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Gustav Klimt (1862–1918): The Kiss (Lovers), oil and gold leaf on canvas (180 × 180 cm); Österreichische Galerie Belvedere, Vienna.
Every society considers incest as a taboo, primarily because the progeny of consanguineous mating shows increased frequency of damaging recessive traits, including mortality. In nearly all societies, mating between parent and offspring, brother and sister, and among first cousins is considered incestuous. Same sex marriage, which is legal in several countries, does not produce children, and thus restrictions on inbreeding do not exist. In theory, same sex marriage could become legal among close cousins. These issues are considered in the article by Prof. Rajko Igić: *Quo vadis homine?* Or *Where the marriage goes?* (pp. 200–2).

Gustav Klimt (1862–1918): Poljubac (Ljubavnici), ulje i listići zlata na platnu (180 × 180 cm); Österreichische Galerie Belvedere, Beč.
Incest je tabu u svim društvenim zajednicama, prvenstveno zbog toga što konsangvinitet često prati veće ispoljavanje recesivnih poremećaja, uključujući i mortalitet potomaka. Zato se u gotovo svim društvima incestuoznim začećima smatraju ona koja su nastala između roditelja i dece, brata i sestre i između sestrića i sestrične. Brakovi između osoba istog pola, koji su legalizovani u nekim zemljama, su neplodni, pa u njima nema potomaka i urođenih poremećaja koji se sreću u mešovitom braku. Zato, teorijski, brakovi istog pola mogli bi postati legalni između bliskih rođaka. O ovim temema raspravlja prof. Rajko Igić u članku: *Quo vadis homine?* Ili: Kuda ide brak*?* (str. 200–2).

ORIGINAL ARTICLES

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Determination of vertical dimension of occlusion by using the phonetic vowel “O” and “E”

Određivanje vertikalne dimenzije okluzije pomoću samoglasnika O i E

Marko Igić*, Nebojša Krunić*, Ljiljana Aleksov*, Milena Kostić†, Aleksandra Igić†, Milica B. Petrović*, Stefan Dačić*, Stevan Igić*, Aleksandar Igić*

***Faculty of Medicine, University of Niš, Niš, Serbia; †Clinic of Dentistry, Clinical Center Niš, Niš, Serbia**

Abstract

Background/Aim. The vertical dimension of occlusion is a very important parameter for proper reconstruction of the relationship between the jaws. The literature describes many methods for its finding, from the simple, easily applicable clinically, to quite complicated, with the use of one or more devices for determination. The aim of this study was to examine the possibility of determining the vertical dimension of occlusion using the vocals “O” and “E” with the control of values o btained by applying cognitive functions. **Methods.** This investigation was performed with the two groups of patients. The first group consisted of 50 females and 50 males, aged 18 to 30 years. In this group the distance between the reference points (on top of the nose and chin) was measured in the position of the mandible in the vertical dimension of occlusion, the vertical dimension at rest and the pronunciation of the words “OLO” and “ELE”. Checking the correctness of the particular value for the word “OLO” was also performed by the phonetic method with the application of cognitive exercises when the patients counted from 89 to 80. The obtained difference in the average values i n determining the vertical dimension of occlusion and the “OLO” and “ELE” in the first group was used as the reference for determining the vertical dimension of occlusion in the second group of patients. The second group comprised of 31 edentulous persons (14 females and 17 males), aged from 54 to 85 years who had been made a complete denture. **Results.** The average value obtained for the vertical dimension of rest for the entire sample was 2.16 mm, for the word “OLO” for the entire sample was 5.51 mm and for the word “ELE” for the entire sample was 7.47 mm. There was no statistically significant difference between the genders for the value of the vertical dimension at rest, “ELE” and “OLO”. There was a statistically significant difference between the values f or the vertical dimension at rest, “OLO” and “ELE” for both genders. There was a statistically significant correlation between the value for the vertical dimension at rest, “OLO” and “ELE”, for both groups of subjects. **Conclusion.** Determining the vertical dimension of occlusion requires 5.5 mm subtraction from the position of the mandible in pronunciation of the word “OLO” or 7.5 mm in pronunciation of the word “ELE”.

Key words:
vertical dimension; dental occlusion; adult; cognition.

Apstrakt

Uvod/Cilj. Vertikalna dimenzija okluzije veoma je važan parametar za pravilnu rekonstrukciju odnosa između vilica. U literaturi su opisane mnoge metode za njeno određivanje, od jednostavnih, klinički lako primenljivih, do prilično komplikovanih, uz primenu jednog ili više uređaja za registraciju. Cilj ovog istraživanja bio je ispitivanje mogućnosti određivanja vertikalne dimenzije okluzije primenom glasova O i E uz kontrolu dobijenih vrednosti primenom kognitivnih funkcija. **Metode.** Ispitivanja su vršena kod dve grupe ispitanika. Prva grupa se sastojala od 50 osoba ženskog i 50 osoba muškog pola, starosti od 18 do 30 godina. Kod ove grupe vršeno je merenje rastojanja između referentnih tačaka (na vrhu nosa i brade) pri položaju mandibule u vertikalnoj dimenziji okluzije, vertikalnoj dimenziji mirovanja (VDM) i izgovoru reči OLO i ELE. Provera korektnosti određene vrednosti za reč OLO vršena je takođe fonetskom metodom uz primenu vežbi kognitivnog tipa pri brojanju od 89 do 80. Dobijena razlika u prosečnim vrednostima pri određivanju vertikalne dimenzije okluzije i OLO i ELE, u prvoj grupi, korišćena je kao referenca za određivanje vertikalne dimenzije okluzije kod druge grupe ispitanika. Drugom grupom obuhvaćema je 31 bezuba osoba (14 žena i 17 muškaraca), starosti od 54 do 85 godina, a kojima su izrađivane totalne proteze. **Rezultati.** Prosečna vrednost dobijena za vertikalnu dimenziju mirovanja za ceo uzorak je 2,16 mm, za reč OLO iznosila 5,51 mm i za reč ELE 7,47 mm. Nije bilo statistički značajne razlike između polova za vrednosti VDM, OLO i ELE. Ustanov-

Correspondence to: Marko Igić, Faculty of Medicine, Clinic of Dentistry, 52 Dr Zoran Djindjić, 18 000 Niš, Serbia.
Phone: +381 18 4533 191. E-mail: saigic@yahoo.com

ljena je statistički značajna razlika između vrednosti za vertikalnu dimenziju mirovanja, OLO i ELE za oba pola. Takođe, ustanovljena je statistički značajna korelacija između vrednosti za vertikalnu dimenziju mirovanja, OLO i ELE za obe grupe ispitanika. **Zaključak**. U praktičnom radu za određivanje vertikalne dimenzije okluzije treba oduzeti 5,5 mm od položaja mandibule pri izgovaranju reči OLO ili 7,5 mm pri izgovoru reči ELE.

