA, CCT and BCVA in PBK group 2.95 ± 0.48 mm, 202.55 ± 115.20 mm^3, 40.73 ± 10.44 derece, 742.41 ± 108.74 µm and 2.06 ± 0.70 LogMAR respectively. ACD, ACV, ICA, CCT and BCVA in FED group 2.63 ± 0.64 mm, 140.75 ± 71.34 mm^3, 34.62 ± 13.58 derece, 757.37 ± 145.99 µm and 1.82 ± 1.12 LogMAR respectively. Statistically significant difference between the 2 groups in terms of ACV and LogMAR BCVA was observed ($p = 0.01$ and $p = 0.001$). Between other parameters as mean age, ACD, ICA and CCT, statistically difference was not observed ($p > 0.05$).

Conclusions: Between two groups in terms of age, ACD, ICA and CCT statistically significant difference was not significant, while in terms of ACV and BCVA LogMAR observed results showed statistically significant difference ($p < 0.05$).

Key words: Pseudophakic bullous keratopathy, fuchs endothelial dystrophy, corneal topography, Sirius.

INTRODUCTION

Due to endothelial pump function deterioration, fluid accumulation in the extracellular space in the stroma leads to corneal edema (1). As a result of changes in morphological properties of the cornea such as surface irregularities and increased interfibrillary space, there is a decrease in visual acuity, pain, irritation and conjunctival hyperemia.

Pseudophakic bullous keratopathy (PBK) is the leading cause of ocular morbidity in cataract surgeons (2). Fuchs endothelial dystrophy (FED) is the cause of primary endothelial dysfunction characterized by Descemet membrane guttata, endothelial erosion and corneal edema (Figure. 1 and 2). In corneal endothelial dysfunctions, surgical treatment is needed when corneal opacity can not be preserved. PBK and FED accounted for 42.4% of the 42,000 corneal transplantations in the United States and are the leading causes of corneal transplant surgeons (3, 4, 5). Figures 1 and 2 show a corneal topographic analysis of the Fuchs endothelial dystrophy in 65-year-old female patient with an anterior segment photograph. Figures 3 and 4 show a corneal

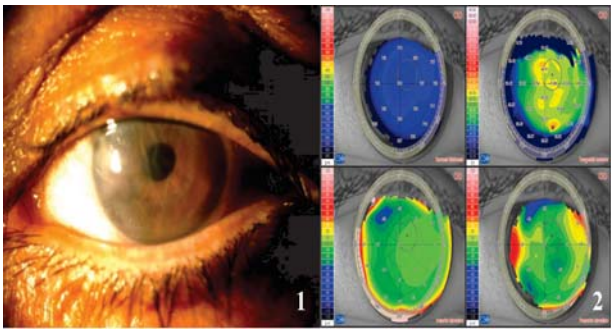

Figure 1. *Fuchs Endothelial Dystrophy in female patient aged 65;* ***Figure 2.*** *Sirius corneal topographic analysis of the patient in Figure 1*

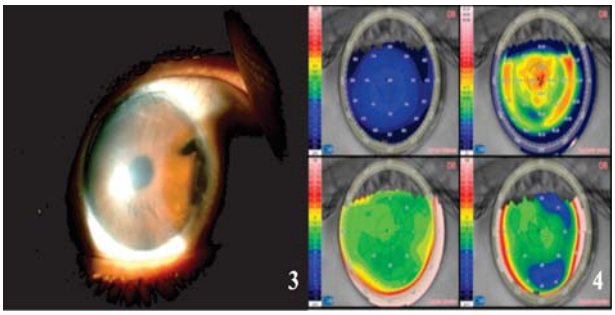

Figure 3. *Pseudophakic bullous keratopathy in 50 years old female patient;* ***Figure 4.*** *Sirius corneal topographic analysis of the patient in Figure 3*

topographic analysis with an anterior segment photograph of a 50 year old patient with pseudophakic bullous keratopathy.

In this study, we aimed to compare PBK and FED disease, primary and secondary endothelial deficiencies, with the help of Scheimpflug camera combined with a Placido disk corneal topographer.

MATERIAL AND METHOD

This retrospective study included patients diagnosed with PBK and FED in our ophthalmology department between January 2012 and February 2015. The study was conducted in accordance with the Helsinki declaration rules and by receiving informed consent forms from patients.

34 eyes of 34 patients diagnosed with PBK disease and 32 eyes of 20 patients diagnosed with FED disease were included in this study. Patients included in the study were divided into 2 groups according to their diseases. Detailed ophthalmological examination including visual acuity, intraocular pressure measurement, anterior and posterior segment evaluation, were performed on all subjects. Those with any ocular or systemic disease that could reduce the level of vision other than PBK and FED were excluded from the study.

Corneal topography was then performed to all patients with an anterior segment analysis system of Sirius (Costruzione Strumenti Ophthalmologist, Florence, Italy), which was operated on a combined Scheimpflug-Placido disk system. PBK and FED disease groups were compared in terms of age, LogMAR best corrected visual acuity (BCVA), anterior chamber depth (ACD), anterior chamber volume (ACV), central corneal thickness (CCT), and iridocorneal angle (ICA).

PBK and FED disease groups were compared in terms of age, ACV, ACD, ICA, CCT and BCVA LogMAR and after showing the normal distribution Independent Sample t-test was performed.

SPSS 15.0 (IBM Corporation, Chicago, IL, USA) program was used for statistical analysis. Independent sample t-test and Chi-square test were used in comparison of the data of the two disease groups and $p < 0.05$ was considered statistically significant.

Sirius topography

The device combines a Monchromatic 360 degree rotated Scheimpflug camera and a 22 ring Placido-disk, taking 25 radial sections through the cornea and anterior chamber. It provides with a single cut-sheet tangential and axial curvature information of both surfaces of the cornea, gives the global refractive power of the cornea, provides biometric measurements of most visible structures, and provides pachymetry and wave front analysis of the cornea. Scheimpflug imaging provides all the measurements of other internal structures while the device delivers the corneal anterior surface measurement data in combination with Placido images and Scheimpflug images as appropriate. 35632 points from the corneal anterior surface and 30000 points from the posterior surface of the cornea are examined with 475 nm blue LED light. Wave front analysis of the cornea with Sirius device is performed by the beam follow-up method (8, 9, 10).

RESULTS

Among the eyes analyzed in the PBK group, 19 were female and 15 were male. Among the eyes analyzed in the FED group 16 were males and 16 females. Chi-square test showed no statistically significant difference between the two groups in terms of gender ($p = 0.658$). The age and measurement parameters of PBK and FED groups are given in Table 1.

Table 1. *Independent t test*

Parameter	PBK	FED	p
Age	64 ± 13.9	66.06 ± 10.5	0.335
ACD (mm)	2.95 ± 0.48	2.63 ± 0.64	0.651
ACV (mm^3)	202.55 ± 115.20	140.75 ± 71.34	0.011
ICA (degree)	40.73 ± 10.44	34.62 ± 13.58	0.292
CCT (μm)	742.41 ± 108	757.37 ± 145	0.343
BCVA logMAR	2.06 ± 0.70	1.82 ± 1.11	0.001

When the PBK and FED groups were compared with the independent sample t test, the frequency of the ACV, PBK group was higher ($p = 0.011$). BCVA was higher in the FED group ($p = 0.011$). There were no significant differences between the two groups in terms of ACD ($p = 0.651$), ICA ($p = 0.292$), CCT ($p = 0.343$) and age ($p = 0.335$).

DISCUSSION AND CONCLUSION

In this study we compared pseudophakic bullous keratopathy which is leading cause of secondary endothelial failure and fuchs endothelial dystrophy which is primary endothelial dysfunction cause with the help of combined Scheimpflug-Placido disc system (Costruzione Strumenti Ophthalmics, Florence, Italy) corneal topography device in terms of anterior chamber morphological features whether or not they differ in the course of endothelial failure.

We have observed rear studies comparing FED and PBK patients with corneal topography aid (6, 7). In one study, PBK and Fuchs patients were divided into 3 groups according to their corneal thickness via CCT and analysis was performed with Orbscan corneal topography (Bausch&Lomb Surgical Inc., San Dimas, CA). In the same study, none of the variables we evaluated were compared.

As far as we know, this study is one of only few studies in which topographic analysis of cornea is performed in edematous corneas. This study aims to measure the functional and biomechanical properties of human cornea with endothelial decompensation. We also think that the differences between these two groups can be used as a point of view in which endothelial keratoplasty surgery may require different techniques in donor preparation and placement.

Basically, even if endothelial keratoplasty procedure is applied in both diseases, Descemet stripping endothelial keratoplasty (DSEK) surgery uses endothelium and some back stroma while Descemet membrane endothelial keratoplasty (DMEK) surgery uses Descemet membrane together with endothelium only. Donor tissue manipulation and anterior chamber stabilization during graft opening can be a bigger problem for DMEK surgeons. We think that careful surgical technique is needed because of the difficulty of surgery and possible complications, especially in FED patients which have a lower ACV compared to PBK patients. Future studies should support these data.

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

Abbreviations

PBK — pseudophakic bullous keratopathy
FED — Fuchs endothelial dystrophy
ACD — anterior chamber depth
ACV — anterior chamber volume
ICA — iridocorneal angle
CCT — central corneal thickness
BCVA — best corrected visual acuity

Licensing

Sažetak

POREĐENJE REZULTATA NALAZA KORNEALNE TOPOGRAFIJE KOD FUCHS-ove ENDOTELIJALNE DISTROFIJE I PSEUDOFAKNE BULOZNE KERATOPATIJE

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Uvod: Poređenje Fuchs-ove endotelijalne distrofije i pseudofakne bulozne keratopatije uz pomoć kombinovanog Scheimplfug kamera-Placido disk topogrfer sistema.

Materijal i metode: 34 oka od 34 pacijenata sa pseudofaknom buloznom keratopatijom (PBK) i 32 oka od 20 pacijenata sa Fuksovom endotelijalnom distrofijom (FED) pregledani su placido-disk kornealnom topografijom kombinovanom sa Scheimpflug kamerom. Dubina prednje očne komore (ACD), volumen prednje očne komore (ACV), iridokornealni ugao (ICA), centralno kornealno zadebljanje (CCT) i najbolja korigovana vidna oštrina (LogMAR BCVA) su bili upoređivani. Osim bolesti povezanih sa kornealnim edemom, ostale bolesti koje mogu da ugroze vid su bile isključene (katarakta, glaukom, bolesti retine).

Rezultati: Prosečna starost pacijenta u grupama PBK i FED bile su 64,9 ± 13,9 i 66,06 ± 10,5. ACD, ACV, ICA, CCT i BCVA u grupi PBK bile su 2,95 ± 0,48 mm, 202,55 ± 115,20 mm^3, 40,73 ± 10,44 derece, 742,41 ± 108,74 μm and 2,06 ± 0,70 LogMAR. ACD, ACV, ICA, CCT i BCVA u FED grupi bile su 2,63 ± 0,64 mm, 140,75 ± 71,34 mm^3, 34,62 ± 13,58 derecea, 757,37 ± 145,99 μm and 1,82 ± 1,12 LogMAR. Statistička značajnost između 2 grupe u pogledu ACV i logMAR BCVA bile su ispitane (p = 0,01 i p = 0,001). Ostali parametri srednja starosna vrednost, ACD, ICA i

CCT izmedju ispitivanih grupa nisu pokazali statističku značajnost ($p > 0,05$).

Zaključak: Razmeđu dve grupe u pogledu godina, ACD, ICA i CCT nije se pokazala kao statistički značajna, dok u pogledu ACV i BCVA logMAR rezultati su se statistički značajno razlikovali ($p < 0,05$).

Ključne reči: pseudofakna bulozna keratopatija; Fuksova endotelijalna distrofija; kornealna topografija; Sirius.

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Original article

IS THERE ANY LINK BETWEEN A KIND OF THYROCYTE DYSFUNCTION, HYPOTHYROIDISM AND INFLAMMATORY HEMATOLOGIC PARAMETERS IN THE CASES HAVING THE BENIGN THYROID NODULES? A 5-YEAR SINGLE-CENTER EXPERIENCE

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Abstract: **Objective:** Microscopically, the thyroid gland is composed of spherical follicles and thyroid parenchyma includes two major cell types, the thyrocytes releasing thyroid hormones and C cells secreting mature calcitonin. Hypothyroidism has been known as being associated with the various abnormalities of the coagulation system. In the present study, it had been purposed to investigate the relationship between inflammatory hematological parameters, RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW and hypothyroid hormonal status in the cases possessing the benign thyroid nodules.

Material and Methods: A total of 313 cases, 202 with hypothyroidism and 111 with euthyroidism possesing the benign thyroid nodules, that was verified with the cytological evaluation after one-endocrine surgeon performed ultrasonography (US) guided fine needle aspiration (FNA) (US-g-FNA), at the Division of Endocrine Surgery, Department of General Surgery, Giresun University Faculty of Medicine, Giresun, Turkey, in conformity with the criteria, were enrolled into the study during the period, from April 2010 to April 2015. The documents that were used to follow consisted of laboratory tests of the cases including both the thyroid hormones, free T3, Free T4, and TSH, and the inflammatory hematological parameters were reviewed and scanned retrospectively. The upper limit of the normal Thyrotropin (TSH) reference range was determined as 4 mU/L in the present study.

Results: No statistically significant difference was found between the inflammatory hematological parameters, RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW, and hypothyroidism ($p > 0.05$).

Conclusion: Inflammatory hematological parameters may not be useful for estimating the hormonal status of the thyroid gland in the cases with the benign thyroid nodules verified with the cytological evaluation, TBSRTC.

Keywords: Thyroid neoplasms; Thyrocytes; Fine needle aspiration cytology (FNAC); Cytology; Thyrotropin (TSH); Hypothyroidism; Hematological parameters.

INTRODUCTION

The thyroid gland, weighing 10 to 20 grams in normal adults in the United States, is measured by ultrasonography (US) is a certain extent greater in men than women, increases with age and body weight, and decreases with increasing iodine intake (1, 2).

Microscopically, the thyroid is composed of the spherical follicles, each composed of a single layer of follicular cells surrounding a lumen filled with colloid (mostly thyroglobulin) and the thyroid parenchyma includes two major cell types, the thyrocytes releasing thyroid hormones and C cells secreting mature calcitonin (3). L-thyroxin (T_4) and to a much lesser extent of l-triidothyronin (T_3), two main thyroid hormones, are synthesized by the follicular epithelial cells, thyrocytes, of the thyroid gland (4).

Electron microscopy demonstrates the normal flat to low cuboidal follicular cells, interdigitating and overlapping one another. They are intimately relevant to the capillaries, surrounding the follicle; microvilli on the apical surface are multiplexed near the cellular

margins. When stimulated, the follicular cells become columnar and the lumen is depleted of colloid; when suppressed, become flat and colloid, accumulating in the lumen (5, 6).

The thyroid hormones frequently have a worthy effect on the erythropoiesis by enhancing it via hyperproliferation of the immature erythroid progenitors and increasing the secretion of erythropoietin (EPO) by resulting in EPO gene expression (7-10). The erythrocyte mass is increased in the most hyperthyroid status, whereas the hypothyroidism have an attenuated erythrocyte mass due to the reduction of plasma volume and may undetectable by routine measurement such as hemoglobin (Hb) concentration (11, 12). The thyroid dysfunction also changes the other hematological parameters, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), white blood cell (WBC) count and platelet count (Plt). However, all the mentioned alterations return to normal if an euthyroid state is sustained (9).

In the present study, the laboratory tests of the patients having the benign thyroid nodules, verified with the cytological evaluation after one-endocrine surgeon performed ultrasonography (US) guided fine needle aspiration (FNA), had been evaluated retrospectively and purposed to investigate the relationship between the inflammatory hematological parameters, consisting red blood cell (RBC), Hb, Htc, red cell distribution width (RDW), WBC, neutrophil, lymhocyte, neutrophil lymhocyte ratio (N/L), Plt, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), and the hypothyroidism.

MATERIALS AND METHODS

The present study had been conducted on a total of 313 cases, from April 2010 to April 2015 in order to matching two groups, the patients with hypothyroidism, 202 cases, and the patients with euthyroidism, 111 cases, control group. In terms of the inflammatory hematological parameters we measured RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW. The five years documents consisted of laboratory tests of the cases included both the thyroid hormones and the inflammatory hematological parameters were reviewed and scanned retrospectively.