Ključne reči:
vertikalna dimenzija; zubi, okluzija; odrasle osobe; mentalni procesi.

Introduction

Several factors are necessary for correct determination of the vertical dimension of occlusion (VDO).

VDO is the height of the lower part of the face measured between the two reference points when the dental arches are in occlusion at maximum intercuspation [1].

Vertical dimension at rest (VDR) is the height of the lower part of the face measured between the two reference points when the mandible is in physiological rest position – inocclusion [1].

Occlusal rest space (ORS) is the distance between the occlusal surfaces of antagonistic teeth when the jaw is in the position of physiological rest. This is the difference between VDO and VDR [1].

Speech area (SA) is the distance between the occlusal surfaces of antagonistic teeth during pronunciation of certain voices.

In edentulous people there is no mutual contact of the teeth and no elements that indicate the relationship of the upper and lower jaw. Jaw relationship when making dentures, in this case, should be reconstructed with artificial dental arches in the proper vertical and horizontal relationships. According to Gutiérrez de Venezia [2] this is one of the most complex procedures in prosthodontics.

One of the most important parameters, without diminishing the importance of others, in making full denture is determination of the correct VDO [3, 4]. With regard to this, Brian and Dale [5] stated: "Determination of VDO is a critical procedure for total and partial dentures". According to Sharry [6] determining VDO is not a precise process, and many experts will come to this dimension using different methods.

Different methods have been proposed for determining VDO [7, 8] and many of them were used by various authors [8, 9] in edentulous people as well as in people with teeth.

Methods for determining VDO mostly date back to the early 20th century [10,] Techniques for determining VDO are numerous and are based on the determination of VDR [11, 12] speaking method [13–15] preextraction registrations [16] photographs [17] measurements of face and intraoral measurements [18] cephalometric radiographs [19] and so on.

The vertical dimension is relatively constant throughout life [20, 21]. According to Atwood [22] interocclusal distance can vary and it may be affected by many factors such as age, fatigue, mental state, some medications, etc.

At the beginning of the 20th century, a physiological rest was considered constant throughout life [3]. Later researchers, Tallgren [23, 24], Basker et al. [25], Berry [26], Coccaro and Lloyd [27], Ash and Ramfjord [28] did not accept this concept in the strictest sense. Researchers who do not accept the constancy of VDR consider that the patient's neuromuscular system can adapt to changes of dentoalveolar complex.

Although researchers raise the question of the constancy of the position of VDR, it is still used as a starting point for determining the VDO [29].

According to Willis [18], the distance between the pupil of the eye and corner of the lip is equal to the distance of subnazal point and lower edge of the chin. According to Chou et al. [30] asymmetry of the face makes the value of this method questionable.

Ward and Osterholtz [31] notes that swallowing can be used only as a guide in determining the VDO and Swerdlow [8] believes that the phonetic method as a method for the determination of interocclusal distance is more reliable than techniques of swallowing.

Mehringer [32] concluded that tooth loss does not affect the speech position of the mandible. According to the Benediktsson's [33] findings during the pronunciation of the consonant "S", SA varies from 0–14 mm (average value is 2.6 mm), and Howel's [34] results are 0–8 mm (average value is 3.1 mm).

According to Petrović [35] SA is a reliable functional indicator for reconstruction occlusal relations and suggests that this data is registered at the time of having of the teeth in the mouth and recorded in the patient's chart and later, after the loss of teeth, used for reconstruction of occlusal relations.

For every sound there is a corresponding position of the mandible in relation to the maxilla, i.e. the distance between the reference points in the vertical direction. The most appropriate consonants for testing, according to Suvin [36], are "M", "F" and "S", and the vowels "O" and "I". During pronunciation of the vowel "O", or words that end in "O", for example *olovo* (lead in English), the lower bite rim should be 6–8 mm away from the upper, in the frontal part.

In 1959 Morrison [37] proposed the use of English words "sixty-six" (66) and "Mississippi" to determine the VDO in edentulous people.

According to Ismail and George [38], VDR itself tunes over time according to VDO. With normal changes in alveolar processes VDO will be adjusted to the length of the muscle [39]. The adaptive process appears to be maintained throughout life so that if necessary, the dimension of alveolar process changes [40].

Dawson [40] showed that VDO was not generally affected by strong abrasion of teeth because VDO compensates by elongation of alveolar process.

Sharry [6] determined VDO by phonetic method using Arabic words and comparing the results with the values for VDO obtained in swallowing. The obtained values of both methods were congruent.

Pound [10] proposed the method of counting for determining the VDR. A patient counts from 50 to 55, and then rests with the lips in touching position.

Čelebić et al. [41] found that head position has a significant impact on the size of free interocclusal space if VDO is determined by physiognomy, while with phonetic method, ("s" and "mi") the size of free interocclusal space remains constant at different positions of the head.

Comparison of the size of interocclusal space between positions of VDR and VDO determined by clinical procedure and using sirognatograph was done by Poštić and Krstić [42]. Higher numerical value of this area has found using clinical method in 71.4%.

The method for determining the VDO on the basis of the differences in the distance between VDR and VDO is quite objective, but because of non-constancy of VDR it is not reliable. Clinically, it is difficult to determine the VDO by this method because the measurements are taken on moving tissues of the skin [7]. VDR is not a stable parameter and it does not define a precise height, so its use is not reliable for determining the VDO [23, 43].

There is an evidence that suggests that sensory feedback information from the oral cavity plays a major role in maintaining cognitive function in the hippocampus. Masticatory stimulation helps cognitive function. The execution of cognitive tasks requires coordinated activation of different cortical and subcortical regions associated with the hippocampus [44]. The prefrontal cortex is one of these cortical areas, and it plays a particularly important role in the formation of arbitrary connections between sensory signals and establishing voluntary actions to perform a specific task.

In the available literature, the authors did not find data on the use of cognitive functions as an auxiliary method for more precise determination of VDO.

The aim of this study was to investigate the possibility of determining of VDO during pronunciation of words that contain the voices "O" and "E" and control of the values obtained by this method by applying cognitive function, starting from the assumption that the use of vowels to determine VDO is more comfortable than the application of consonants for that purpose.

Methods

The samples of this study were the two groups of patients. The first group was an experimental group of dentistry students at the University of Niš. The second are consisted of edentulous patients of the Clinic of Dentistry, Clinical Center Niš.

The first group included 50 female and 50 male students aged 18–30 years. All the subjects had the full dental arch (except those with no wisdom teeth), Class I occlusion, with no abnormalities, surgery or trauma, no previous orthodontic treatment and temporomandibular disorders. The first group of respondents included students with the mentioned characteristics of stomatognathic system starting from the premise that they can get relevant information on practical application. All the participants were informed about the nature of the study and gave their consent for participation in the study.

The subjects were sitting upright, without head restraints, and occlusal surfaces of upper teeth were parallel to the floor in accordance with the recommendations by Silverman [14].

The reference points were marked with a thin marker at the top of the nose and chin. For each phase, the position of the reference points at the top of the nose and jaw were marked in a chart and later distances measured using a digital Nonius S·H made in China. The obtained values were rounded up to 0.5 mm.

In the first phase the value of the distance of the reference points for VDO was registered (teeth at maximum intercuspation).

In the second stage VDR was registered (using the position of the mandible at rest, the pronunciation of the consonant M combined with swallowing and the appearance of the patient).

In the third phase the subjects uttered the word "OLO" repeatedly, quickly and without pause, while the distance of reference points was noted.

In the fourth phase the subjects counted backwards from 89 to 80. The previously obtained distance between the reference points for the word "OLO" was compared with the value obtained by counting. Registration of the reference points was carried out at the start of pronouncing the number 8, i.e. the vowel "O" (*osam* in Serbian).

In the fifth phase the subjects were asked to pronounce the word "ELE" repeatedly, quickly and without pause, and the distance of the reference points was determined using the same principle as for the word "OLO".

The procedure was repeated three times and then the mean value was calculated.

In the first group of respondents the starting position of the mandible was VDO, because all the subjects had teeth that determined this position of the mandible. This position was given a numeric value of 0.

The second group, representing the control group, consisted of 14 female and 17 male edentulous persons aged 50–82 years who needed full dentures.

In the second group with no natural teeth to determine the relationship between the jaws, the initial position of the mandible for further research was the position of the mandible during the pronunciation of the word "OLO" and it got a numeric value of 0.

The obtained results in the first group (the average distance between the reference points on the chin and the tip of the nose during the pronunciation of the word "OLO") were compared with the position of reference point on the chin during pronunciation of the numbers from 89 to 80. From the obtained values 5.5 mm were subtracted, which corresponds to the position of the mandible for VDO. VDO determination was also done during pronunciation of the word "ELE" by subtracting 7.5 mm from the obtained value (the approximate average value between the reference points during the pronunciation of the word "ELE" and VDO).

VDO position control, obtained by using the words "OLO" and "ELE" in the second group of respondents, was performed by determining the position of VDR, and from that value 2 mm were subtracted. As the position of the mandible for VDR, in relation to the position for the word "OLO" (numeric value 0) is in the opposite direction from the position of the mandible for the word "ELE", numerical values for VDR have a negative sign and for the word "ELE" positive.

Determining the position of the mandible for the words "OLO", "ELE" and VDR was performed under the same criteria as in the first group.

A specific VDO was also checked when the dentures were tried out with the word "OLO" and during pronunciation of numbers from 89 to 80. The patients with disturbed cognitive functions were counting forwards. A specific VDO was also checked during the pronunciation of the word "ELE".

The second group also underwent statistical analysis of parameters o btained by measuring the values of the distance between the position of the reference point for VDR, "OLO" and "ELE".

The obtained results were statistically analyzed using the statistical software package – Statistical Package for Social Science (SPSS) software, version 17. Depending on the characteristics tested, methods of descriptive statistics and the parametric Student's *t*-test, Friedman's nonparametric test and Pearson's correlation test were used.

The study was conducted in accordance with the ethical standards of the Committee for Experiments on Humans and the obtained approval from the competent ethics committee for this study (the decision of the Faculty of Medicine in Nis no. 01-890-11).

Results

Statistical analysis led to the following results presented in Tables 1 and 2.

The average value of VDR between female and male subjects did not differ significantly (2.10 mm and 2.23 mm, respectively; $t = 0.852$, $p > 0.05$). There were also no statistically significant differences in the average value for "OLO" (5.61 mm for women, 5.41 mm for male; $t = -0.612$, $p > 0.05$) and the average value for "ELE" – (7.53 mm for women, 7.42 mm for male; $t = -0.423$, $p > 0.05$). Friedman's test was used to check whether the average values of variables for the VDR, "OLO" and "ELE" measured in male and female subsample differ significantly. On the basis of the values obtained statistically significant difference (χ^2 199.504, $p < 0.01$) was determined.

We studied the correlation between the VDR, "OLO" and "ELE" for female and male subjects, and statistically

Table 1

Characteristics of the first group of respondents (with the full dental arch, Class I occlusion without previous oral and orthodontic treatment or temporomandibular disorders)

First group	Minimum	Maximum	x̄	SD
Women (n = 50)				
Age (years)	18.00	30.00	21.3000	2.91548
VDO, mm	0.00	0.00	0.0000	0.00000
VDR, mm	1.00	4.00	2.1000	0.82065
OLO, mm	2.50	10.00	5.6100	1.67603
ELE, mm	5.00	11.00	7.5300	1.36804
Distance „OLO" ↔ VDR, mm	1.50	6.50	3.5000	1.30540
Distance „ELE" ↔ VDR, mm	3.50	8.00	5.4300	1.07860
Distance „OLO" ↔ „ELE", mm	0.50	3.50	1.9200	0.82906
Man (n = 50)				
Age (years)	18.00	30.00	23.4800	2.34077
VDO, mm	0.00	0.00	0.0000	0.00000
VDR, mm	1.00	4.00	2.2300	0.70138
OLO, mm	2.50	10.00	5.4100	1.59300
ELE , mm	5.00	10.00	7.4200	1.23040
Distance „OLO" ↔ VDR, mm	1.00	6.00	3.1800	1.25259
Distance „ELE" ↔ VDR, mm	3.00	7.00	5.1900	0.91968
Distance „OLO" ↔ „ELE", mm	0.00	4.00	2.0100	0.75248
Total sample (n = 100)				
Age (years)	18.00	30.00	22.3900	2.84940
VDO, mm	0.00	0.00	0.0000	0.00000
VDR, mm	1.00	4.00	2.1650	0.76229
OLO, mm	2.50	10.00	5.5100	1.62987
ELE, mm	5.00	11.00	7.4750	1.29563
Distance „OLO" ↔ VDR, mm	1.00	6.50	3.3400	1.28291
Distance „ELE" ↔ VDR, mm	3.00	8.00	5.3100	1.00448
Distance „OLO" ↔ „ELE", mm	0.00	4.00	1.9650	0.78899
Valid N (listwise) 50				