An elevated serum thyroid stimulating hormone (TSH) was determined as a TSH concentration above the upper limit of the normal reference range, typically accepted as 4 to 5 mU/L in the most laboratories. Presently a considerable controversy exist over the appropriate upper limit of normal for serum TSH that some authors have suggested that the true upper limit is only 2.5 or 3 mU/L in healthy individuals without any thyroid disease, whereas the others argue that the serum TSH distribution shifts towards higher values with age, independent of the presence of antithyroid antibodies (13), or in obesity. It is recommended for these cases that the normal upper limit could be as high as 6 to 8 mU/L in healthy octogenarians, or as high as 7.5 mU/L in morbid obesity (14). The upper limit of the normal TSH reference range was determined as 4 mU/L in the present study. Hypothyroidism has known as being associated with the various abnormalities of the coagulation system, such as the modification of coagulation proteins and bleeding tendency.

The study was performed for the cases which had been undergone US guided FNA (US-g-FNA) cytology (US-g-FNAC) and all the US-g-FNAC results had been reported according the guidance of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), a 6-diagnostic-category system which was constituted through multidisciplinary formulation, proposed at the National Cancer Institute (NCI) Thyroid Fine Needle Aspiration State of the Art and Science Conference held in Bethesda, Maryland, 2007. TBSRTC is at present the most used and accepted reporting system for reporting FNA cytology (FNAC) worlwide (15). The use of TBSRTC also has been endorsed by 2015 American Thyroid Association (ATA) management guidelines (16) as 2009 ATA guidelines (17) which is a revision of 2006 ATA guidelines (18).

The criteria for including patients into the Study

The screening outcome revealed the 313 cases, 202 with hypothyroidism, 111 with euthyroidism, in conformity with the criteria, were incorporated into the study during the period, from April 2010 to April 2015. The exclusion criteria had been the hematologic disorders, cardiac disorders, autoimmune diseases, inflammatory or infective diseases, endocrinologic disease and diabetes, liver diseases, renal failure, recurrent disases, thyroid malignancies and the previous or accompanying other malignancies, as well as those who had medical records as to the usage of steroids, anticoagulants, and alcohol along with those with a medical history of hepatitis and patients with the inappropriate samples.

Statistical Analysis

The statistical analyses were performed by using SPSS 23.0 computer program. Some descriptive statistics were calculated for control and hypothyroid groups. Some indexes of groups were compared by using Mann-Whitney U test due to the non-normality of the data sets.

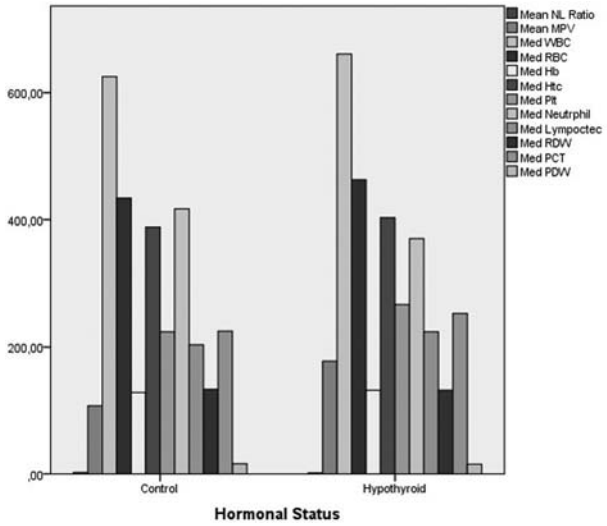

Figure 1. *The comparison of the inflammatuar hematological paramaters with the hormonal status of the thyroid*

The results were expressed as mean ± standard deviation (SD) and $p < 0.05$ were considered as statistically significant.

RESULTS

111 (35.46%) out of 313 cases were possesing the euthyroid state, whearas 202 (64.54%) had the hypothyroid condition. It had not been detected any statistically significant difference between the cases with hypothyroidism, Group 1 and cases with the euthyroidism, Group 2, Control, in terms of the inflammatory hematological parameters, RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW ($p > 0.05$) (Figure 1). Therefore, in accordance with the statistical test results, no any difference between the inflammatory hematological parameters and hypothyroidism was detected (Table 1).

DISCUSSION

Thyroid, a crucial endocrine organ, has a notable effect on the erythropoiesis by inducing EPO secretion and also the proliferation of erythroid progenitors (8, 11, 19). Hypothyrodism reported as cooccurence with some coagulation system abnormalities, the most rele-

Table 1. *The comparison of the inflammatuar hematological paramaters between the patients with hypothyroidism and euthyroidism, control*

Hematologic Parameters	Hormonal Status	n	Min	Max	Mean	SD	*p*-value
N/L	Control	111	1,03	4,86	2,3022	1,38137	
	Hypothyroid	202	0,00	5,57	1,8435	0,86573	0,459
MPV	Control	111	101,00	122,00	107,3333	8,77876	
	Hypothyroid	202	8,00	1114,00	177,8951	240,82600	0,137
WBC	Control	111	157,00	762,00	544,6667	215,28090	
	Hypothyroid	202	6,00	1662,00	621,9020	267,47184	0,395
RBC	Control	111	412,00	492,00	442,3333	31,92909	
	Hypothyroid	202	146,00	692,00	465,3333	49,48820	0,155
Hb	Control	111	114,00	140,00	128,1667	8,30462	
	Hypothyroid	202	11,00	841,00	135,6373	59,18326	0,513
Htc	Control	111	343,00	438,00	388,5000	30,87880	
	Hypothyroid	202	35,00	551,00	394,8693	69,99557	0,302
Plt	Control	111	165,00	319,00	229,0000	57,00175	
	Hypothyroid	202	131,00	452,00	272,3235	54,12551	0,066
Neutrophil	Control	111	212,00	1209,00	493,8333	361,91956	
	Hypothyroid	202	7,00	1216,00	381,6993	153,05536	0,756
Lymphocyte	Control	111	172,00	266,00	211,0000	43,27586	
	Hypothyroid	202	2,00	434,00	223,1373	81,44708	0,623
RDW	Control	111	128,00	155,00	136,6667	9,58471	
	Hypothyroid	202	13,00	288,00	131,0490	33,26398	0,421
PCT	Control	111	202,00	321,00	243,3333	46,16781	
	Hypothyroid	202	12,00	741,00	238,5869	93,00368	0,61
PDW	Control	111	11,80	17,90	14,9500	2,55402	0,546
	Hypothyroid	202	8,70	279,00	15,9886	21,16918	

N/L; neutrophil lymphocyte ratio; MPV, mean platelet volume; RBC, red blood cell; Hb, Hemoglobin; Hct, Hemotocrit; Plt, platelet; RDW, red cell distribution width; PCT, plateletcrit; PDW, platelet distribution width

vant one is expressed as acquired von Willebrand disease (20). The aim of the present study was investigate whether any commitment between a kind of thyrocyte dysfunction, hypothyroidism, and inflammatory hematologic parameters, consisting RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW.

Geetha and Srikrishna (21) reported RBC indices, comparing in the cases with hypothyroidism and hyperthyroidism and the study revealed that RDW and MCV in these groups in comparison to the euthyroid individuals had statistically significant difference. Hovewer, the other RBC parameters, such as Hb and Hct, did not exhibit any significant difference in comparison with the euthyroid hormonal status. Kawa et al (9) reported that RBC, Hb in the cases with hypothyroidism attenuated, while Hct was increased. They also showed that MCH, MCHC were lower and MCV was increased in hypothyroid group in comparison with the control group.

In the present study, the upper limit of the normal TSH reference range was determined as 4 mU/L and the comparision of the cases with hypothyroidism and the euthyroid ones had been performed for investigating the prediction of the current hormonal status of the thyroid gland by means of their inflamatuar hematologic parameters. However, it was not detected any significant difference between the inflammatory hematologic parameters, RBC, Hb, Htc, RDW, WBC, neutrophil, lymhocyte, N/L, Plt, MPV, PCT, PDW and a type of thyroid hormone disturbance, hypothyroidism.

CONCLUSION

The present study investigated just hypothyroidism, performed on the cases that had benign thyroid nodular diseases in the duration of five years. The limitations of the present study may be the retrospective design, studying on the cases with the benign thyroid nodular diseases and not analyzing the thyroid antibodies, like antithyroid peroxidase Ab (anti-TPO Ab) or antithyroid microsomal Ab, antithyroglobulin antibody (anti-Tg Ab), and thyroid stimulating immunoglobulin (TSI Ab).

In conclusion, the usage of the inflammatory hematological parameters may not be beneficial for estimating the hypothyroid hormonal status of the thyroid gland in cases with the benign thyroid nodules that was verified with the cytological evaluation, TBSRTC.

DECLARATION OF INTEREST

No any conflict of interest relevant to this article has been declared.

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It has not been used any funding for the present work. DS had contributed in constituting the notion and hypothesis, intellectual planning and management of the study, collecting the data, performing the statistical analysis, writing the whole manuscript, its linguistic and academical revisions. IS had contributed in examining and follow-up of the patients, collecting the data, academical revision of the manuscript. All the authors finally approved the submitted and proof versions without any conflict of interest.

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Abreviations

T_4 — L-thyroxin
T_3 — L-triidothyronin
EPO — Erythropoietin
MCV — Mean corpuscular volume
MCH — Mean corpuscular hemoglobin
US — Ultrasonography
FNA — Fine needle aspiration
US-g-FNA — US guided FNA
FNAC — FNA cytology
RDW — Red cell distribution width
PDW — Platelet distribution width
N/L — Neutrophil lymphocyte ratio
MPV — Mean platelet volüme
Plt — Platelet
TSH — Thyroid stimulating hormone
TBSRTC — The Bethesda System for Reporting Thyroid Cytopathology
ATA — American Thyroid Association
anti-TPO Ab — Antithyroid peroxidase antibody
anti-Tg Ab — Antithyroglobulin antibody
TSI Ab — Thyroid stimulating immunoglobulin

Sažetak

DA LI POSTOJI VEZA IZMEĐU TIPA TIREOCITNE DISFUNKCIJE, HIPOTIREOIDIZMA I ZAPALJENSKIH HEMATOLOŠKIH PARAMETARA U SLUČAJEVIMA SA BENIGNIM TIROIDNIM NODUSIMA? 5-GODIŠNJE ISKUSTVO JEDNOG CENTRA

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Uvod: Mikroskopski posmatrano, tireoidna žlezda je sastavljena od sferičnih folikula i tireoidnog parenhima koji uključuje dva glavna ćelijska tipa, tireocite koji oslobađaju hormone i C ćelije koje sekretuju zreli kalcitonin. Poznato je da je hipotireoidizam povezan sa mnogim abnormalnostima sistema za koagulaciju. U ovoj studiji, cilj je bio da se ispita povezanost između hematoloških parametara, RBC, Hb, Htc, RDW, WBC, neutrofila, limfocita, N/L, Plt, MPV, PCT, PDWi hipotireoidnog hormonskog statusa kod pacijenata sa benignim tireoidnim nodulima.

Materijal i metode: Ukupno 313 slučaja, 202 sa hipotireoidizmom, 111 sa eutireodizmom i benignim tireoidnim nodulima, koji su verifikovani citološkom evaluacijom nakon što je urađena ultrasonografijom (US) vođena aspiracija tankom iglom (FNA) (US-g-FNA) od strane endokrinog hirurga na Odseku za endokrinu hirurgiju, odeljenja opšte hirurgije, Medicinskog fakulteta, Univerziteta Giresun u Turskoj je učestvovalo u studiji u periodu od aprila 2010-te godine do aprila 2015-te godine. Petogodišnji dokumenti su se sastojali od laboratorisjkih testova za slučajeve koji su uključivali tireoidne hormone, slobodni T3, slobodni T4 i TSH i inflamatorne hematološke parametre koji su prikazani i analizirani retrospektivno. Gornja granica za normalni tireostimulirajući hormone (TSH) bila je 4 mU/L za potrebe studije.

Rezultati: Nije pokazana statistički značajna razlika između inflamatornih hematoloških parametara, RBC, Hb, Htc, RDW, WBC, neutrofila, limfocita, N/L, Plt, MPV, PCT, PDW i hipotireodizma ($p > 0,05$).

Zaključak: Inflamatorni hematološki parametri verovatno nisu dovoljno korisni za procenu hormonskog statusa tireoidne žlezde u slučajevima sa benignim tireoidnim nodulima koji su verifikovani citološkom evaluacijom, TBSRTC.

Ključne reči: tireoidna neopazma, tireociti; aspiracija tankom iglom (FNAC); citologija; tireotropin (TSH); hipotireoidizam; hematološki parametri.

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Case report

ACUTE RESPIRATORY DISTRESS SYNDROME AS A COMPLICATION OF VIRAL PNEUMONIA — CASE REPORT

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Abstract: ARDS is a life-threatening condition that requires monitoring in intensive care units. There is no specific treatment. We present a 49 year-old female patient with ARDS and its complications, ventilation assisted pneumonia (VAP) andbilateral pneumothorax.Good knowledge of the process can help to choose the appropriate treatment and to prevent or to recognize possible complications. Adequate oxygen therapy takes important place in treatment of these patients.

Key words: ARDS, intensive care unit, ventilation assisted pneumonia, bilateral pneumothorax, oxygen therapy

INTRODUCTION

The definition of ARDS was given in 2011 by The European Society of Intensive Care Medicine, supported by The American Thoracic Society and the Society of Critical Care Medicine and it is known as the Berlin Definition. According to it, ARDS is defined by time (one week from a clinical insult or a worsening of the chronic condition); radiographic changes (bilateral shadows, not fully explained by effusion, consolidation, atelectases); presence of lung edema in the absence of left heart failure and PaO2 / FIO2 ratio with a minumum of 5 cm^2 H20 continuous positive airway pressure (CPAP). By definition, 3 ARDS categories have been identified. Subtypes are based on the degree of hypoxemia: mild (PaO2 / FIO2 ≤ 300 mm Hg), moderate (PaO2 / FIO2 ≤ 200 mm Hg), and severe (PaO2 / FIO2 ≤ 100 mm Hg) (1, 2).

ARDS implies diffuse alveolar injury (DAD) and injury to the capillary endothelium in the lungs. Injuries of the capillary endothelium and alveolar epithelium lead to impaired fluid transport through alveoli and fluid accumulation rich in proteins within the alveoli, eventually leading to diffuse alveolar injury, with the release of proinflammatory cytokines, such as Tumor Necrosis Factor (TNF), IL-1 and IL-6 (3). Neutrophils are activated, releasing toxic mediators, proteases and free radicals (4). Abnormalities of transcription factors, including NF-cap B needed for gene transcription for many pro inflammatory mediators, are present in ARDS (5). Endothelin-1, angiotensin-2 and phospholipase A-2 also significantly increase vascular permeability.

The loss of epithelial integrity in ARDS has many consequences. First, under normal conditions, the epithelial barrier is much less permeable than the endothelial. Thus, epithelial injury contributes more to alveolar leakage. Secondly, the loss of epithelial integrity and injuries of epithelial cells type II impairs normal fluid and ion exchange, leading to edema within the alveolar space. Thirdly, pneumocyte type II injury reduces the production of surfactants leading to known abnormalities. Fourth, loss of the epithelial barrier can lead to septic shock in patients with bacterial pneumonia. Finally, if the injury of the alveolar epithelium is serious, the inability to regenerate ultimately leads to fibrosis. The fibrosis process was stimulated by interleukin (IL) -1. Progression to fibrosis can be predicted by the increased values of procollagen peptide III (PCP-III) in the sample obtained by BAL. The diseases most commonly associated with ARDS can be both lungs and systemic (Table 1). Mycobacteria pneumoniae, although associated with unilateral pneumonia, can also lead to changes that correspond to acute respiratory distress syndrome (6, 7).