VDO – vertical dimension of occlusion; VDR – vertical dimension at rest.
Note: Details about parameter measured see in the section Methods.

Table 2

Characteristics of the second group of patients (edentulous persons who needed full dentures)

Second group	Minimum	Maximum	Mean	Std. Deviation
Women (n = 14)				
Age (years)	51.00	76.00	61.5714	6.39368
VDR, mm	-4.50	-2.50	-3.5714	0.64621
OLO, mm	0.00	0.00	0.0000	0.00000
ELE, mm	1.00	2.50	1.9286	0.51355
Distance OLO ↔ VDR, mm	2.50	4.50	3.5714	0.64621
Distance ELE ↔ VDR, mm	5.00	6.00	5.4643	0.45844
Men (n = 17)				
Age (years)	50.00	82.00	68.2353	8.69288
VDR, mm	-4.50	-2.00	-3.3824	0.80096
OLO, mm	0.00	0.00	0.0000	0.00000
ELE, mm	1.00	3.00	2.1765	0.61087
Distance OLO ↔ VDR, mm	2.00	4.50	3.3824	0.80096
Distance ELE ↔ VDR, mm	3.50	6.50	5.4706	0.69531
Total sample (n = 31)				
Age (years)	50.00	82.00	65.2258	8.32950
VDR, mm	-4.50	-2.00	-3.4677	0.72956
OLO, mm	0.00	0.00	0.0000	0.00000
ELE, mm	1.00	3.00	2.0645	0.57361
Distance OLO ↔ VDR, mm	2.00	4.50	3.4677	0.72956
Distance ELE ↔ VDR, mm	3.50	6.50	5.4677	0.59070
Valid N (listwise) 14				

VDO – vertical dimension of occlusion; VDR – vertical dimension et rest.
Note: Details about parameter measured see in the section Methods.

significant correlation was obtained (r = 0.637, 0.633, and 0.879, respectively; $p < 0.01$).

The average distance between the reference points for "OLO" and VDR in the females was 3.5 mm and 3.18 mm for the males. There was no statistically significant difference between them (t = -1.251; $p > 0.05$). The average distance between the reference points for "ELE" and VDR in the females was 5.43 mm and 5.19 mm for the males. In both of these variables, there was no statistically significant difference (t = -1.197, Sig > 0.05). The average distance between the reference points for "OLO" and "ELE" in the female subjects was 1.92 mm and 2.01 mm for males and between them there is also no statistically significant difference (t = 0.568, $p > 0.05$).

In the fourth phase of testing control of the obtained value for the word "OLO" was done. In all cases, when counting from 89–80, the reference point on the lower jaw, at the beginning of the word that starts with the voice "O" (*osam* in Serbian), coincided with the reference point on the carton for the voice "O", and later, when other voices uttering (s, a, m, d...) oscillated around the point marked on the carton. Measuring the amplitude of oscillation of the reference point was not conducted due to the complexity of the procedure.

In the second group the average value obtained for VDR (OLO-VDR) for female subjects was -3.57 mm, -3.38 mm for the males and for the entire sample it was -3.46 mm. The average value for "ELE" ("OLO" + "ELE") for the females was 1.92 mm, for males 2.17 mm and for the entire sample 2.06 mm. There was no statistically significant difference between the values for VDR for the females and the males (t = 0.712, $p > 0.05$) and "ELE" (t = 1.207, $p > 0.05$). There was a correlation between the values for VDR and "ELE" in the entire sample of the second group (r = 0.771, $p < 0.01$).

This group was also tested for determining the distance between the average values o f the reference points for "OLO" and VDR between female and male participants. In females the distance was 3.57 mm, and 3.38 mm for the males. Between the tested groups there was no statistically significant difference (t = -0.712, $p > 0.05$). The same procedure was also performed for the value of the distance between the reference points for "ELE" and VDR. For the females the average distance was 5.46 mm, and 5.47 mm for the males. In this case there was no statistically significant difference between the variables (t = 0.029, $p > 0.05$).

The values of the distance between "OLO" and "ELE" in both groups (whole sample) were compared and no statistically significant difference found (t = 0.767 $p > 0.05$).

The same was done for VDR-OLO values b etween both groups, and no statistically significant difference was found (t = 0.697; $p > 0.05$).

Discussion

For a comprehensive prosthetic reconstruction determination of VDO is often referred to as the central issue, the core problem [45]. Change in VDO affects facial appearance, creates difficulties in pronunciation and discomfort in muscles [46]. Correctly determined VDO provides adequate patient appearance, enables efficient chewing and prevents jaw joint dysfunction.

Among many methods available for determining VDO some authors argue that the most comfortable are applied in practice. Vidya and Gopinathan [47] proposes the choice of method for VDO according to their accuracy, repeatability of

measurements, the adaptability of techniques, type and complexity of equipment and duration of registration. Sadowsky [48] proposes combining several methods to obtain adequate interocclusal distance.

The method for VDO determining by swallowing and the phonetic method of Gittelson [49] are universal for all people. The main advantage of these techniques is easy functional determination of height, and the adequacy of the results can be evaluated. According to Dowson [50] the phonetic method is ideal for determining the vertical dimension of occlusion in edentulous patients, or in wrongly determined vertical relationship. In practice he uses the Silverman's SA method during the pronunciation of the consonant "S" (patient counts from 60–66 in English).

Pouysségur et al. [51] propose the use of the letter "S", surrounded by a neutral vowel ("E", "EU") as an ideal phonetic instrument for determining the vertical dimension.