The main symptoms include breathing difficulties (dyspnoea), rapid breathing (tachypnoea), and extremely deep breathing (hyperventilation) and reduced oxygen levels in the circulation (hypoxemia). Usually

Table 1. *ARDS related diseases and conditions*

Pulmonary diseases or conditions	Systematic diseases or conditions
Pneumonia	Sepsis
Aspiration of gastric contents	Difficult trauma:Multiple fractures Head injuries Burns
Lung Contusion	Multiple Transfusion
Drowning	Overdose of narcotics
Inhalation lung injury	Pancreatitis
	Post Cardiopulmonary bypass

it occurs 24 to 48 hours after the onset of the underlying disease or worsening of the existing one. One of the most significant characteristics of ARDS is that there is hypoxemia refractor to oxygen therapy, and therefore patients are subjected to mechanical ventilation. One of the most common complications of mechanical ventilation is bacterial pneumonia, which is usually caused by gram negative bacteria (P. aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia) (40%), then Enterobacteriaceae (29%) and MRSA (21%) In the laboratory tests we often find an increased number of white blood cells, which speaks for pneumonia or sepsis. Acido base status may show reduced H < 7.4. On the RTG image of the lung we find the presence of edema. CT may sometimes be needed, but usually a RTG record is sufficient. Ultrasound of the heart helps to exclude heart problems. Monitoring with arterial pulmonary catheter excludes the existence of pulmonary hypertension. Bronchoscopy can be considered if there is a need for evaluation of lung condition.

CASE REPORT

A 49 years old female was admitted to the Clinical Hospital Center of Montenegro pulmology department through Emergency Center due to choking, dry cough, weakness and fatigue, elevated body temperature. The illness started seven days before with mentioned problems that intensified by time, after which she was admitted to the General Hospital Berane. During treatment in the Berane General Hospital, a PCR test for influenza A and B was performed. The findings were sent for analysis to the Public Health Institute. Lung RTG was performed and bilateral pneumonia was noticed. In past medical history she reported diabetes mellitus type 2 with metformin therapy.

On admission to the Emergency Center, she was conscious, oriented, mobile.Discrete dyspnoea atrest was present, tachycardia, temperature 38.3 °C, cyanotic lips, dry plated tongue with herpetic changes in the labial region. The conclusion was that she leaves the impression of a medium sick patient. A skin was of a reduced turgor, with no signs of hemorrhagic syndrome. Auscultatory fine crackels were heard at basal parts of lung. In the obtained laboratory tests, the increase in inflammatory parameters with elevated values of D dimer and liver function parameters were verified (WBC 14.3, Hgb 124, PLT 331, CRP 147.6, AST 142, ALT 240, GGT 227, LDH 751, CK 68, K 3.8, Na 137, D dimer >36.436). The performed ABB showed a global respiratory insufficiency, metabolic compensated (p H 7.43, p CO2 6.1, p O2 5.1, HCO3 28.4, hco3 STD 26.1, BE 5.3, with O2 84%). On the performed RTG recording of the lungs in the UC, the bilateral shading of the lower and middle lung fields was described. CT of lung arteries excluded the presence of lung thromboembolism and described the consolidation of the lung parenchyma starting from lung apexand going through the middle and dorsobasal segments with the manifestation of typical signs of pulmonary edema. Hospital treatment was indicated

Soon after the admission to the pulmonary department, the patient's condition worsened. Central cyanosis occurred and repeated ABB showed: p H 7.51, p CO2 5.3, p O2 3.8, HCO3 30.4, BE 8.2, SaO2 63.5,

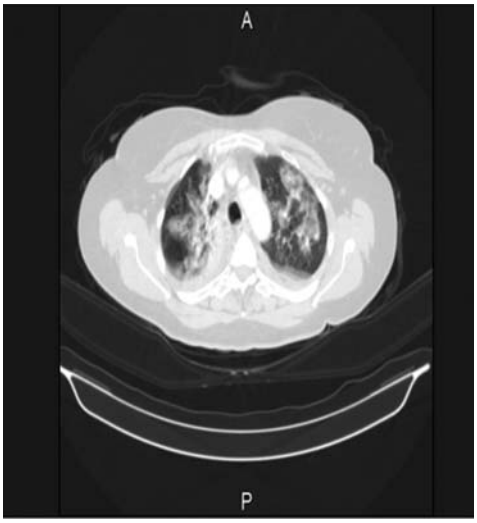

Figure 1 *— CT of patient's lungs*

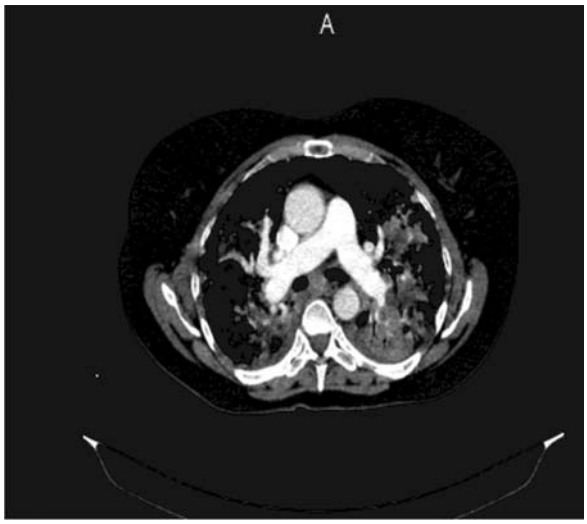

Figure 2 *— CT of patient's lungs arteries*

lactates 2.2. Due to the need for monitoring of vital functions, the patient was transferred to the Intensive Unit of the Internal Clinic.

After receiving the patient, an anesthesiologist was consulted, the patient was intubated and connected to mechanical ventilation A / C f12, FiO2 0.5. In the further course of the day, the patient was monitored by anesthetist for control of the respiratory pattern. The mode of mechanical ventilation was changed on several occasions depending on the condition of the patient (A/C, BiLevel, spontaneous). A therapy was given by pulmologists (corticosteroids, theophylline preparations, bronchodilatators, oseltamivir, combination of antibiotics for parenteral administration, antimycotics).

Subsequently, the arrival of the medical documentation from Publich Health Institute, a throat swab confirmed the presence of Influenza A, Real Time PCR was positive, as well.

The applied therapy led to a decrease in the value of CRP while maintaining high values of leukocytes. In the longer course of the treatment, a bronchoscopy was repeatedly made, respiratory tract toilete was done, and large amount of dense bleeding content was aspirated. BAL has been taken. Microbiological analysis showed the presence of Acinetobacter spp, which was accompanied bynew increase of inflammatory parameters (CRP, Le). The therapy included the antibiotic Collistin, due to the resistance of the bacterium to the standard antibiogram. Controlled MSCT lung arteries weremade-no signs of thrombotic changes. There were signs of bronchopneumonia on both sides.

Due to the need for further respiratory support, a tracheostomy has been done on the twelfth day of intubation. The day after tracheotomy at the control RTG, a pneumothorax on the leftside was diagnosed. A chest surgeon was consulted and a thoracic drain was placed. Two days after due to repeated pain in the chest and abdomen, a new RTG of the lung was made which diagnosed the existence of a right-sided pneumothorax and the thoracic drain was placed in the right pleural space. The patient's condition was gradually improving (ABB: p CO2 5.5, p O2 7.2, CRP 56.4), and on the seventh day after the placement of the thoracic drains, the patient was extubated. Serial lung radiographs were obtained which showed re-expansion of both lungs. On the 11th day after the placement of the first thoracic drain, the left thoracic drain was removed, and the right one two days later. The patient was then transferred into the pulmonology department for further monitoring where oral antibiotic therapy continued during the next two weeks, as well as other supportive therapy. The patient was discharged in good general condition, hemodynamically stable for further ambulatory monitoring.

DISCUSSION AND CONCLUSION

People in whom ARDS is recognized often require treatment in intensive care units. There is no specific therapy. The treatment is primarily supportive. Mechanical respiration and adequate use of oxygen play a major role. A key advancement in therapy is the knowledge that lung transduction with positive pressure can exacerbate the existing condition. This attitude has contributed to the development of a new strategy in the treatment of mechanical ventilation using small breathing volumes (6ml/kg) in combination with positive pressure at the end of the expiry (PEEP). Appropriate oxygen therapy in other medical conditions can also prevent secondary development of ARDS. Determan and associates performed a controlled randomized study with 150 patients that compared the use of small breathing volumes versus standard patients with critical illness and pointed to reduced production of inflammatory cytokines in patients treated with low air volume (8). Then, there are also adequate nutrition and hydration. Antibiotic therapy is mandatory, most often ex-iuvantibus. Corticosteroids are occasionally administered to resolvethe primary condition, otherwise their use is controversial. Correction of acid base status and other therapies (diuretics, analgetics, anxiolytics, antihypertensives) is regulated as needed. If the recovery does not occur in the first seven days, there is a greater likelihood that progressive lung injury will develop followed by inflammation of the interstitium, and later fibrosis.

Our patient is just an example of this treatment. Complications such as ventialtion-assisted pneumonia and bilateral pneumothorax have prolonged her healing. According to the International Nosocomial Infection Control Consortium (INICC), the frequency of VAP is 13.6 versus 1.000 days spent on ventilation sup-

port, although the incidence varies depending on the hospital groups and hospital conditions, so that the frequency of VAP ranges between 13-51 and 1000 days spent on ventilation. Patients who survive the ARDS episode usually have lasting effects that are reflected in reduced HRQOL (health related quality of life). Usually we talk about neurocognitive impairment and psychiatric illness. Proper treatment certainly reduces this risk (9, 10).

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

Abbreviations:

ARDS — acute respiratory distress syndrome
VAP — ventilation assisted pneumonia
PaO2 — arterial partial pressure of oxygen
FiO2 — fraction of inspired oxygen
CPAP — continuous positive airway pressure
TNF — Tumor Necrosis Factor
IL-1 — Interleukin 1
IL-6 — Interleukin 6
ABB — acide base balans
DAD — diffuse alveolar damage
NF kappa B — Nuclear factor-kappa B
PCP III — procollagen peptide III
BAL — Bronchoalveolar lavage
MRSA — Methicillin-resistant Staphylococcus aureus
CT — computerized tomography scan
RTG — radioisotope thermoelectric generator
A/C ventialtion — Assist Control ventilation
PCR test — polymerase chain reaction test
WBC — white blood cells
Hgb — hemoglobin
PLT — platelet
CRP — C reactive protein
AST — aspartate aminotransferase
ALT — alanine aminotransferase
GGT — gamma glutamiletransferase
LDH — lactat dehydrogenase
CK — creatine kinase
K — kalium ion
Na — natrium ion
D dimer — fibrin degradation product
PEEP — Positive end-expiratory pressure
INICC — International Nosocomial Infection Control Consortium
HRQOL — health related quality of life

Sažetak

AKUTNI RESPIRATORNI DISTRES SINDROM KAO KOMPLIKACIJA VIRUSNE PNEUMONIJE — PRIKAZ SLUČAJA

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ARDS je po život opasno stanje koje zahteva monitoring u jedinicama intenzivne nege. Ne postoji specifični način lečenja. Predstavljamo 49-godišnju pacijentkinju sa ARDS sa komplikacijama, kao što su ventilacijom izazvana pneumonia (VAP) i bilateralni pneumotoraks. Dobro poznavanje procesa može biti od pomoći pri odabiru odgovarajućeg načina lečenja i pri prevenciji, kao i pri prepoznavanju mogućih komplikacija. Adekvatna oksigeno terapija zauzima veoma bitno mesto u lečenju ovih pacijenata.

Ključne reči: ARDS, jedinica intenzivne nege, ventalicijom izazvana pneumonia, bilateralni pneumotoraks, oksigeno terapija.

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Case report

KLEPTOMANIA AND ATTENTION DEFICIT HYPERACTIVITY DISORDER — CASE REPORT

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Abstract: Kleptomania as a type of impulse control disorder (ICD) characterized by an inability to resist urges to steal objects not valuable or needed for personal use. Kleptomania may co-occurs with many psychiatric disorders frequently other impulse control disorders, obsessive-compulsive disorder, anxiety disorders, affective disorders, eating disorders and substance use disorders. We presented two adolescent cases admitted to Marmara University Child and Adolescent Psychiatry outpatient clinic because of stealing behavior and diagnosed with Kleptomania and ADHD. Both cases had improvement in stealing behavior after ADHD treatment.Careful monitoring of comorbid conditions in the psychiatric evaluation of Kleptomania cases is very important in terms of treatment and prognosis.

Key words: psychiatry, kleptomania.

INTRODUCTION

Kleptomania as a type of impulse control disorder (ICD)characterizedby an inability to resist urges to steal objects not valuable or needed for personal use (1). The average age is about 17, although 35% of the patients reports the onset of kleptomania as early as at age 11 (2). The prevalence and etiology of the disease is unknown due to low incidence of disease and not applying to hospital because of social stigma (3). The disorder is often diagnosed when patients seek help for comorbid disorders. Kleptomania may co-occurs with obsessive-compulsive disorder, anxiety disorders, affective disorders, eating disorders and substance use disorders (4).

The reare reports in the literature that Kleptomania cases benefit from different medications such as SSRIs, Lithium, Valproate, Opioid antagonists, stimulants in relation to the co-occuring psychiatric disorder. Subtyping of Kleptomania according to similarities to other psychiatric disorders may be useful to decide on treatment interventions (5). In this presentation, two adolescent cases who diagnosed with Attention Deficit Hyperactivity Disorder (ADHD)and Kleptomania and remitted after adding ADHD treatment will be described.

CASE 1

A 14-year-old girl was brought to our out-patient clinic because of her stealing behavior. In the interviews made with the mother, it was learnt that the behavior of the patient to receive non-essential objects had been presented for 5 years. It was also learned that she was a very active child, fidgeting in her seat, speaking too much, interrupting others and could not sit more than ten minutes while doing homework in her childhood. The patient expressed her complaints of unhappiness, irritability and forgetfulness too. The patient, who was embarrassed while talking about stealing behavior, said that in the third grade for the first time she stole her friends' pens and continued to steal without need. She also said that she had been feeling anxiety before this behavior, and she was feeling relief while stealing. Afterwards she regretted and put the stolen objects back. The mood of the patient was depressive, and the affect was markedly anxious. She felt guilty and remorse. She was diagnosed with Kleptomania, ADHD and Major Depressive Disorder due to history and psychiatric interviews. Patient's treatment was 1 mg of Risperidone and 50 mg of Sertraline daily. OROS MPH (osmotic release oral system Methylphenidate) 18 mg per day was initiated and planned dose increase.

CASE 2

A fifteen-year-old boy admitted to our outpatient clinic because of stealing money or goods belonging to

others. His father said that the patient stole these objects although he did not need and that the patient continued to this behavior, even though his mother was ill after she heard what he had been done. It was also learned that the patient was easily distracted and delayed homework during the school years and was overactive in childhood, but had no behavioral problems, such as opposing to authority figures, harming animals or someone else's property. The patient verbally communicated, but gave short answers to the questions. Mental status examination revealed that patient's mood was depressiveand his affect was appropriate with depressive mood. Thought process was normal. There was regret and depressive themes about stealing behavior in thought contents. The patient was diagnosed with ADHD, Major Depressive Disorder, and Kleptomania. and Sertraline 25 mg perday, Risperidone 0,5 mg per day treatment was initiated. Subsequent interviews indicated that the patient was morally better but the desire to steal continued to be less. Significant improvement in the condition of the patient has been seen since the use of Risperidone medicine discontinued and OROS MPH added to treatment. The patient's treatment continues as Sertraline 25 mg, OROS MPH 27 mg per day.

DISCUSSION AND CONLUSION

We presented two adolescent cases admitted to Marmara University Child and Adolescent Psychiatry outpatient clinic because of stealing behavior and diagnosed with Kleptomania and ADHD. Both cases had improvement in stealing behavior after methylphenidate treatment. Kleptomania is defined as an impulse control disorder and the impulsivity is one of the main symptoms of the syndrome of ADHD. Dopaminergic systems have been implicated in impulsivity and impulse control disorders. Dysregulation of the dopamine system has been implicated in ADHD, too (6). The number of studies investigating the relationship between Kleptomania and other impulse control disorders in child and adolescents are rare. In one study, researchers reported that 15% of patients diagnosed with Kleptomania meet criteria for ADHD (5). Although the relation between Kleptomania and ADHD has not been proven, there are case reports indicating that the stealing behavior reduced after treatment of ADHD. Hergüner et al. reported that a 16 year-old girl diagnosed with ADHD and Kleptomania and remitted during methylphenidate treatment. They suggested that improving in Kleptomania may be related to the effect of MPH on dopaminergic systems (7). The other case report presents a school-age girl with ADHD suggested that the positive effects of methylphenidate on Kleptomania may be related to its ability to suppress the urges linked to experiencing reward and pleasure (8).

In the present case; it's indicated that MPH is effective in the treatment of Kleptomania comorbid with ADHD. Comorbid conditions need to be considered as they may affect the course and outcome of Kleptomania.

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

Abbreviations:

ICD — impulse control disorder

ADHD — attention deficit hyperactivity disorder

OROS MPH — osmotic release oral system Methylphenidate

Licensing

Sažetak

KLEPTOMANIJA I POREMEĆAJ PAŽNJE I KONCENTRACIJE — PRIKAZ SLUČAJA

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Kleptomanija kao vrsta impulsivnog poremećaja kontrole (ICD) karakteriše se nemogućnošću da se kontroliše nagon za krađom stvari, koje nisu od vrednosti ili koje nisu potrebne osobi. Kleptomanija može da se javi zajedno sa mnogim drugim psihijatrijskim poremećajima kontrole, opsesivno-kompulsivnog poremećaja, poremećajima povezanim sa anksioznošću, afektivnim poremećajima, poremećajima sa unosom hrane i zloupotrebom supstanci. Predstavićemo dva slučaja gde su pacijenti adolescenti koji su primljeni u Marmara Univerzitetsku dečiju bolnicu i Dnevnu bolnicu za mentalne poreća-

je adolescenata zbog ponašanja povezanog sa krađom i dijagnozom Kleptomanije i ADHD. U oba slučaja se pokazao značajan napredak u pogledu ponašanja povezanog sa krađom nakon lečenja ADHD. Pažljiv monitoring komorbidnih stanja u psihijatrijskoj evaluaciji kleptomanije je od ključnog značaja za lečenje i prognozu.

Ključne reči: kleptomanija, psihijatrija.

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Review article

IDENTIFICATION OF NEW MOLECULAR BIOMARKERS — PROTEOMICS

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Abstract: The pathogenesis of the tumor is extremely complex and can not be fully explained by the existing methodological approaches. Proteomics is an interdisciplinary science that deals with the study of proteins, carriers of the biological functions of the organism. It encompasses a series of methods for protein analysis and provides exceptional possibilities for understanding the molecular basis of the disease, the possibilities of early diagnosis, and the production of new drugs. Proteomic analyzes of the malignancy altered tissue have revealed proteins involved in the progression of the disease, and thus contributed to the discovery of potential drug treatment methods. Proteomics provides a better understanding of the molecular basis of these diseases, plays a role in the diagnosis of the same, and it is expected to make a significant contribution to the development of new more effective drugs and the development of personalized therapy.

Key words: proteomics, proteins, biomarkers, tumors.

IDENTIFICATION OF NEW MOLECULAR BIOMARKERS — PROTEOMICS

The pathogenesis of the tumor is extremely complex and it is not possible to fully clarify it with existing methodological approaches. It is therefore extremely important to get a more accurate knowledge of the molecular basis of this disease. Understanding changes at protein level represents a step closer to understanding tumor pathogenesis (1).

Different parts of the protein are accumulated in the exocomes of lung cancer cells that could be used for the early diagnosis of this cancer.

Jakobsen et al. reported that CD317 and epidermal growth factor receptor (EGFR) were highly expressed on exosomal surface, by analyzing the extracellular vesicles secreted by lung cancer cells. These molecules are reliable biomarkers for diagnosing non-small cell lung cancer (NSCLC). Research has shown that human leucine rich alpha-2-glycoprotein 1 (LRG1) in urinary exosomes was a potential biomarker for diagnosing NSCLC. Sandfeld et al. used 49 antibodies to detect exosomal proteins from 431 lung cancer patients and 150 healthy individuals. They found that CD171, CD151 and tetraspanin 8 were significantly highly expressed in patients as compared to healthy individuals. In squamous-cell carcinoma and small-cell lung cancer patients, CD151 is also an independent biomarker. Recently, exosomes in peripheral blood were reported to contain 30 specific biomarkers.

Latent membrane protein 1 (LMP1) in exosomes from nasopharyngeal cell lines infected with Epstein Barr virus (EBV), nasopharyngeal cancer cells could release HLA II and exosomes containing galectin 9 and/or LMP1. LMP1 could inhibit T cell viability. Klibi et al. found exosomes carrying LMP1 in blood and saliva from the nasopharynx of cancer patients. Houali et al. detected LMP1 and BARF1 coded by EBV in serum and saliva from teenagers and adults, and in adult nasopharyngeal cancer patients' serum and saliva at 62% and 100%, respectively. Animal experiments demonstrated that LMP1 secretion was related to exosomes. Both proteins were good markers for nasopharyngeal cancer diagnosis, especially BARF1, because it covered the entire age range. Their pro-mitotic activities facilitated the occurrence and development of nasopharyngeal cancer. Cancer exosomes could be continuously detected in the plasma of nasopharyngeal cancer patients. The increase in serum exosomal concentration of nasopharyngeal cancer patients was closely related to terminal-stage lymphatic metastasis and poor prognosis.

Glypican-1 (GPC1)-positive exosome is a diagnostic index of early stage pancreatic cancer. Circulating exosomes containing GPC1 (GPC1 + Exos) were isolated from blood of 250 pancreatic cancer patients, which helped to distinguish between chronic pancreatitis and pancreatic cancer patients. In animal experi-

ments, GPC1 + Exos in blood were significantly increased, before cancer imaging could be used. GPC1-positive exosomes could also be used as a preoperative and postoperative prognostic index. GPC1 + Exos was a significantly better prognostic marker of pancreatic cancer than CA19–9. Thus, GPC1 + Exos could be used to diagnose pancreatic cancer at early and terminal stages with high accuracy and sensitivity, and as a detection index for therapy. Macrophage migration inhibitory factor (MIF) was found to promote hepatic metastasis of cancers, and could be used as an early stage diagnostic marker for pancreatic cancer hepatic metastasis.

A mouse liver damage model was established to analyze urinary exosomal proteomics. Twenty-eight novel exosomes closely related to disease were found, in which CD26, CD81, S1C3A1 and CD10 could be used as markers for hepatic damage. In cholangiocarcinoma model caused by Opisthorchis viverrini, 154 proteins were disrupted after cancer onset. To find the specific marker for diagnosing cholangiocarcinoma caused by Opisthorchis viverrini in circulating body fluids, exosomes from peripheral circulation of patients were extracted and compared with those from cholangiocarcinoma cell line KKU055. Finally, 27 specific proteins were identified, which provided an experimental basis for cholangiocarcinoma diagnosis.

In gastric cancer exosomes play an important function in the interaction between cancer cells, the vascular endothelial cells and the macrophages. Exosomes derived from gastric cancer cells could also stimulate the activation of the NF-kB pathway in macrophages to promote cancer progression . Recent evidence has found that AZ-P7a, a metastatic gastric cancer cell line, released let-7 miRNAs via exosomes into the extracellular environment to maintain the oncogenesis. The enrichment of let-7 miRNA family in the exosomes from AZ-P7a cells may reflect metastasis in gastric cancer. CD97 promotes gastric cancer cell proliferation and invasion in vitro through exosomes-mediated MAPK signaling pathway, and exosomal miRNAs are probably involved in the activation of the CD97-associated pathway. the Cbl family of ubiquitin ligases might be involved in regulation of exosome-induced apoptosis of Jurkat T cells by increasing PI3K proteasome degradation, inactivation of PI3K/ Akt signaling, thus mediating some effects of caspase activation.. The role of tetraspanin 8-containing exosomes is associated with cell growth and invasion in GC; tetraspanin 8 is an independent prognostic factor in patients with gastric cancer. Gastric cancer cells triggered the differentiation of human umbilical cordderived mesenchymal stem cells to carcinoma-associated fibroblasts by exosomes-mediated TGF-ß transfer and activation of the TGF-ß/Smad pathway, which may represent a novel mechanism for MSCs-to- CAFs transition in cancer. Furthermore, the Cbl family of ubiquitin ligases might be involved in regulation of exosome-induced apoptosis of Jurkat T cells by increasing PI3K proteasome degradation, inactivation of PI3K/ Akt signaling, thus mediating some effects of caspase activation. Exosomes derived from human mesenchymal stem cells promote gastric cancer cell growth and migration via induction of the epithelial-mesenchymal transition and the activation of the Akt pathway. CD97 promotes gastric cancer cell proliferation and invasion in vitro through exosomes-mediated MAPK signaling pathway, and exosomal miRNAs are probably involved in the activation of the CD97-associated pathway. The role of tetraspanin 8-containing exosomes is associated with cell growth and invasion in GC; tetraspanin 8 is an independent prognostic factor in patients with gastric cancer. Additionally, TEX may play a critical role in the development of peritoneal metastases of gastric cancer, which may partially be due to the increased expression of the adhesion molecules fibronectin 1 (FN1) and laminin gamma 1 (LAMC1) in mesothelial cells. Baran et al. found that the number of exosomes was significantly higher in gastric cancer patients than in the normal control group. Expressions of human epidermal growth factor receptor (HER-2/neu) and human chemokine receptor-6 (CCR6) were significantly increased on exosomal surface in blood. Cancer markers such as HER-2/neu, melanoma antigen (MAGE) and c-Met as well as extracellular matrix metalloproteinase inducer (EMMPRIN) could be detected in exosomes from normal controls and gastric cancer patients. However, the patients expressed higher levels of these markers, of which MAGE-1 and HER-2/neu mRNA had significantly higher expression in exosomes from gastric cancer patients. Adenomatous polyposis coli (APC) mutation was found in early stage colorectal cancer, invisible chromosome familiar adenomatous polyposis and most sporadic colorectal cancers, and might lead to its occurrence and development. Comparison between SW480 cells transfecting APC gene plasmid and exosomal proteome secreted by SW480 cells showed that dickkopf-related protein 4 (DKK 4) was highly expressed in exosomes of SW480 cells transfecting APC gene plasmid. In these cells, methylation level of DKK 4 gene promoter was decreased, suggesting that colorectal epithelial cells might up-regulate DKK 4 transcription and expression by down-regulating methylation of DKK 4 gene promoter, and further promote occurrence and development of colorectal cancer by exosomes secreting DKK 4 and inducing APC gene mutation. The comparison of exosomal proteome between KRAS wild type DKS-8 cells of human

colon adenocarcinoma cells DLD-1 and K-RAS mutant type DKO-1 cells indicated that DKS-8 secreted by DKO-1 exosomes was not only significantly proliferated but its invasion capacity was also increased. These experiments demonstrated that colorectal cancer exosomes played a critical role in maintaining cancer cell survival, proliferation and invasion of microenvironment. Silva et al. quantitatively detected plasma exosomes from 91 colorectal cancer patients and found that the number of exosomes was significantly higher than in the control group, and also significantly correlated with carcinoembryonic antigen (CEA). Plasma exosomes in colorectal cancer patients can be used as a cancer marker that is closely related to disease development and poor prognosis (2)

Some of the biomarkers used in clinical work (diagnostic, predictive, prognostic and biomarkers for disease monitoring) are shown in Tables 1-4 (2, 3).

Table 1. *Diagnostic biomarkers*

Acute leukemia	PML-RARA	
	BCR-ABL1	
	CBFB-MYH11	
	ETV6-RUNX1	
	RUNX1-RUNX1T1	
	MLL-rearranged	
	TCF3-PBX1	
	RBM15-MKL1	
MPD	JAK2	
Sarcoma	SS18-SSX1/SSX2	*Synovial sarcoma*
	PAX3/PAX7-FOXO1A	*Alveolar rhabdomyosarcoma*
	EWSR1-FLI1 EWSR1-ERG	*Ewing's sarcoma*
	EWSR1-NR4A3 TAF15-NR4A3	*Extraskeletal myxoid chondrosarcoma*
	EWSR1-ATF1 EWSR1-CREB1	*Clear cell sarcoma and angiomatoid fibrous histiocytoma*
	ASPSCR1-TFE3	*Alveolar soft-part* *Sarcoma and renal cell carcinoma*
	FUS-DDIT3	*Myxoid liposarcoma*
	FUS-CREB3L2	*Low-grade fibromyxoid sarcoma*
	JAZF1-SUZ12	*Endometrial stromal sarcoma*
	ETV6-NTRK3	*Congenital fibrosarcoma and secretory breast carcinoma*

Table 2. *Predictive biomarkers*

NSCLC	**EGFR**	*Mutations predict response to TKI*
	ALK	*Rearrangements predict response to ALK-inhibitors*
GIST	**KIT and PDGFRA**	*Mutations predict response to c-KIT/PDGFRA inhibitors*
mCRC	**KRAS**	*Mutations predict lack of response to anti-EGFR antibodies*
Melanoma	**BRAF**	*Mutations predict response to specific BRAF inhibitors*
Breast cancer	**HER2**	Amplifications predict response to anti-HER2 antibodies

Table 3. *Prognostic biomarkers*

CLL	**TP53** **IGHV**	*Mutations are indicative of poor outcome* *Lack of mutations is indicative of poor outcome*
AML	**FLT-3-ITD**	*Mutations are indicative of poor outcome*
mCRC	**BRAF**	*Mutations are indicative of poor outcome*
Breast cancer	**OncotypeDx** **Mammaprint** **IHC4**	*Risk stratification (21-gene expression signature)* *Risk stratification (70-gene expression signature)* *Risk stratification (4-protein IHC expression)*

Table 4. *Biomarkers for disease monitoring*

CML	**BCR-ABL1**	*Minimal residual disease detection*
APML	**PML-RARA**	*Minimal residual disease detection*
ALL	**IGHV-TCR rearrangements**	*Minimal residual disease detection*

Proteomics is an interdisciplinary science that deals with the study of proteins, carriers of the biological functions of the organism. It encompasses a series of methods for protein analysis and provides exceptional possibilities for understanding the molecular basis of the disease, the possibilities of early diagnosis, and the production of new drugs. The task of proteomics is extremely complex and includes the monitoring of the status of a proteome that represents a set of all proteins and protein forms that the body produces throughout life. Although it has been estimated that the total number of genes is close to 30.000, the entire human protease consists of several million types of proteins due to various modifications of the RNA transcript and chemical modifications of the proteins themselves (4).

Proteins as molecular effectors of biological processes play an important role in the pathogenesis of the disease, and it is precisely the detection of proteins that are associated with a certain disease that is a step towards diluting the disease. Proteomics methods allow simultaneous monitoring of several thousand different proteins and their isoforms. The modified protein can enter into new interactions with other molecules with which another normal protein chemically does not react. The importance of viral oncogens is known, namely cells modified by the input of viral genes often exhibit new virus-associated antigens that can recognize the immune system. Oncogenic viruses are DNA or RNA type depending on the genetic information carried by the intact virus. It has been found that several human DNAs contain potential oncogenes and are associated with malignancy (e.g., Epstein - Barr virus and nasopharyngeal carcinoma, Burkitt lymphoma and Hodgicon lymphoma, a link between HPV and cervical, anorectal and cutaneous carcinoma). Both viral and cellular oncogenes in certain situations can lead to the transformation of the normal cell. Cellular oncogenes encode a range of proteins that can be normal or altered structures, such as cellular enzymes (protein kinases), nucleic and membrane proteins, making the cell's malignant immunologically different from the normal cell (5).

The molecular basis of the disease can not be understood only by studying the gene, but it is necessary to analyze the genetic protein products. Signal pathways in which proteins are involved have been altered in tumor cells, which confirms that protein analysis can provide an answer to the pathogenesis of the disease (6, 7).

The expression of the gene or protein expression provides the possibility of classifying the tumor. However, gene studies follow the level of information RNA expression where the strength of gene expression does not always correspond to the protein expression. Proteomics research provides more important information in understanding the mechanisms of protein activation and posttranslational changes that are responsible for the tumor cell phenotype and the processes that occur in them (1).

Using the proteomics method want:

• determine the difference in the expression profile between the individual groups, and determine which proteins are differently expressed between these groups (e.g., the difference in the expression profile between the histological tumor subtypes or the identification of proteins whose level is disrupted by cell exposure to the effect of a new experimental drug)

• determine the subgroup of proteins in a sample with respect to the expression pattern
(for example, the discovery of an unknown lymphoma subspecies based on an espression profile certain groups of gene)

• anticipate the phenotype using information obtained from the expression of the expression profile (for example, in which patient a severe symptomatology will be experienced after using a drug, or which patients with a breast tumor diagnosis and "negative" lymph nodes will experience relapses after two years of illness (4).