For the reconstruction of the intermaxillary relation in edentulous patients there are no absolutely safe parameters.

The choice of the specific amount of vertical dimension is primarily based on clinician's clinical experience and practice. Despite the large number of different methods for determining VDO there is still no precise method. Individually, the methods are not very valuable, but a combination of several methods may lead to the diagnosis [2].

The methods for determining the VDO using special measuring devices provide more accurate results, but due to the complicated procedure and the need for having these devices are not favored in comparison to the conventional methods.

VDO determination on the basis of VDR according to Tallgren [23, 24], Berry [26], Coccaro and Lloyd [27], Atwood [22], Ash and Ramfjord [28], Willis [18], is not a fair method considering the volatility of VDR. However, determining VDO on the basis of VDR is widespread in practice because of its simple and fast methodology to obtain the results which was pointed to by Johnson and Stratton [29].

All the classic phonetic methods for VDO determining use pronunciation of certain vocals (s, m i.) simultaneously registering the interocclusal space. This space is small (average value is 1–2 mm – Silverman [14, 15], 2.6 mm – Benediktsson [33], 3.1 mm – Howell [34]) and the lips are close together so it is not possible to observe the interocclusal space. All the authors who have used the phonetic method for determining the VDO aimed at getting the value for the SA and then that value was used to obtain values f or VDO. Most authors dealt with the influence of the letter S on the size of interocclusal space. During pronounciation of the voice "M" words as Mississippi, a reference point on the mandible oscillates vertically so the verification of the position of the point is uncertain. In principle, a reference value should be obtained which is a starting point for obtaining the VDO.

Compared to other sounds, during pronunciation of the vowels "O" and "E", we get much greater value of interocclusal space, so it was also the reason that the authors opt for this method bearing in mind that the amount of mouth opening in this case is within the limits of pure rotation of the mandible [20]. Application of this method allows visual monitoring of the situation in the mouth unlike with other phonetic methods.

For determining VDO the words "OLO" and "ELE" were selected, with the presence of voices "O", "E" and "L". During pronunciation of the the voice "O" in the so-called vowel trapezium (Figure 1) (where ordinate shows the position of the tongue in height and the abscissa position of voice creation), the vertical position of the tongue is at the junction of middle and upper thirds of the vocal trapeze and horizontally rear. During the pronunciation of voice "E" position of the tongue along the vertical is the same as the voice "O" and horizontally it occupies the front position.

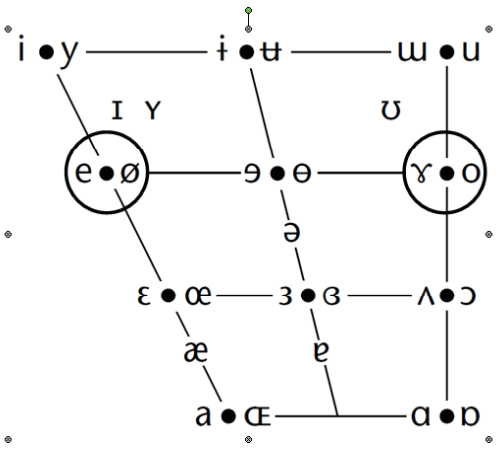

Fig. 1 – Vowel trapezium.

During pronunciation of the consonant "L", position of tongue is the dorzo-velar by the place of creation, and by the manner of creation it is alveolar lateral. Consonant "L" is inserted between the two vowels "O" and "E" to form a melodic word of voices that are close by the place of creation, i.e. it is not necessary to move the lower jaw horizontally nor vertically, it requires only a slight movement of the tongue [52]. During pronunciation of the vowel "O", the position of lips is formed, i.e. the mouth opening is slightly smaller than for the vowel "E", but sufficient for visual monitoring of the position of bite rims of the upper and lower jaw and the distance between them. During pronunciation of the vowel "E" the position of the lips is unshaped, the lips are maximally stretched horizontally and vertically, allowing maximum insight into the location and distance of the occlusal rim and the teeth.

Average values o f the distance between the reference points, obtained in this study, at the position of VDR, in the first group, were 2.1 mm for the female respondents and 2.23 mm for the male, which agrees with the findings by Okeson [53], Benediktsson [33], Silverman [14, 15], but differs from the findings of other authors [11, 12, 29] for about 30%.

The test of values for VDR, "ELE" and "OLO", in the first group, provided a statistically significant correlation between the variables for both groups (r = 0.637, 0.633 and 0.879, respectively; $p < 0.01$), which is logical, and points to the value of the research and complies with Ismail et al. [54] research (VDR has a tendency to follow VDO).

The average distance between the reference points at VDO and the position of the mandible during pronunciation of the voice "O" in the female subjects was 5.61 mm, and 5.41 mm in the male and the average value for the whole sample was 5.51 mm. Between the variables for "OLO" for the female and the male subjects there is no statistically significant difference (t = -0.612, p > 0.05) which simplifies the use of this method. Considering that the SA according to Benediktsson [33] is 0–14 mm, and according to Howell [34] 0–8 mm, the average value between VDO and the position of the mandible during pronunciation of the voice "O" of 5.51 mm which was determined by this examination, is consistent with the findings of these authors.

When using the methods of registering VDO by the sound "O" the distance between the reference points is on average approximately 5.51 mm, using the sound "E" 7.47 mm, which is the maximum value for the pronunciation of certain voices. In this case, the lips are distant from each other so that it is possible to visually observe the situation in the mouth or the distance between the occlusal rims or artificial teeth. In this case, VDO is obtained by subtracting 5.5 mm from the value obtained during the pronunciation of the words "OLO" or 7.5 mm for the word "ELE". Approximate measurement of the distance between walls or teeth is made using a plastic strip with the width of 5.5 and 7.5 mm, and inserted between the rims in the front during pronunciation of the word "OLO" or "ELE".

The lack of statistically significant difference between the parameters for the "OLO" – "ELE" and VDR – "OLO", between the first and the second group indicates the constancy of these positions during life.

The fact that the value of the obtained interocclusal space during pronouncing of the sounds "O" or "E" is within the hinged movement of the mandible during the initial opening of the mouth indicates that this method is in accordance with the gnathological principles.

Based on statistical processing of parameters in clinical practice, it is possible to check the correctness of the author's method by comparing it with data obtained by some other method, as Millet et al. [55] say there is no perfect technique that will ensure success.