Characteristics of proteins, such as their complex nature and variability, require the development of a very sensitive and selective technology that will allow simultaneous analysis of thousands of proteins. The function of the protein depends on a number of different factors, such as the level of expression, posttranslational modification, interactions with other proteins or DNA / RNA molecules, mechanisms of activation and repression. The expression of protein in the biological composition changes with the stage of development, by the action of the environmental factors, disease progression, and the number of proteins in the eukaryotic cell is high. In molecular medicine, several modern proteomic techniques are available that enable the exploration of protein expression, protein modification analysis, cellular location analysis, and protein interaction monitoring. The disadvantages of proteomic methods are that proteomics are sometimes quite compli-

cated and time-consuming technology. There is also a need for further improvement of proteomic methods in order to find a link between genes, proteins and the onset of disease, improvement of methods in the detection and characterization of proteins, both in the field of analysis of low molecular weight proteins and peptides (below 500 Da), as well as in the field of analysis of extremely large protein structure (above 120 kDa), and in improving quantification (8).

METHODOLOGY OF PROTEIN RESEARCH

The methodology of protein research uses a classical approach based on gel analysis ("shotgun" approach) using immobilized pH gradients by which proteins are separated based on their isoelectric points. Then, separation in the second dimension based on the molecular weight by using sodium dodecyl sulfate polyacrylamide gel electrophoresis, the gel provides a number of points representing proteins, various isoforms of the same protein or its posttranslational modification. Following the separation of the proteins on the gels, the identification of the separated and quantified proteins on the mass spectrometer is followed. In this way, the expression and type of proteins in the patient can be determined in relation to the healthy tissue.

MALDI-TOF (matrix-assisted laser desorption ionization time of flight) is a method for identifying proteins derived from the gel, based on the principle of degradation of each protein with the help of trypsin and their ionization. Thereafter, a comparison of the mass of the fragments with the spectra found in the database is performed, and thus the type of protein is determined.

In the analysis of ESI-MS / MS (electrospray ionization tandem mass spectrometry), the sample is ionised in the form of fine spray spray, after evacuation into the vacuum the water is evaporated and the molecules in the solution take up the charge. In contrast to the MALDI analysis, the molecular ions in the ESI-MS / MS analysis are generally multiply charged. The ESI-MS / MS analysis analyzes the samples in liquid state, and this method is often associated with high performance liquid chromatography (HPLC). The combination of HPLC and ESI-MS / MS is basically a "shotgun" approach that involves the isolation of hundreds of proteins from extremely complex mixtures obtained by proteolytic protein breakdown (eg in body fluids), followed by MS sequencing. This LC-MS / MS (liquid chromatography MS / MS) method is better than the classic proteomic approach. Namely, the LC-MS / MS method allows the separation and identification of analytes in the low femtolomolar range so that a large part of the biomarker detection research will be carried out in this way.

MudPIT (multidimensional protein identification technology), ICAT (isotope-coded affinity tags) and ICPL (isotope-coded protein labels) are also important "shotgun" techniques.

MudPIT is a method for identifying proteins from complex mixtures. The MudPIT method is based on a chromatographic separation of the protein in two dimensions, so that the proteins are first separated on the basis of the charge in the SCX column (strong cation exchange column), followed by reversed chromatography by which the peptides are separated based on their lipophilicity. This method is compatible with the ESI method in which its advantage is reflected.

ICAT and ICPL methods are based on the labeling of light and heavy isotope proteins in two analyzed samples. Subsequently, by means of mass spectrometry, the relative amount of the labeled molecules is determined based on the mass of the stable isotope used, such as carbon isotope. Thus, quantitative changes can be made in protein cells induced by some disease or therapeutic procedure.

Also, there is an ongoing tendency to research posttranslational modifications (eg phosphorylation, glycolization and ubiquitination) as these chemical modifications of proteins often determine protein activity and stability. In the pathogenesis of the tumor, phosphorylation of the amino acid tyrosine occurs in some regulatory proteins as a result of mutation or excessive expression of signal proteins. The traditional approach to posttranslational modification studies involved the purification of this protein, the peptide analysis and the identification of phosphorylated peptide regions by the method of determining the N-terminal sequence. However, mass spectrometry is increasingly used to isolate phosphoprotein-containing peptides from cellular extracts using antibodies specific to phosphotyrosine, followed by identification by MS / MS. The study of these modifications in complex protein mixtures has been improved over the past years thanks to the cation exchange chromatography method, which specifically binds the phosphate group of phosphorylated proteins, and thus the isolated proteins can be identified by the technique MS.

The SELDI-TOF-MS method (surface-enhanced laser desorption ionization - TOF-MS) is a method for detecting markers in various tumors. It is based on the use of different types of protein chips, depending on which protein fraction will be analyzed. The most commonly used chemical chips (anionic, cationic, hydrophobic, hydrophilic, metal ions) and biochemical chips (immobilized antibody, receptor, DNA, enzyme) on which the desired protein from the mixture is retained. After binding of the protein from the mixture to the surface of the chip, a laser directed to them is used,

the proteins or protein fragments are transferred to the gaseous phase and analyzed in the objectives of the TOF mass spectrometer. This method was important for the detection of numerous diagnostic markers for tumors, as well as for the characterization of a large number of phosphorylated and glycolized proteins and transcription factors (6, 9).

The disadvantage of all of the aforementioned methods is that they do not clarify the biological functions of the protein and their role in signaling pathways in malignant tumors. However, for this purpose, protein chips are used which enable the analysis of various signal proteins and their activation state. Based on this approach, information about the type of protein, expression, protein interactions, binding of receptor ligands and enzymatic activity can be obtained (6).

There are two types of protein chips:

1. An analytical protein chip: contains antibodies, antigens or other proteins to determine the amount of labeled proteins in the sample.

2. Functional protein chip: contains a large number of cellular proteins or tissue proteins, various biochemical activities such as protein-protein, protein-lipid, protein-nucleic acid interaction and enzyme-substrate interactions are examined.

After binding of proteins from the mixture onto the chips, if the antibodies are applied, the activated proteins can easily be detected and the activation status of the entire signaling pathways can be determined (for example, because the phosphospecific antibody binds to the phosphorylated protein interacting with the peptide on the chip) (6).

APPLICATION OF PROTEOMICS

A number of studies have been published on the application of proteomics in clinical practice. In a study on ovarian tumors, a hypothesis was found that pathological changes within the organs reflect the serum proteomic profile and how precisely the serum can be used as a material for early detection of the disease. The authors of the study indicated that pathological changes within the ovaries could be reflected on the proteomic serum profile, which would aim to differentiate neoplastic ovaries from the rest. The authors made a proteomic serum analysis using mass spectrometry. The results showed that the proteomic profile enabled the identification of all 50 patients with cancer. Of the 66 non-malignant samples, as many as 63, the proteomic profile was recognized. This study has shown that it is possible to apply proteomic methods for the detection of all stages of ovarian tumors (10).

Carcinoma of the breast is one of the carcinoma of very high frequency. An example of breast cancer has revealed that human growth hormone (hGH) is of great importance in the progression of this disease. Namely, growth hormone can be one of the main drivers of the metastasis process. By coagulating the breast carcinoma line MCF-7, it was found that autocrine production of hGH in cells was the driving force of their migration into the surrounding matrix through the process of transforming E-cadherin. Autocrine regulation of hGH in breast cancer was found to be associated with the activation and localization of Pax-5 protein into the nucleus, which is sufficient to induce proliferation of tumor cells. In addition to the importance of autocrine regulation of breast tumors during proteomic research, a number of proteins have been discovered that are important for understanding the molecular basis of breast tumors. It was found that these proteins participate in cell growth, oncogenic progression to cell death processes. Using the protein chips that contain immobilized antibodies on its surface, the activation of the ERBB receptor has been analyzed, which is an important factor in the malignant breast cancer phenotype. Methods of proteomics enabled the thorough investigation of the role and mode of action of the receptor and proteins of this signaling pathway associated with metastasis, progression and poor clinical prognosis of the disease. The proteomic profile of a healthy and malignant breast tissue sample was investigated, with a number of proteins with increased expression found in malignant tissue. Among the other proteins are casein kinases, p53, annexin XI, CDC25C, elF-4E, and MAP kinase 7, and in malignant tissue decreased expression of the multifunctional regulator 14-3-3e. Using the 2-DEV gel electrophoresis method after which the differential expression proteins are identified by the MS-MS (MALDI-TOF) technique and thanks to this approach in tomoral breast cancer, numerous possible new biomarkers. They include proteins that may be associated with the onset or progression of this disease, which are galectin-1, annexin-5, annexin-1, LDH-B, GST-pi, actin, vimentin, HSP70, CK18 and moezin.

The significance of cytookeratin 19 in cellular events that resulted in severe malignant proliferation of breast cancer cells was also established. A number of proteins significantly related to the metastasis of breast cancer, such as osteopontin and osteonectin, have also been discovered, and it has been found that metalloproteinases of matrix 1 and annexin 1 are associated with the phenotype of non-metastatic cells.

A study conducted on four tumor cell lines, which is basically a common genetic background. These cell lines gradually gained metastatic potential through culture growth. Using the iTRAQ ESI-LC / MS / MS method (isobaric tag for relative and absolute quantification electrospray ionization-liquid chromatography), chan-

ges were found likely to cause a change in phenotype, and it was found to be protein from the kinase family, phosphatase and some transcriptional factors.

With increased invasiveness of the cells, the expression of SH3GLB1 protein would decrease, and the expression of the protein SUB1, SND1 and TRIM28 increased. Also, multidimensional protein identification methods have identified activity for more than 50 proteins, and up to one third of that number have not been linked to breast cancer until then.

SELDI-TOF (Surface-Enhanced Laser Desorption / Ionization-Time Of Flight) was compared to tumor and healthy tissue, and in this way identified 38 expressed protein expressions (Wdr1, korornin-1A and p34-Arc) and 15 reduced-expression proteins (1, 11).

In patients with urinary bladder carcinoma using proteomic methods in protein analysis in urine samples, psoriasic protein was identified as an early marker of this diseases (6).

THE ROLE OF PROTEOMICS IN TUMOR THERAPY

Proteomics enable understanding of the molecular basic disease, provides the possibility of early diagnosis of the disease, so it is somewhat understandable that the proteomy will also contribute to the design of a new generation of drugs. Protein profiles can be used as significant markers in diagnosis of the disease, however, a large number of proteins that have a significant role in cellular processes relevant to the development of malignant tumors have still not been detected (12, 13).

Radioresistance continues to be a major problem in the treatment of NPC. The molecular mechanisms underlying NPC radioresistance are still unclear, and till now, there have not been effective biomarkers for predicting NPC radiosensitivity. Identification of NPC radioresistance–associated proteins will be helpful for finding biomarkers to estimate NPC response to radiotherapy and deciphering the molecular mechanisms of NPC radioresistance (14).

Proteomic methods increasingly find their place in discovering the early stages of the disease, discovering new targets and biomarkers, and determining the therapy depending on the condition of the patient. Using proteomic methods it is expected that in contrast to the drugs currently used and aimed at one molecular target, in the future, the target will be a whole set of proteins in the signal path (6, 15).

The pharmaceutical proteomics can be divided into:

1. Functional proteomics - includes the study of protein interactions, determination of the function and location of protein in the cell, as well as the interaction between proteins between each other and the protein and the DNA and RNA molecules.

2. Expression proteomics - includes protein expression expression. Investigates global changes in the expression of proteins produced in response to internal or some external factor (drug, environmental factors). By comparing proteins expressed in tissue samples or body fluids of healthy individuals compared to samples of patients (serum, plasma, liquor), cell processes and biochemical pathways of proteins that are significant in the onset and progression of the disease can be determined. This is the principle on which the identification of proteins, which would be used as biomarkers of the disease and as potential targets for the drug, would be based (6).

Proteomic tissue analyzes that have been affected by malignant disease have revealed proteins involved in the progression of the disease, and thus contributed to the discovery of potential drug treatment methods. A common problem in the therapeutic approach is resistance to chemotherapy. It is precisely thanks to the proteomic analysis of the cells that are sensitive to the drug in relation to those that are resistant, the identification of a specific resistance marker group is possible, which contributes to the development of new therapeutic approaches and consequently expects a better response of the patient to the administered drug (6).

By detecting the pattern of tumor formation and the network of signaling pathways of the receptors, there is an objection to the question of how to effectively treat tumors. All of this leads us in the time of personalized molecular medicine, where each patient will receive treatment after analysis of the diseased tissue depending on the expression profile of the tumor (1).

CONCLUSION

Proteomics provides a better understanding of the molecular basis of malignancies, plays a role in the diagnosis of the same, and it is expected to make a significant contribution to the development of new more effective drugs and the development of personalized therapy. Taking into account the importance of malignant diseases, the high rate of their morbidity and mortality, it is clear that the proteomics range can be of great importance and may lead to revolutionary changes in the diagnosis and treatment of malignancies.

DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests

Abbreviations:

et al. — and others
e.g. — for example

EGFR — epidermal growth factor receptor
NSCLC — non-small cell lung cancer
LRG1 — leucine rich alpha-2-glycoprotein 1
LMP1 — latent membrane protein 1
EBV — Epstein Barr virus
GPC1 — glypican-1
MIF — migration inhibitory factor
FN1 — fibronectin 1
LAMC1 — laminin gamma 1
HER-2/neu — human epidermal growth factor receptor
CCR6 — human chemokine receptor-6
APC — adenomatous polyposis coli
DKK 4 — dickkopf-related protein 4
CEA — carcinoembryonic antigen
ESI-MS / MS — electrospray ionization tandem mass spectrometry
HPLC — high performance liquid chromatography
LC-MS / MS — liquid chromatography MS / MS
MudPIT — multidimensional protein identification technology
ICAT — isotope-coded affinity tags
ICPL — isotope-coded protein labels
SCX column — strong cation exchange column
SELDI-TOF-MS method — surface-enhanced laser desorption ionization — TOF-MS
hGH — human growth hormone
iTRAQ ESI-LC / MS / MS method — isobaric tag for relative and absolute quantification electrospray ionization-liquid chromatography
SELDI-TOF — Surface-Enhanced Laser Desorption / Ionization-Time Of Flight

Licensing

Sažetak

IDENTIFIKACIJA NOVIH MOLEKULARNIH BIOMARKERA —PROTEOMIKA

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Patogeneza tumora izuzetno je složena i nije je moguće u potpunosti razjasniti postojećim metodološkim pristupima. Proteomika je interdisciplinarna nauka koja se bavi proučavanjem proteina, nosilaca bioloških funkcija organizma. Obuhvata niz metoda za analizu proteina i pruža izuzetne mogućnosti razumevanja molekularne osnove oboljenja, mogućnosti ranog dijagnostikovanja, ali i proizvodnje novih lekova. Proteomske analize tkiva koja su zahvaćena malignim oboljenjem otkrile su proteine koji učestvuju u progresiji oboljenja, a samim tim doprineli su otkrivanju potencijalnih metoda za delovanje lekova. Proteomika omogućava bolje razumevanje molekularne osnove ovih oboljenja, ima ulogu u dijagnostici istih, a od nje se očekuje značajan doprinos u razvijanju novih efikasnijih lekova i razvoju personalizovane terapije.

Ključne reči: proteomika, proteini, biomarkeri, tumori.

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Review article

PURE RED CELL APLASIA INDUCED BY ERYTHROPOIETIN

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Abstract: **Introduction:** Recombined human erythropoietin has been present in clinical practice for more than 20 years, in these therapeutic indications: anemia in kidney insufficiency, anemia during chemotherapy of tumors, prevention of anemias that appear in premature born babies, it is used for increasing autologous blood cell levels before blood transfusion, AIDS joined anemia (intensified by zidovudine), anemia joined with chronic inflammatory conditions such as rheumatoid arthritis(still in research phase). During the course of Erythropoietin treatment side effects have been noticed, that include multiple organ systems, and have different levels of frequency. Major number of studies shows connection between erythropoietin treatment and bone marrow aplasia, but small number of them states clearly defined side-effect that explains this phenomenon.

Objective: Goal of this paper is to analyze available case studies of bone marrow aplasia during erythropoietin application, access their quality and causality of every study.

Method: Research of literature used for the preparation of this systematic review has been conducted during the period of November- December 2017. In search for literature medical base PubMed has been used. Inclusion criteria were: available full article, publications in English language, publications conducted on humans, and case report studies. Eight studies passed selection.

Results: results were presented by 5 charts: documentation size, credibility, number of case study reports of side-effects in the paper that was graded, Naranjo causality score, data extraction chart. Mean grade value of the studies quality was 7,0, while mean Naranjo score was 6,6.

Key words: erythropoietin, erythropoietin side effects, anti-erythropoietin antibodies, pure red cell aplasia.

INTRODUCTION

Erythropoietin regulates the development of erythroid cell line from proerythroblast to erythrocyte. Loss of blood, and/or low tissue oxygen levels are the basic stimulus for its release into the bloodstream. Erythropoietin is produced in the juxtaglomerular cells of the kidney and for one small part in the macrophages. Basic effect of erythropoietin is to stimulate proliferation of erythrocyte precursor cells and create new erythrocytes. As a consequence of kidney disease, due to diminished erythropoietin synthesis, anemia can occur (1).

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes, caused by different etiologic factors, associated with abnormal kidney function and a progressive decline in glomerular filtration rate, often leading to the end stage renal disease (ESRD). *Term end-stage renal disease* represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the *uremic syndrome*. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation (2). Anemia occurs in more than 80% of patients with compromised kidney function (3). In patients with CKD the main cause of normocytic, normochromic anemia is insufficient erythropoietin production in damaged kidneys (4). Factors contributing to the occurrence of anemia can be: loss of iron due to various diagnostic procedures, blood retention in the dialysis machine, gastrointestinal bleeding, hyperparathyroidism, acute and chronic inflammatory diseases, aluminum toxicity, lack of folic-acid (5).

In order to solve the problem of anemia in dialysis patients, a group of researchers in 1985 cloned a human gene for erythropoietin. Two years later, the successful results of this study were published by The New England Journal of Medicine, latter In 1989, FDA approved the use of this hormone, in patients with CKD on dialysis (6). Erythropoietin is a glycoprotein structured hormone. The average molecular weight is 32, 00040,000 Daltons. The protein portion accounts for about 58% of the molecular weight (165 amino acids). Within its molecule there are four carbohydrate

chains linked through 3 N-glycosidic linkages and one O-glycoside linkage. The amino acid sequence and carbohydrate part in recombinant erythropoietin are identical to those in the endogenous human erythropoietin isolated from the urine of anemic mice (7). Recombinant human erythropoietin has been present in clinical practice for more than 20 years, for therapeutic indications: anemia in renal failure, anemia during chemotherapy in malignant tumors, prevention of anemia occurring in preterm infants, an increase in autologous blood production before donation, anemia in AIDS, (potentiated by zidovudine), anemia in chronic inflammatory conditions such as rheumatoid arthritis (still in research phase) (8).

Adverse effects of erythropoietin include: flu-like syndrome that is transient, hypertension, which can cause encephalopathy with headache disorientation and sometimes convulsions. Iron deficit can occur due to increased need for it caused by intense erythropoiesis. Increase in blood viscosity and hematocrit can also occur, which can lead to thrombosis. The emphasis in writing this paper will be the red cell aplasia due to the development of anti-erythropoietic antibodies during treatment with any erythropoietin medication (9). The period between 1998 and 2001 was marked by an increased concern for safety of erythropoietin use, due to the increased number of registered cases of pure red cell aplasia caused by neutralizing, anti-erythropoietin antibodies. A severe anemia, resistant to erythropoietin therapy, has developed in this group of patients. Pure red cell aplasia (PRCA) was registered primarily in those patients who were treated with subcutaneous administration of erythropoietin alpha, and it is attributed to changes in the product stabilization formulation and failure to comply with the cold chain principle (7). Isolated red cell aplasia due to the use of erythropoietin is a bone marrow disease followed by severe anemia due to hypoplasia of erythroid lineage precursor cells. The other precursors are not affected by this disease, so the patients present with normochromic, normocytic anemia with values of thrombocytes and neutrocytes within the normal range (9).

The aim of this paper is to analyze the available case reports of red cell aplasia due to erythropoietin use, evaluation of their quality and causality for each study separately.

MATERIAL AND METHOD

For the purposes of this systematic review article a search through PubMed database was performed. Before the search, the following criteria were set: in relation to the type of article - case report, in terms of availability - entire texts and in terms of population-humans were population in the searched studies. The search was carried out in November 2017 and the inclusion criteria were: Free full article, English language, Case report studies, Studies that describe the occurrence of bone marrow disorders due to erythropoietin use

The exclusion criteria were: studies conducted on animals, studies that are not “case reports” designs, “Letters to editor”, case reports available in the form of an abstract.

Only studies conducted on humans were taken into consideration, and there were no restrictions in terms of age and sex. Keyword searched: erythropoietin hematological side effects, resulting in 15 studies; anti-erythropoietin antibodies in the search result was 30 studies; erythropoietin inducted pure red cell aplasia, resulting in 18 studies. Several studies appeared as a result of the search after using all three keyword combinations, and the last used combination of keywords included all the studies that appeared as search results. The most important criteria for inclusion were related to the following aspects: the study had to have one to two case reports; these reports were related to bone marrow aplasia due to erythropoietin administration. Diagnostic data for the bone marrow aplasia was necessary, since this side effect of erythropoietin is the subject of research in this paper. This paper includes 8 different studies.

Studies that did not pass the selection deviated from the required design of the study and the desired intervention. Studies that showed series of cases were excluded. Also, studies in which, instead of the administration of erythropoietin, patients received another drug or bone marrow aplasia occurred as a result of another disease, were excluded.

RESULTS

The results of this review paper are shown in the table’s bellow, for all the studies that met the inclusion criteria. **The assessment of the volume of the documentation** for each study equals the sum of the elements present; to indicate the presence, not the absence of an element. The aim is to determine whether the data in the study are complete in order to draw conclusions about the cause-and-effect relationship between drug use and the occurrence of an adverse event.

The assessment of the credibility of each study is equal as the sum of the elements present; to indicate the presence, not the absence of an element. The goal of the table is to display information about when and where the event occurred and who recorded it.

By looking at Table 2... We note that all selected studies contain information on the time and location of the adverse event, as well as information about a medi-

Table 1. *Volume of the documentation*

studies	Has the time interval from application of the medication to appearance of adverse effect been noted?	Has dechallenge been described?	Has rechallenge been described?	Has that adverse effect already been documented?	Have there been alternative causes of side effect?	Has there been diagnostic confirmation?	Is there rational explanation for the mechanism of adverse effect?	points
study 1 (10)	yes	yes	no	yes	no	yes	yes	3
study 2 (11)	yes	yes	no	yes	no	yes	yes	3
study 3 (12)	yes	yes	no	yes	no	yes	yes	3
study 4 (13)	yes	yes	no	yes	no	yes	yes	3
study 5 (14)	yes	yes	no	yes	no	yes	yes	3
study 6 (15)	yes	yes	no	yes	no	yes	yes	3
study 7 (16)	yes	yes	no	yes	no	yes	yes	3
study 8 (17)	yes	yes	no	yes	no	yes	yes	3

scoring system: >4 elements - 3 points; 2-4 elements - 2 points; 1 element - 1 point; 0 elements - 0 points

Table 2. *Credibility of the studies*

study	Are there timeline data?	Are there data of location of the adverse effect?	Are there data about medical worker that made the report?
study 1	yes	yes	yes
study 2	yes	yes	yes
study 3	yes	yes	yes
study 4	yes	yes	yes
study 5	yes	yes	yes
study 6	yes	yes	yes
study 7	yes	yes	yes
study 8	yes	yes	yes
number of elements present		grade	
3		3	
2		2	
1		1	
0		0	

cal worker who has documented the undesirable effects. The presence of these data points to the significant credibility of the selected studies.The number of cases described in the analyzed studies: one case carries a grade of 1, while studies describing 2 or 3 cases carry a score of 2.

Table 3. *Number of cases descr*

study	number of cases described
study 1	1
study 2	1
study 3	1
study 4	1
study 5	1
study 6	1
study 7	1
study 8	1

Table 4. *The number of elements present of cases*

number of elements present	grade
1	1
>1	2

Naranjo score was used to evaluate the cause-and-effect relationship between drug use and the occurrence of an adverse event. It contains questions relating to the time period between the use of the medicine and the occurrence of an adverse reaction, what happens after the cessation of use, or the re-administration of the drug, whether there are alternative causes for the occurrence of an adverse event, whether there is a laboratory confirmation, etc.

Table 5. *Naranjo causality score*

Naranjo causality score			
question	**yes**	**no**	**do not know**
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse events appear after the suspected drug was given?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
4. Did the adverse reaction appear when the drug was readministered?	+2	-1	0
5. Are there alternative causes that could have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1		0
Scoring: ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR			

study	Are there previous conclusive reports on this reaction?	Did the adverse events appear after the suspected drug was given?	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Did the adverse reaction appear when the drug was readministered?	Are there alternative causes that could have caused the reaction?	Did the reaction reappear when a placebo was given?	Was the drug detected in any body fluid in toxic concentrations?	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Did the patient have a similar reaction to the same or similar drugs in any previous exposure??	Was the adverse event confirmed by any objective evidence?	grade
1[10]	+1 (yes)	+2 (yes)	+1 (yes)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	7 (probable)
2[11]	+1 (yes)	+2 (yes)	+1 (yes)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	7 (probable)
3[12]	+1 (yes)	+2 (yes)	0 (don't know)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	6 (probable)
4[13]	+1 (yes)	+2 (yes)	+1 (yes)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	7 (probable)
5[14]	+1 (yes)	+2 (yes)	+1 (yes)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	7 (probable)
6[15]	+1 (yes)	+2 (yes)	+1 (yes)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	7 (probable)
7[16]	+1 (yes)	+2 (yes)	0 (don't know)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	6 (probable)
8[17]	+1 (yes)	+2 (yes)	0 (don't know)	0 (don't know)	+2 (no)	0 (don't know)	0 (don't know)	0 (don't know)	0 (don't know)	+1 (yes)	6 (probable)

Data extraction: The goal of the table is to synthesize data on each case analyzed, such as the patient's sex and age, the dose of erythropoietin, how long was the patient monitored and the outcome.

Table 6. *Data extraction*

extraction date	study name and authors	study quality grade	study population	intervention	outcome	length of monitoring	Naranjo score
30. 11. 2017.	Yoshimi M, Kadowaki Y, Kikuchi Y, Takahashi T. Coomb s negative autoimmune hemolytic anemia followed by anti-erythropoetin receptor antibodyassociated pure red cell aplasia: A case report and review of literature.[10]	7	female, 26 years old	erythropoietin 1000IU/ weeksubcutaneous	withdrawal of adverse effect and bone marrow reactivation	4 weeks	7
30. 11. 2017.	Lucio Manenti, Augusto Vaglio. Pure red cell aplasia followed by disseminated intravascular coagulation in a haemodialysis patient receiving erythropoietin-ß.[11]	7	male, 79 years old	erythropoietin beta, 4000IU/week subcutaneous	withdrawal of adverse effect and bone marrow reactivation	9 weeks	7
30. 11. 2017.	Okoshi Y et al. A patient with acquired pure red cell aplasia showing a positive antiglobulin test and the presence of inhibitor against erythroid precursors.[12]	7	male, 66 years old	erythropoietin beta, 10000 IU/week subcutaneous	withdrawal of adverse effect	8 weeks	6
30. 11. 2017.	Renaud Snanoudjaet al. Recovery from Pure Red Cell Aplasia Caused by Anti-Erythropoietin Antibodies After Kidney Transplantation.[13]	7	patient sex and age not available	erythropoietin alpha, 1000 IU then 4000IU/ week subcutaneous	withdrawal of adverse effect and bone marrow reactivation	6 weeks	7
30. 11. 2017.	Lee H, Yang J, Kim H et al. Improvement in erythropoieisstimulating agentinduced pure red-cell aplasia by introduction of darbepoetin-α when the anti-erythropoietin antibody titer declines spontaneously.[14]	7	female, 36 years old	erythropoietin alpha 3000-6000 IU/week subcutaneous	withdrawal of adverse effect and bone marrow reactivation	5 weeks	7
30. 11.2017.	Ashwin Asari, Ram Gokal. Pure Red Cell Aplasia Secondary to Epoetin alpha Responding to Darbepoetin Alpha in a Patient on Peritoneal Dialysis. [15]	7	male, 82 years old	erythropoietin beta 3000IU/week intraperitoneal	withdrawal of adverse effect	8 weeks	7
30. 11. 2017.	Gertrud Weber, Johann Gross, Arno Kromminga, Hans-H. Loew, Kai-Uwe Eckardt. Allergic Skin and Systemic Reactions in a Patient with Pure Red Cell Aplasia and Anti-Erythropoietin Antibodies Challenged with Different Epoetins.[16]	7	female, 48 years old	erythropoietin alpha 3x2000IU/week subcutaneous	withdrawal of adverse effect and bone marrow reactivation	7 weeks	6
30. 11. 2017.	Chng WJ, Tan LK, Liu TC. Cyclosporine treatment for patients with CRF who developed pure red blood cell aplasia following EPO therapy. [17]	7	patient sex and age not available	erythropoietin alpha 2000/ week subcutaneous	withdrawal of adverse effect	7 weeks	6

DISCUSSION

The primary aim of this systematic review article was to conduct a detailed search of medical databases, selecting appropriate studies, and processing, and pooling the results of these studies, to answer the question of whether there is a connection between the use of erythropoietin and bone marrow aplasia. In addition, this paper has the task of examining the literature on the safety of the use of erythropoietin, assessing the seriousness of the undesirable effect, and the mechanism of their emergence. We can see that in all the selected studies, the time interval from the use of the drug to the occurrence of an adverse drug reaction is described. All studies also contain information on what happens after the cessation of the drug (Dechallenge), while (Rechallenge) has not been performed in any study. This points to the fact that doctors mostly avoid exposure of patients to drugs that are suspected of having caused an unwanted effect by prior use.

The average value of the evaluation of the quality of the study was 7.0. The results of this systematic review article in terms of causality are similar to the results of the previous studies on the same subject. The calculated mean value of Naranjo causality score is 6.6 (5-8 probable causality), we can conclude that there is a likely correlation between the use of erythropoietin and bone marrow aplasia. The average age of patients was 56.1 years (the oldest patient was 82 years old and the youngest 26 years old). Three patients were female, three male, while for two patients, data on age and sex were not given. Erythropoietin-induced bone marrow aplasia, as a serious (life-threatening) adverse effect, carries the risk of aplastic anemia and aggravation of disseminated intravascular coagulation, as described in the analyzed studies. Particularly sensitive patients are those who start erythropoietin therapy after receiving kidney transplant, in order to prevent anemia (15, 16). The most used erythropoietin forms were erythropoietin alpha and beta (17). Erythropoietin was mostly used for described therapeutic indication which is anemia in patients on hemodialysis, one of the studies included patient on peritoneal dialysis which received erythropoietin (17).

Generally, the aplasia appeared several weeks (8 to 10 on average) after erythropoietin administration, which is explained by the lifetime of the erythrocytes synthesized prior to administration, which is about 120 days. After their degradation in the spleen, the bone marrow damaged by the use of erythropoietin would no longer produce new erythrocytes, and signs of anemia would appear (13). The first symptoms that caused these patients to visit their nephrologist or the general physician were dizziness, fatigue, decreased appetite and rapid heart rate. In suspected cases, routine blood tests in which decreased erythrocytes were observed (below $4\text{-}4.5*10^{12}$/l for women and $4.5\text{-}5*10^{12}$/l for men), decreased hemoglobin levels (below 120g/l) and hematocrit (below 0.45%) (17). The literature states that there is a mechanism of action that causes erythropoietin to cause bone marrow aplasia.

Bone marrow aplasia, with a previously history of erythropoietin administration, must be confirmed by laboratory tests. These include measuring hemoglobin levels, hematocrit number of erythrocytes, and serum iron levels (13, 14, 15). Therefore, each of the analyzed studies contained a mandatory laboratory confirmation for this adverse effect. In addition to these routine laboratory analyzes, for the final confirmation of erythropoietin-induced aplasia, staining of bone marrow samples was performed. Immunochemical methods and staining of bone marrow preparations, provided an explanation of the mechanism by which erythropoietin leads to bone marrow aplasia. This led to the detection of neutralizing anti-erythropoietin antibodies responsible for the occurrence of this adverse effect (13, 16, 17.) In order for the bone marrow to recover, it is necessary to exclude erythropoietin and administer immunosuppressant (cyclosporine) (17). To monitor the rate of recovery, an analysis of the number of reticulocytes was carried out which proved that after a certain period of time the bone marrow starts regenerating, producing the peripheral blood young erythrocytes-reticulocytes (13).