Thus, check of a certain position of mandible for VDO using this method can be done by comparing the position of the reference point on the mandible during pronunciation of the words "OLO" or "ELE", so to determine the position of the mandible for VDR using other method, and measure the distance of the mandible for the position for "OLO" – VDR and for "ELE" – VDR. It should be about 3.34 mm, and about 5.31 mm, respectively.

Taking into account the results and opinion proposed by Harper [56] for determination of VDO by VDR, the method for determining VDO using the sounds "O" and "E" gains importance. Dowson's [50] opinion is in accordance with the previous and he believes that the phonetic method is ideal for determining VDO.

In the next phase, when dentures are tried out, after the experience acquired with this method, it is possible to very easily verify the correct VDO. In continuous, rapid repetition of the words "OLO" and "ELE" the mandible is in a static position, meaning without moving, and the registration of the distance between the reference points is simple.

During counting from 89–80 the reference point on the mandible oscillates around the point on the paper determined by pronouncing the sound "O". Counting from 89 to 80 (in Serbian) requires constant repetition of voice "O" (10 times) whereby the value of the previously registered interocclusal spaces is controlled. Counting forward (80–89) is usually done automatically and is resistant to the effects of aging. Counting backwards is a cognitive operation that requires patient's concentration which deteriorates with age. Counting backwards (89 to 80) moves thoughts away from dental procedures, has a relaxing effect on the masticatory muscles and contributes to obtaining a more accurate value of VDO.

In the second group of subjects, in the patients with disturbed cognitive functions, which is often the case in older people who generally require full dentures, it turned out that they were not able to count backwards, which was not pleasant for them. In this case the forward counting method is applied (80 to 89), which was much easier and allowed the authors to obtain data for the VDO, i.e. its control. Counting forward for patients with disturbed cognitive functions, however, was enough for the patients to stop thinking about the current intervention which enabled control of the registered position of the mandible.

This study did not focus on examining cognitive function, but the count was intended to decenter a patient from the current intervention, in order to achieve more precise determination of the position of the mandible during pronunciation of the sounds "O" or "E".

To apply this method to other people with different linguistic background, it is necessary to apply other numbers with the sound "O" at their beginning. For example, in Greek *ogdonda enea* (*ογδόντα εννέα*) – 89, in Italian *ottanta nove* – 89, in Czech *osmdesát-devět* – 89. Similarly, it is possible to use this method with the sound "E" for the English-speaking area (eighty-nine, 89), and Greek *ενενήντα εννέα* (*eneninda enea*) – 89.

Depending on the native language, appropriate words are used, containing the desired sounds. So Burnett and Clifford [57] used the words with sh, s, j, z, ch, zh in the assessment of SA.

Fuad [4] used the phonetic method with the Arabic words for determining VDO.

The distance between VDR and VDO is about 3 mm according to Niswonger [11], Pyott and Schaeffer [19], Pleasure [12], but may be in the range 1.5–6 mm [18] or from 2–4 mm [53]. The results obtained by the author are 2.16 mm (just under the average of the findings of these authors), but in accordance with the rank.

The exact determination of VDO on the basis of intra- or extraoral measurements is impossible due to the technique of measurement (diameter of the two reference points, types of measuring devices, sample cards, a ruler, or a more accurate measuring device, the mobility of marked points on the skin or a sticking plaster, removing or deleting reference points with a handkerchief or the patient's hand when wiping the chin and the nose after rinsing the mouth with water, etc.).

Rivera-Morales and Mohl [58] believes that for the vertical dimension there is certain optimal space and that it is not just a point. Rebibo et al. [45] think that perhaps there is a great ability to adapt to changes in VDO, but only under the rotation about hinged axis. Lim and van Waas [59] says: "Determination of VDO seems a combination of art, science and experience".

However, Millet et al. [55] consider that VDR determination by VDO is one of the most commonly used clinical methods, and according to Burnett and Clifford [57] the phonetic method is one of many available techniques for determining the VDO.

Based on examination, Willie [60] finds that the most commonly applied method for determining the VDO is aesthetic appearance and the phonetic method, and the most common combination of methods is phonetic, aesthetic appearance and swallowing.

Conclusion

Despite a large number of methods for determining the vertical dimension of occlusion based on different systems, techniques and clinical experience, an absolutely safe method for vertical dimension of occlusion is currently lacking.

The phonetic method for determining the vertical dimension of occlusion, using pronunciation of the vowels "O" and "E" is simple, economical and easy to perform. It does not require special operating conditions, equipment, nor training of the doctors.

An approximate value of interocclusal space during vowel pronunciation "O" of 5.5 mm and 7.5 mm of vowel "E" pronunciation can be used to determine the vertical dimension of occlusion in both genders.

Using cognitive functions during counting from 89 to 80 while checking correctness of vertical dimension of occlusion is a simple and good method for checking certain vertical dimension of occlusion in practice. In cases of patients who cannot count backwards, the method of forward counting is applied (80–89).

Previous experience of authors indicates that the proposed method for determining and controlling the vertical dimension of occlusion is clinically acceptable.

Studies have confirmed the hypothesis that the determination of vertical dimension of occlusion using the vowels "O" and "E", and control of the obtained position with the use of a cognitive type of exercises is quite reliable, practical and easy to use in clinical practice.

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Morphometric analysis of the fascicular organisation of the optic nerve

Morfometrijska analiza fascikularne organizacije optičkog nerva

Miroslav Radunović*, Zdravko Vitošević†, Mila Četković‡, Aleksandra Vuksanović-Božarić*, Nemanja Radojević*, Miodrag Radunović*

***Faculty of Medicine, University of Montenegro, Podgorica, Montenegro; †Faculty of Medicine, University of Pristina, Kosovska Mitrovica, Serbia; ‡Faculty of Medicine, University of Belgrade, Belgrade, Serbia**

Abstract

Background/Aim. The optic nerve is anatomically observed in four segments: intrabulbar, orbital, canalicular, and cranial. According to the literature, the surface of the transversal cut of the nerve is different through it. The aim of this study was to evaluate the fascicular organisation of the optic nerve, throughout its three segments from the eye. **Methods.** Five pairs of optic nerves, obtained from the autopsies were examined. Using Heidenhain's (azan) staining, the cuts were prepared for microscopy. Morphometric analysis was performed using the stereological methods for morphometric cytology – the Weible's testing system M42. The following measures were established: the surface of the transverse cut of the nerve, the entire surface of fasciculi, the entire surface of connective tissue and blood vessels, the number of fasciculi, the surface of a single fasciculus. **Results.** The surface of the transverse cut of the nerve was found to grow from the orbital to the cranial segment, as well as the entire surface of fasciculi. While their number is significantly lower in the cranial segment, the number of fasciculi varied slightly between the orbital and the canalicular segment. The surface of a single fasciculus grows from the bulb to the chiasma. There is probable a cause to believe that this may be due to fusion of the "small" fasciculi in the orbitocranial direction. **Conclusion.** There are significant differences among the examined parameters of the different parts of the optic nerve.

Key words:
optic nerve; autopsy; microscopy; anatomy.

Apstrakt

Uvod/Cilj. Optički nerv je anatomski podeljen u četiri segmenta: intrabulbarni, intraorbitalni, intrakanalikularni i intrakranijalni. Prema podacima iz literature, površina poprečnog preseka nerva različita je u pojedinim segmentima. Cilj ove studije bio je da razmotri fasciklarnu organizaciju optičkog nerva kroz njegova tri segmenta od izlaska iz očne jabučice pa do hijazme. **Metode.** Ispitivano je pet pari očnih nerava dobijenih iz autopsijkog materijala. Korišćeno je Hajdenhajmovo azan bojenje i isečci su pripremani za mikroskopiju. Morfometrijska analiza vršena je Weibleovim testnim sistemom M42, stereološkom metodom za morfometrijsku citologiju. Upoređivani su površina poprečnog preseka nerva, ukupna površina fascikulusa, ukupna površina vezivnog tkiva i krvnih sudova, broj fascikulusa i površina pojedinačnog fascikulusa. **Rezultati.** Površina poprečnog preseka nerva raste od orbitalnog ka intrakranijalnom delu, kao i ukupna površina fascikulusa. Broj fascikulusa značajno opada u kanalikularnom segmentu, dok broj fascikulusa blago varira poredeći orbitalni i kanalikularni segment. Površina pojedinačnog fascikulusa raste od očne jabučice ka hijazmi. Razlog ovome najverovatnije je u činjenici da dolazi do fuzije malih fascikulusa u pravcu hijazme. **Zaključak.** Postoji značajna razlika među ispitivanim parametarima različitih segmenata optičkog nerva.

Ključne reči:
n. optikus; autopsija; mikroskopija; anatomija.

Introduction

While the anatomo-topographical, neuro-ophthalmologi cal, and neurosurgical aspects of the optic nerve have been well established [1–3], its ultrastructure has yet to be defined outside of animal models [4].

The embryological origin of the retina and the optic nerve is neuroectoderm in nature, closely linked to the development of the central nervous system [5]. The axons of the retinal ganglion cells pass through the outer retinal layers, the choroid layer, and the *lamina cribrosa,* where they obtain a myelin layer and form the fasciculi of the optic nerve [6]. Since the axons of the optic nerve have a central origin, oligodendrocytes are involved in forming its myelin layer, whilst the fasciculi are formed by astrocytes and connective tissue [4].

Correspondence to: Nemanja Radojević, Department of Forensic Medicine, Faculty of Medicine, University of Montenegro, Ljubljanska 1, 20 000 Podgorica, Montenegro, Fax: +382 20 412 283. E-mail: com_nr@yahoo.com

The optic nerve is anatomically observed in four segments: intrabulbar, orbital, canalicular, and the cranial [7]. According to the outcomes of Jonas et al.[8] study, the surface of the transversal cut of the nerve is different throughout, ranging from 3.93 mm^2 to 8.15 mm^2 (mean 5.92 ± 1.06 mm^2), with 73.2 ± 5.8% of the surface belonging to fasciculi (optical fibres).

The aim of this study was to evaluate the fascicular organisation of the optic nerve, throughout its three segments from the eye.

Methods

We examined five pairs of optic nerves, obtained from the autopsies of 3 male and 2 female bodies, of 42 to 74 years of age, who showed no signs of central nervous pathology. The post-mortem interval (the time from death to autopsy) ranged from 10 to 24 hours in length.

Removal of the brain was done according to the standard autopsy techniques, cutting the optic nerves in the region of the optic chiasma. After removing the orbital roof and opening the optic channel, a detailed preparation of the optic nerves was performed. The orbital, canalicular, and cranial segments of the nerve were all separated.

Using Heidenhain's (azan) staining [9], the cuts were prepared for microscopy. Morphometric analysis was performed by the stereological methods for morphometric cytology; specifically by the Weible's testing system M42, with 42 test dots and 21 test lines [10, 11].

The following measures were established: the surface (area) of the transverse cut of the nerve (A_N) and its mean value ($\bar{x}A_N$), the entire surface (area) of fasciculi (A_F) and their mean value ($\bar{x}A_F$); the entire surface (area) of connective tissue and blood vessels ($A_{CV} = A_N - A_F$), and their mean value ($\bar{x}A_{CV}$); the number of fasciculi (N); the surface (area) of a single fasciculus (A_{FS}) and its mean value ($\bar{x}A_{FS}$) –

$$[A_N \text{ (or } A_F, \text{ or } A_{CV}, \text{ or } A_{FS},) = P_D \cdot a]$$

were P_D = the number of dots of the test system that are present on the examined surface; a = the area that belongs to a single dot of the testing system calculated by the formula $a = (d^2 \cdot \sqrt{3}) / 2$; and d = the distance between two dots, depending on microscope magnification (for magnification ×10, d = 0.16 mm, a = 0.0221702 mm^2).

The number of fasciculi was established by manual counting from the microphotographs of a magnification ×25 to ×75 (Figure 1).

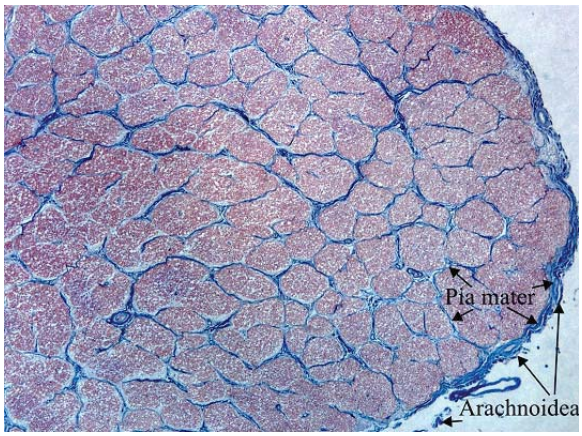

Fig. 1 – Microphotograph of the optic nerve [Heidenhain's (azan) staining (× 75)].