Considering that men physiologically have a higher number of erythrocytes due to hormonal status, bone marrow is regenerated faster in a male patients, as well as in younger patients compared to the older ones (17). As reported in the available literature, erythropoietin causes bone marrow aplasia rarely. In all cases after cessation of the drug that was suspected to lead to aplasia of the red cell line, the undesirable effect has withdrawn (10-17.) In all eight studies, there are no alternative causes that could trigger the investigated adverse event, which is of great importance for linking the investigated drug with an unwanted event. All of the above facts speak of the likely causality between the use of erythropoietin and the onset of bone marrow aplasia.

CONCLUSION

Treatment of anemia in dialysis patients with erythropoietin can, rarely leads to serious (life-threatening) adverse effects. Symptoms and signs of bone marrow aplasia can be recognized and prevented early by careful monitoring of the patients by the nephrologist or clinical pharmacologist. There is clear risk for occurrence of this adverse effect, so careful use and do-

sing of erythropoietin are to be advised. It is also important to inform patients about the first symptoms of aplasia, but also to increase the involvement of healthcare professionals in terms of reporting this adverse effect to the National Pharmacovigilance Center.

Declaration of interest

There is no conflict of interest between the authors of this paper.

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Abbreviations

AIDS — acquired immunodeficiency syndrome
CKD — chronic kidney disease
ESRD — end stage renal disease
FDA — Food and Drug Administration
ADR — Adverse drug reaction

Sažetak

APLAZIJA KOŠTANE SRŽI USLED PRIMENE ERITROPOETINA

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Uvod: Rekombinovani humani eritropoetin prisutan je u kliničkoj praksivišeod 20 godina, za terapijske indikacije: anemija kod bubrežne insuficijencije, anemija u toku hemioterapije kod malignih tumora, prevencija anemija koje se javljaju kod nedonoščadi, za povećanje proizvodnje autologne krvi pre donacije, anemija kod AIDS-a (potencirana primenom zidovudina), anemija u hroničnim zapaljenskim stanjima kao što je reumatoidni artritis (u fazi istraživanja). Tokom terapije eritropoetinom, uočena su neželjena dejstva na nivou različitih sistema organa, i različitog stepena učestalosti. Veliki broj studija ukazuje na povezanost između primene eritropetina i pojave aplazije koštane srži, ali mali broj njih navodi jasno definisano neželjeno dejstvo koje ovu povezanost objašnjava.

Cilj rada: Cilj ovog rada je analiza dostupnih prikaza slučajeva aplazije koštane srži usled primene eritropoetina, procena njihovog kvaliteta i kauzalnosti za svaku studiju pojedinačno.

Metod: Pretraga literature koja je korišćena za izradu ovog sistematskog preglednog članka izvršenaje u periodu novembar - decembar 2017. godine. Za pretraživanje literature korišćena je medicinska baza podataka. PubMed. Kriterijumi za uključenje bili su: publikacije dostupne u celosti, publikacije na engleskom jeziku, publikacije sprovedene na ljudima, i studije u kojima je opisan klinički slučaj (case report). Osam studija je prošlo selekciju.

Rezultati: Rezultati su tabelarno predstavljeni kroz pet tabela: opsežnos tdokumentacije, verodostojnost, broj opisanih prikaza slučajeva neželjenih dejstava u radu koji se ocenjuje, Naranjo skor kauzalnosti, tabela za ekstrakciju podataka. Srednja vrednost ocena kvaliteta studija iznosila je 7,0 dok je srednja vrednost Naranjo skora iznosila 6,6.

Ključne reči: erythropoietin, erythropoietin side effects, anti-erythropoietin antibodies, pure red cell aplasia.

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BIBLIOGRAPHY OF SANAMED JOURNAL (2014-2017)

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Abstract: This paper presents a bibliography of Sanamed, journal of medical and health science, founded by a group of doctors from Novi Pazar. The Journal published original articles, case reports, literature reviews, articles on history of medicine, articles for practitioners, book reviews, and other medical information in the field of medicine, dentistry, pharmacology and pharmaceutical sciences. The bibliography contains 101 bibliographic units and includes the period from 2014 to 2017 (4 years). The aim of this bibliography is to be exhanstive at including all the contribution published in all the numbers of individual years. The material is completely formally described and all bibliography units are objectively classified – they have UDK numbers and subjects, which are systematized in the subject sense

INTRODUCTION

Sanamed is journal of medical and health science, founded 2006 by a group of doctors from Novi Pazar. The Journal published original articles, case reports, literature reviews, articles on history of medicine, articles for practitioners, book reviews, and other medical information in the field of medicine, dentistry, pharmacology and pharmaceutical sciences. This is an open access journal. From 2006 to 2013, the Journal was published twice a year, since 2014, it was published three times a year.

Editor-in-Chief is prim. Dr. Avdo Ćeranić and assosiate editors are dr. Džemail Detanac and dr. Dženana Detanac.

The Journal is published both in electronic and print format.

This bibliography of periodicals is in its character special bibliography and it was made up „de visu".

The bibliography contains 101 bibliographic units and includes the period from 2014 to 2017 (4 years). The aim of this bibliography is to be exhanstive at including all the contribution published in all the numbers of individual years. It should be noted that such contribution as introduction parts, editorials, book reviews, advertisements, etc. they were no processed due to their negligible informative value and importance for the journal.

Since the elements for the bibliographic description are taken from primary source, the cover pages and preliminaries of journal, the bibliography has the primary character. During the bibliographic work, a letter and a language were respected and subject heading is cyrillic.

The material is completely formally described and all bibliography units are objectively classified – they have UDK numbers and subjects, which are systematized in the subject sense.

The bibliography was made in accordance with the International Standard ISBD (CP), communicated format for machine–readable cataloging and exchange bibliographic informations – COMARC/B, and in accordance with "The Rulebook and the Manual for the Preparation Alphabetical Catalogs I and II" by Eva Verona, and other expert literatures (professional dictionaries, encyclopedias, lexicons, electronic databases etc.).

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617 Surgery

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617.7 Ophthalmology

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618 Gynaecology. Obstetrics

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SM - 101

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DECLARATION OF INTEREST

The autors declare that there are no conflicts of interests.

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CORRECTION

Correction: Comparative analysis of diagnostic methods in knee injuries (Vol. 11, No. 1, p. 39-45, 2016)
Ispravka: Komparativne analize dijagnostičkih metoda kod pacijenata sa povredom kolena (Vol. 11, No. 1, p. 39-45, 2016)

Dzoleva-Tolevska Roza,[1] Poposka Anastasika,[1] Georgieva Daniela,[1] Bozinovski Zoran,[1] Nanceva Jasminka,[1] Gjoshev Stojan[2]

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CORRECTION: The Editorial Board of "Sanamed" journal, in agreement with authors of the paper "Comparative analysis of diagnostic methods in patients with knee injury" (Dzoleva-Tolevska Roza, Poposka Anastasika, Georgieva Daniela, Bozinovski Zoran, Nanceva Jasminka, Gjoshev Stojan), published in this journal Vol. 11 from 2016 (p. 39-45), made the decision, due to the unnoticed oversight (based on CEON checks), which is reflected in the omission of references from which individual textual references were used, to do the necessary corrections of those parts of the paper in which reference sources are not adequately cited, as well as the corrections in the references list, in accordance with the prescribed procedure. Primary work, as well as mentioned reference sources, are part of doctoral dissertation of the lead author. Results from doctoral dissertation, related to the meniscal, ligamentary and articular cartilage lesions, combined and compared to one another, have been published in Sanamed journal, while in other two journals are published results for meniscus lesions in one and articular cartilage lesions in other. Within this correction the author's Acknowledgment that the paper is part of the corresponding doctoral dissertation is added. We thank the Center for Evaluation in Education and Science (CEON) for assistance in detecting errors in primary work.

ISPRAVKA: Uredništvo časopisa "Sanamed" je u dogovoru sa autorskim timom stručnog rada pod nazivom "Komparativne analize dijagnostičkih metoda kod pacijenata sa povredom kolena" (Dzoleva-Tolevska Roza, Poposka Anastasika, Georgieva Daniela, Bozinovski Zoran, Nanceva Jasminka, Gjoshev Stojan) koji je publikovan u ovom časopisu Vol. 11 iz 2016. godine (str. 39-45) donelo odluku da se zbog uočenog previda (na osnovu provere CEON-a), koji se ogleda u izostavljanju referenci iz kojih su korišćeni pojedini tekstualni navodi, izvrši neophodna ispravka onih delova rada u kojim pomenuti referentni izvori nisu adekvatno citirani, kao i ispravke u listi referenci, a u skladu sa propisanom procedurom. Primarni rad, kao i pomenuti referentni izvori, su deo doktorske disertacije autora. U časopisu "Sanamed" su objavljeni rezultati istraživanja vezani za meniskusne, ligamentarne i hrskavične lezije kolena, objedinjeni i komparirani međusobno, dok su u drugim časopisima, u dva rada, objavljeni delovi doktorata koji se tiču samo meniskusne i hrskavične lezije kolena. U okviru ispravke dodaje se i potvrda autora o tome da je rad deo odgovarajuće doktorske disertacije. Zahvaljujemo se Centru za evaluaciju u obrazovanju i nauci (CEON) na pomoći pri otkrivanju grešaka u primarnom radu.

In the section *"Results"* with the subtitle *"Meniscal lesions"* the following update was made:

a) at the end of the paragraph that begins with *"Sensitivity of clinical diagnosis versus MRI diagnosis for medial meniscus ..."*, omitted reference (19) is inserted

b) at the end of the paragraph that begins with *"Sensitivity of clinical diagnosis versus MRI diagnosis for lateral meniscus..."* omitted reference (19) is inserted

c) at the end of the paragraph that begins with *"Diagnostic accuracy of clinical diagnosis..."* omitted reference (19) is inserted

In the section *"Results"* with the subtitle *"Articular cartilage lesions"* the following update was made:

a) at the end of the paragraph that begins with *"We had 51 patients with clinically diagnosed articular cartilage injury..."* omitted reference (20) is inserted

b) at the end of the paragraph that begins with *"The sensitivity (91.8% vs. 79.6%)..."* omitted reference (20) is inserted

In the section "Discussions" the following update was made:

a) at the end of the paragraph that begins with *" We have better results for sensitivity (91.8% vs. 79.6%)..."* omitted reference (20) is inserted

Due to the omitted references insertion, the reference numbers are corrected in the relevant sections of the paper:

in the section *"Discussions"* reference **(21)** should stand instead of **(19)**; reference **(22)** should stand instead of **(20)**; reference **(23)** should stand instead of **(21)**; reference **(24)** should stand instead of **(22)**; reference **(25)** should stand instead of **(23)**; reference **(26)** should stand instead of **(24)**; reference **(27)** should stand instead of **(25)**; reference **(28)** should stand instead of **(26)**; reference **(29)** should stand instead of **(27)**; reference **(30)** should stand instead of **(28)**; reference **(31)** should stand instead of **(29)**; reference **(32)** should stand instead of **(30)**; reference **(33)** should stand instead of **(31)**; reference **(34)** should stand instead of **(32)**; reference **(35)** should stand instead of **(33)**; reference **(36)** should stand instead of **(34)**; reference **(37)** should stand instead of **(35)**; reference **(38)** should stand instead of **(36)**; reference **(39)** should stand instead of **(37)**; reference **(40)** should stand instead of **(38)**; reference **(41)** should stand instead of **(39)**; reference **(42)** should stand instead of **(38)**.

Due to the omitted references insertion, the order in the original list of references is corrected:

Ref. (19): Rayan F, Bhonsle S, Shukla DD. Clinical, MRI, and arthroscopic correlation in meniscal and anterior cruciate ligament injuries. Int Orthop. 2009; 33(1): 129–132. is corrected to: Dzoleva Tolevska R, Poposka A, Samardziski M, Georgieva D. Comparative analysis of diagnostic methods in meniscal lesions. Contributions,. Sec. Biol. Med. Sci, MASA. 2013; 34(3): 79-83. **Ref. (20):** Rose NE, Gold SM. A comparison of accuracy between clinical examination and magnetic resonance imaging in the diagnosis of meniscal and anterior cruciate ligament tears. Arthroscopy. 1996; 12(4): 398-405. **is corrected to:** Dzoleva-Tolevska R, Poposka A, Samardziski M, Georgieva D. Comparative diagnosis of diagnostic methods in articular cartilage injuries of the knee. Archives of public health. 2013; 5(1): 42-5. **Ref. (21):** Kocabey Y, Tetik O, Isbell WM, Atay OA, Johnson DL. The value of clinical examination versus magnetic resonance imaging in the diagnosis of meniscal tears and anterior cruciate ligament rupture. Arthroscopy. 2004; 20(7): 696-700. **- is corrected to:** Rayan F, Bhonsle S, Shukla DD. Clinical, MRI, and arthroscopic correlation in meniscal and anterior cruciate ligament injuries. IntOrthop. 2009; 33(1): 129–32. **Ref. (22):** Bohnsack M, Rühmann O, Sander-Beuermann A, Wirth CJ. Comparison of clinical examination with NMR spectroscopy in the diagnosis of meniscal lesions in daily practice. Z Orthop Ihre Grenzgeb. 1999; 137(1): 38-42. **is corrected to:** Rose NE, Gold SM. A comparison of accuracy between clinical examination and magnetic resonance imaging in the diagnosis of meniscal and anterior cruciate ligament tears. Arthroscopy. 1996; 12(4): 398-405. **Ref. (23):** Mohan BR, Gosal HS. Reliability of clinical diagnosis in meniscal tears. Int Orthop. 2007; 31(1): 57-–60. **is corrected to:** Kocabey Y, Tetik O, Isbell WM, Atay OA, Johnson DL. The value of clinical examination versus magnetic resonance imaging in the diagnosis of meniscal tears and anterior cruciate ligament rupture. Arthroscopy. 2004; 20(7): 696-700. **Ref. (24):** Dutka J, Skowronek P, Dutka L. Arthroscopic verification of objectivity of the orthopaedic examination and magnetic resonance imaging in intra-articular knee injury. Retrospective study. WideochirInne Tech Malo Inwazyjne. 2012; 7(1): 13-8. **is corrected to:** Bohnsack M, Rühmann O, Sander-Beuermann A, Wirth CJ. Comparison of clinical examination with NMR spectroscopy in the diagnosis of meniscal lesions in daily practice. Z Orthop Ihre Grenzgeb. 1999; 137(1): 38--42. **Ref. (25):** HardyJC, Evangelista GT, Grana WA, Hunter RE. Accuracy of Magnetic Resonance Imaging of the Knee in the Community. Sports Health. 2012; 4-(3): 222-31. **is corrected to:** Mohan BR, Gosal HS. Reliability of clinical diagnosis in meniscal tears. IntOrthop. 2007; 31(1): 57–60. **Ref. (26):** Miller GK. A prospective study comparing the accuracy of the clinical diagnosis ofmeniscus tear with magnetic resonance imaging and its effect on clinical outcome. Arthroscopy. 1996; 12(4): 406-13. **is corrected to:** Dutka J, Skowronek M, Skowronek P, Dutka L. Arthroscopic verification of objectivity of the orthopaedic examination and magnetic resonance imaging in intra-articular knee injury. Retrospective study. Wideochir Inne Tech MaloInwazyjne. 2012; 7(1): 13-8. **Ref. (27):** Aydingöz U, Firat AK, Atay OA, Doral MN. MR imaging of meniscal bucket-handle tears: a review of signs and their relation to arthroscopic classification. EurRadiol. 2003; 13(3): 618-25. **is corrected to:** Hardy JC, Evangelista GT, Grana WA, Hunter RE. Accuracy of Magnetic Resonance Imaging of the Knee in the Community. Sports Health. 2012; 4(3): 222-31. **Ref. (28):** Cellár R, Sokol D, Lacko M, S, Gharaibeh A, Vasko G. Magnetic resonance imaging in the diagnosis of intra-articular lesions of the knee. Acta Chir

Orthop Traumatol Cech. 2012; 79(3): 249-54. **is corrected to:** Miller GK. A prospective study comparing the accuracy of the clinical diagnosis ofmeniscus tear with magnetic resonance imaging and its effect on clinical outcome. Arthroscopy. 1996; 12(4): 406-13. **Ref. (29):** Esmaili Jah AA, Keyhani S, Zarei R, Moghaddam AK. Accuracy of MRI in comparison with clinical and arthroscopic findings in ligamentous and meniscal injuries of the knee. Acta Orthop Belg. 2005; 71(2): 189-96. **is corrected to:** Aydingöz U, Firat AK, Atay OA, Doral MN. MR imaging of meniscal bucket-handle tears: a review of signs and their relation to arthroscopic classification. EurRadiol. 2003; 13(3): 618-25. **Ref. (30):** van Eck CF, van den Bekerom MP, Fu FH, Poolman RW, Kerkhoffs GM. Methods to diagnose acute anterior cruciate ligament rupture: a meta-analysis of physical examinations with and without anaesthesia. Knee Surg Sports Traumatol Arthrosc. 2013; 21(8): 1895-903. **is corrected to:** Cellár R, Sokol D, Lacko M, S, Gharaibeh A, Vasko G. Magnetic resonance imaging in the diagnosis of intra-articular lesions of the knee. Acta Chir Orthop Traumatol Cech. 2012; 79(3): 249-54. **Ref. (31):** Jain DK, Amaravati R, Sharma G. Evaluation of the clinical signs of anterior cruciate ligament and meniscal injuries. Indian J Orthop. 2009; 43(4): 375-8. **is corrected to:** Esmaili Jah AA, Keyhani S, Zarei R, Moghaddam AK. Accuracy of MRI in comparison with clinical and arthroscopic findings in ligamentous and meniscal injuries of the knee. Acta Orthop Belg. 2005; 71(2): 189-96. **Ref. (32):** Kim SJ, Kim HK. Reliability of the anterior drawer test, the pivot shift test, and the Lachman test. Clin Orthop Relat Res. 1995; (317): 237-42. **is corrected to:** van Eck CF, van den Bekerom MP, Fu FH, Poolman RW, Kerkhoffs GM. Methods to diagnose acute anterior cruciate ligament rupture: a meta-analysis of physical examinations with and without anaesthesia. Knee Surg Sports Traumatol Arthrosc. 2013; 21(8): 1895-903. **Ref. (33):** Laoruengthana A, Jarusriwanna A. Sensitivity and specificity of magnetic resonance imaging for knee injury and clinical application for the Naresuan University Hospital. J Med Assoc Thai. 2012; 95(Suppl 10): S151-7. **is corrected to:** Jain DK, Amaravati R, Sharma G. Evaluation of the clinical signs of anterior cruciate ligament and meniscal injuries. Indian J Orthop. 2009; 43(4): 375-8. **Ref. (34):** Gelb HJ, Glasgow SG, Sapega AA, Torg JS. Magnetic resonance imaging of knee disorders. Clinical value and cost-effectiveness in a sports medicine practice. Am J Sports Med. 1996; 24(1): 99-103. **is corrected to:** Kim SJ, Kim HK. Reliability of the anterior drawer test, the pivot shift test, and the Lachman test. Clin Orthop Relat Res. 1995; (317): 237-42. **Ref. (35):** Duc SR, Koch P, Schmid MR, Horger W, Hodler J, Pfirrmann CW. Diagnosis of articular cartilage abnormalities of the knee: prospective clinical evaluation of a 3D water-excitation true FISP sequence. Radiology. 2007; 243(2): 475-82. **is corrected to:** Laoruengthana A, Jarusriwanna A. Sensitivity and specificity of magnetic resonance imaging for knee injury and clinical application for the Naresuan University Hospital. J Med Assoc Thai. 2012; 95 (Suppl 10): S151-7. **Ref. (36):** Friemert B, Oberländer Y, Schwarz W, Häberle HJ, Bähren W, Gerngross H, Danz B. Diagnosis of chondral lesions of the knee joint: can MRI replace arthroscopy? A prospective study. Knee Surg Sports TraumatolArthrosc. 2004; 12(1): 58-64. **is corrected to:** Gelb HJ, Glasgow SG, Sapega AA, Torg JS. Magnetic resonance imaging of knee disorders. Clinical value and cost-effectiveness in a sports medicine practice. Am J Sports Med. 1996; 24(1): 99-103. **Ref. (37):** Munk B, Madsen F, Lundorf E, et al. Clinical magnetic resonance imaging and arthroscopic findings in knees: a comparative prospective study of meniscus anterior cruciate ligament and cartilage lesions. Arthroscopy. 1998; 14(2): 171-5. **is corrected to:** Duc SR, Koch P, Schmid MR, Horger W, Hodler J, Pfirrmann CW. Diagnosis of articular cartilage abnormalities of the knee: prospective clinical evaluation of a 3D water-excitation true FISP sequence. Radiology. 2007; 243(2): 475-82. **Ref. (38):** D'Erme M, Ventura M, Di Giacomo G, Pasquali Lasagni M. Magnetic resonance and arthroscopy of the knee. A double-blind study in 40 patients. Radiol Med. 1992; 84(5): 553-6. **is corrected to:** Friemert B, Oberländer Y, Schwarz W, Häberle HJ, Bähren W, Gerngross H, Danz B. Diagnosis of chondral lesions of the knee joint: can MRI replace arthroscopy? A prospective study. Knee Surg Sports Traumatol Arthrosc. 2004; 12(1): 58-64. **Ref. (39):** Kijowski R, Blankenbaker DG, Davis KW, Shinki K, Kaplan LD, De Smet AA. Comparison of 1.5- and 3.0-T MR imaging for evaluating the articular cartilage of the knee joint. Radiology. 2009; 250(3): 839-48. **is corrected to:** Munk B, Madsen F, Lundorf E, et al. Clinical magnetic resonance imaging and arthroscopic findings in knees: a comparative prospective study of meniscus anterior cruciate ligament and cartilage lesions. Arthroscopy. 1998; 14(2): 171-5. **Ref. (40):** Trieshmann HW Jr, Mosure JC. The impact of magnetic resonance imaging of the knee on surgical decision making. Arthroscopy. 1996 Oct; 12(5): 550-5. **is corrected to:** D'Erme M, Ventura M, Di Giacomo G, Pasquali Lasagni M. Magnetic resonance and arthroscopy of the knee. A double-blind study in 40 patients. Radiol Med. 1992; 84(5): 553-6. **Ref. (39):** Kijowski R, Blankenbaker DG, Davis KW, Shinki K, Kaplan LD, De Smet AA. Comparison of 1.5- and 3.0-T MR imaging for evaluating the articular cartilage of the knee joint. Radiology. 2009; 250(3): 839-48. **becomes Ref. (41). Ref. (40):** Trieshmann HW Jr, Mosure JC. The

impact of magnetic resonance imaging of the knee on surgical decision making. Arthroscopy. 1996 Oct; 12(5): 550-5. **becomes Ref. (42).**

Acknowledgment: This study is part of author's doctoral dissertation, which was performed at University clinic for orthopedic surgery in Skopje, Republic of Macedonia. The title of the dissertation is "Comparative analysis of diagnostic methods in knee injuries", 2014, Medical faculty, University "St. Cyril and Methodius", Skopje, R. of Macedonia.

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CORRECTION

Correction: Relationship between physical activity and health-related quality of life in elderly people: a cross section study (Vol 12, No 2, p. 87-92, 2017)
Ispravka: Povezanost nivoa fizičke aktivnosti i kvaliteta života kod starih osoba: studija preseka (Vol 12, No 2, p. 87-92, 2017)

Walid Kamal M. Abdelbasset,[1, 2] Gopal Nambi S.[1]

[1] Department of physical therapy and health rehabilitation, College of applied medical sciences, Prince Sattam Bin Abdul Aziz University, Alkharj, KSA
[2] Department of physical therapy, Kasr Al-Aini Hospital, Cairo University, Egypt

The Editorial Board of "Sanamed" journal, in agreement with authors (Walid Kamal M. Abdelbasset and Gopal Nambi Subash) of the paper " Relationship between physical activity and health-related quality of life in elderly people: a cross section study" (Vol. 12, No 2, p. 87-92, 2017) who pointed out the technical errors that occurred after the paper was published, made the decision to do the necessary corrections in accordance with the prescribed procedure. We apologize the authors for errors that occured in published paper and thank them for assistance in detecting them.

The following updates were made:

a) In 10th column of the Table 1, number 34 should stand instead of number 24

b) Under the title of the paper on page 87 instead of Walid Kamal M. Abdelbasset, Gopal Nambi S. should steand Abdelbasset WK, Subash GN.

c) Under the title of the paper in the section "Summary" on page 91, instead of Walid Kamal M. Abdelbasset, Gopal Nambi S. should steand Abdelbasset WK, Subash GN.

d) In the header of pages 88, 90 i 92, instead of Kamal M. Abdelbasset Walid, Nambi S. Gopal should stand Abdelbasset WK, Subash GN.

According to the corrections that are mentioned, paper should be cited in the following way: Abdelbasset WK, Subash GN. Relationship between physical activity and health-related quality of life in elderly people: a cross section study. Sanamed. 2017; 12(2): 87-92.

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CORRECTION

Correction: Additional effect of Trigger pont therapy and Myo fascial release on second stage Frozen Shoulder among industrial workers (Vol 12, No 2, p. 93-100, 2017)
Ispravka: Dodatni efekat terapije tačaka okidanja i tehnike miofascijalnog oslobađanja na drugi stadijum „smrznutog“ ramena među industrijskim radnicima (Vol 12, No 2, p. 93-100, 2017)

Gopal Nambi S.,[1] Walid Kamal M. Abdelbasset[1, 2]

[1] Department of physical therapy and health rehabilitation, College of applied medical sciences, Prince Sattam Bin Abdul Aziz University, Alkharj, KSA
[2] Department of physical therapy, Kasr Al-Aini Hospital, Cairo University, Egypt

The Editorial Board of "Sanamed" journal, in agreement with authors (Gopal Nambi Subash and Walid Kamal M. Abdelbasset) of the paper "Additional effect of Trigger point therapy and Myo fascial release on second stage Frozen Shoulder among industrial workers" (Vol. 12, No 2, p. 93-100, 2017) who pointed out the technical errors that occurred after the paper was published, made the decision to do the necessary corrections in accordance with the prescribed procedure. We apologize the authors for errors that occurred in published paper and thank them for assistance in detecting them. During the correction of those technical errors, the editorial board noticed a technical error in serbian translation of the paper's title. According to that, the appropriate correction was made.

The following updates were made:

a) Under the title of the paper on page 93, instead of Gopal Nambi S, Walid Kamal M. Abdelbasset, should stand Subash GN, Abdelbasset WK.

b) Under the title of the paper in the section "Summary" on page 99, instead of Nambi S. Gopal, Abdelbasset M. Kamal Walid, should stand Subash GN, Abdelbasset WK

c) In the header of pages 94, 96, 98 i 100, instead of Gopal Nambi S , Walid Kamal M. Abdelbasset, should stand Subash GN, Abdelbasset WK.

According to the corrections that are mentioned, paper should be cited in the following way:

Subash GN, Abdelhasset WK. Additional effect of Trigger point therapy and Myo fascial release on second stage Frozen Shoulder among industrial workers. Sanamed. 2017; 12(2): 93-100.

d) In the section "Sažetak" on page 99, serbian translation of paper's title instead of „Dodatni efekat terapije tačaka okidanja i tehnike miofascijalnog oslobađanka na drugi stadijum smrznutog ramena među industrijskim radnicima“ should be „Dodatni efekat terapije tačaka okidanja i tehnike miofascijalnog oslobadanja na drugi stadijum „smrznutog“ ramena među industrijskim radnicima“

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RETRACTED ARTICLE: VALIDITY OF CORE NEEDLE BIOPSY IN THE HISTOPATHOLOGICAL VERIFICATION OF PAROTID GLAND LESIONS

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The article "VALIDITY OF CORE NEEDLE BIOPSY IN THE HISTOPATHOLOGICAL VERIFICATION OF PAROTID GLAND LESIONS" (Oroz Aleksandar, Kanjevac Tatjana, Vasovic Miroslav, Milosevic Marija, Jevdjic Jasna), published in this journal Vol. 11 N02, from 2016 (p. 123-127), has been retracted at the request of the Editor-in-Chief.

During a routine check, it was noticed that the peer-review process was not performed according to the publishing policies of the Sanamed journal, and publishing ethics standards.

We apologize to the readers of the journal that this lapse was not detected during the submission process.

UPUTSTVO AUTORIMA

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

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Prispeli rukopis Uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene ili dopune, kopija recenzije se dostavlja autoru s molbom da unese tražene izmene u tekst rada ili da argumentovano obrazloži svoje neslaganje s primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik.

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

OPŠTA UPUTSTVA

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

Rukopis mora biti organizovan na sledeći način: naslovna strana, sažetak na srpskom jeziku, sažetak na engleskom jeziku, ključne reči, uvod, cilj rada, bolesnici i metodi/materijal i metodi, rezultati, diskusija, zaključak, literatura, tabele, legende za slike i slike.

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

Obim rukopisa. Celokupni rukopis rada, koji čine naslovna strana, kratak sadržaj, tekst rada, spisak literature, svi prilozi, odnosno potpisi za njih i legenda (tabele, slike, grafikoni, sheme, crteži), naslovna strana i sažetak na engleskom jeziku, mora iznositi za originalni rad, saopštenje, rad iz istorije medicine i pregled literature do 5.000 reči, a za prikaz bolesnika, rad za praksu, edukativni članak do 3.000 reči; radovi za ostale rubrike moraju imati do 1.500 reči.

Provera broja reči u dokumentu može se izvršiti u programu *Word* kroz podmeni *Tools-Word Count* ili *File-Properties-Statistics*.

Sva merenja, izuzev krvnog pritiska, moraju biti izražena u internacionalnim SI jedinicama, a ako je neophodno, i u konvencionalnim jedinicama (u zagradi). Za lekove se moraju koristiti generička imena. Zaštićena imena se mogu dodati u zagradi.

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

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

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

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

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

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

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

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

izboru ključnih reči koristiti Medical Subject Headings — MeSH.

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

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

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

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

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

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

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

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

Treba navesti statističke metode koje su korišćene u obradi rezultata.

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

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

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

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

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

Primeri:

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

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

2. **Knjiga:**

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

3. **Poglavlje ili članak u knjizi:**

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

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad.

Slike. Sve ilustracije (fotografije, grafici, crteži) se smatraju slikama i označavaju se arapskim brojevima u tekstu i na legendama, prema redosledu pojavljivanja. Treba koristiti minimalni broj slika koje su zaista neophodne za razumevanje rada. Slova, brojevi i simboli moraju biti jasni, proporcionalni, i dovoljno veliki da se mogu reprodukovati. Pri izboru veličine grafika treba voditi računa da prilikom njihovog smanjivanja na širinu jednog stupca teksta neće doći do gubitka čitljivosti. Legende za slike se moraju dati na posebnim listovima, nikako na samoj slici.

Ako je uveličanje značajno (fotomikrografije) ono treba da bude naznačeno kalibracionom linijom na samoj slici. Dužina kalibracione linije se unosi u legendu slike.

Uz fotografije na kojima se bolesnici mogu prepoznati treba poslati pismenu saglasnost bolesnika da se one objave.

Za slike koje su ranije već objavljivane treba navesti tačan izvor, treba se zahvaliti autoru, i treba priložiti pismeni pristanak nosioca izdavačkog prava da se slike ponovo objave.

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The journal is published in English, with the summary translated into Serbian.

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The manuscript should be arranged as following: title page, abstract, key words, introduction, patients and methods/material and methods, results, discussion, conclusion, references, tables, figure legends and figures.

Each manuscript component (title page, etc.) begins on a separate page. All pages are numbered consecutively beginning with the title page.

References in the text are designated with Arabic numerals in parentheses, and the order in which they appear in the text.

Manuscript volume. The complete manuscript, which includes title page, short abstract, text of the article, literature, all figures and permisions for them and legends (tables, images, graphs, diagrams, drawings), title page and abstract in English, can have the length up to 5000 words for original paper, report, paper on the history of medicine and literature overview, while for patient presentation, practice paper, educative article it can be up to 3000 words, and other papers can be up to 1500 words.

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Title page. The title page contains the title, short title, full names of all the authors, names and full location of the department and institution where work was performed, acknowledgments, abbreviations used, and name of the corresponding author. The title of the article is concise but informative, and it includes animal species if appropriate. A subtitle can be added if necessary.

A short title of less than 50 spaces, for use as a running head, is included.

A brief acknowledgment of grants and other assistance, if any, is included.

A list of abbreviations used in the paper, if any, is included. List abbreviations alphabetically followed by an explanation of what they stand for. In general, the use of abbreviations is discouraged unless they are essential for improving the readabillity of the text.

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Avoid using abstracts as references and abstract older than two years are not cited.

References are cited by the so-called Vancouver rules, which are based on formats that use the National Library of Medicine and Index Medicus. The following are examples:

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

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

2. **Book:**

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

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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