The standard statistical protocol for descriptive statistics was used, including Student's *t*-test for independent samples at 95% confidence intervals.

Results

Regarding sex and age variations between the examined parameters of the nerves no differences were found (sex: $p < 0.01$; age: $p = 0.03$), so the sample was homogenous.

The values of the measured morphometric parameters (A_N, A_F, A_{CV}, and A_{FS}) were different for the three segments of the nerve (Tables 1 and 2).

By using *t*-test, no statistically significant difference was found between the orbital and the canalicular surface of

Table 1

Mean values of the defined surfaces in mm^2

Segments of the optic nerve	$\bar{x}A_N$	$\bar{x}A_F$	$\bar{x}A_{CV}$
Cranial	8.77 ± 0.78 (0.35)	6.56 ± 0.66 (0.29)	2.21 ± 0.26 (0.11)
Canalicular	7.86 ± 0.42 (0.19)	5.62 ± 0.29 (0.13)	2.23 ± 0.14 (0.06)
Orbital	7.60 ± 0.34 (0.15)	5.33 ± 0.24 (0.10)	2.25 ± 0.14 (0.06)

The values are the mean value ± standard deviation and standard error in parentheses.
$\bar{x}A_N$ – the mean value of the nerve's surface; $\bar{x}A_F$ – the mean value of the fascicular surface;
$\bar{x}A_{CV}$ – the mean value of the connective tissue and blood vessels's surface.

Table 2

Mean value of the number of fasciculi ($\bar{x}N_F$) and the mean value of the single fascicular surfaces in mm^2 ($\bar{x}A_{FP}$)

Segments of the nerve	$\bar{x}N_F$	$\bar{x}A_{FP}$
Cranial	811 ± 21.36 (9.55)	0.0080 ± 0.00072 (0.00032)
Canalicular	912 ± 25.75 (11.51)	0.0061 ± 0.00017 (0.00008)
Orbital	928 ± 34.62 (15.48)	0.0057 ± 0.00023 (0.00010)

The values are the mean value ± standard deviation and standard error in parentheses.

the nerve, ($p = 0.313$), as well as between the canalicular and the cranial surface of the nerve ($p = 0.053$). Nonetheless, there was a statistically significant difference between the orbital and the cranial segment ($p = 0.016$).

By analysing the A_F, a statistically significant difference was found between the orbital and the cranial ($p = 0.005$), as well as between the canalicular and the cranial segment ($p = 0.021$), but not between orbital and canalicular one ($p = 0.131$).

No significance was found between the A_{CV} of any segment of the nerve.

Table 2 presents the number of fasciculi by the segments. According to *t*-test, a high statistically significant difference was found between the canalicular and the cranial, as well as between the orbital and the cranial ($p < 0.000$), but not between the orbital and the canalicular segment ($p = 0.415$). In addition, Table 2 notes the values of A_{FS}. A statistically significant difference was found among all the three segments: orbital *vs* canalicular ($p = 0.013$) canalicular *vs* cranial ($p < 0.000$), orbital *vs* cranial ($p < 0.000$).

Figure 2 shows the ratios between the A_F and the A_{CV} for each segment of the nerve.

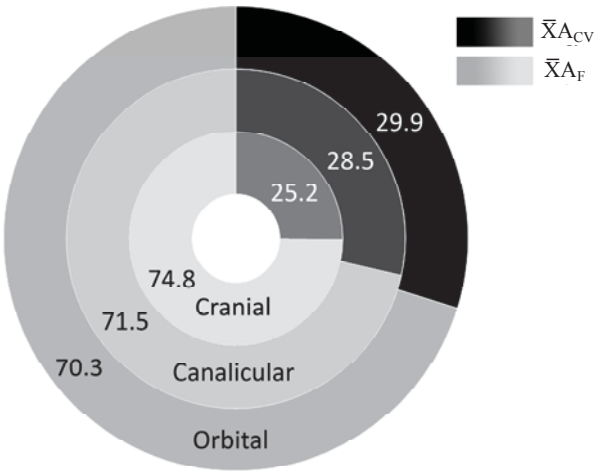

Fig. 2 – The ratios between the A_F and the A_{CV} for each segment of the nerve.

A_F – area of fasciculi;
A_{CV} – area of connective tissue and blood vessels

Discussion

We used stereological analysis simple and cheap, but somewhat out-of-fashion method to establish the morphometric parameters of histo-anatomy. The method is especially useful for cases in whom qualitative analysis does not prove sufficient, e.g. for small differences between the groups or for a high variability in parameters which hides the differences between them. Moreover, it is a well-established fact that the interobserver difference is recorded as extant in similar cases [12]. Both of these factors contributed to choosing of the morphometric method of the Weible's testing system M42 for stereological examination.

The results of the study demonstrate significant differences between the examined parameters of the different parts of the nerve. Therein, the surface of the whole nerve is significantly different between the orbital and the cranial segment, which is in accordance with the outcomes of Jonas et al. study [8]. Since the surfaces under study here were examined in the segment-by-segment fashion, the presented results are more valuable in gaining a better understanding of the fascicular organisation of the nerve.

The surface of the transverse cut of the nerve was found to grow from the orbital to the cranial segment, as well as the entire surface of the fasciculi. Similar results were presented in Tao et al. study [13]. While their number was significantly lower in the canalicular segment, the number of the fasciculi varied slightly between the orbital and the canalicular segment. The surface of a single fasciculus grows from the bulb to the chiasma. A similar finding has been repeatedly published for animal models [14–17]. Jeffery et al. [18] also noticed the lowest number of fasciculi to be in the central area of the orbital segment, the highest pic in the canalicular segment, and a constant decrease throughout the cranial segment.

Even numerous studies demonstated the age-related decrease in fibers in the optic nerve, with cca 5,000 fibers *per* year [19–21], the paper under review here did not establish the decrease in the number of fasciculi, nor the surface of a single fasciculus regarding age.

The fascicular organisation of the optic nerve is strongly dependent on the number of fibrous astrocytes, namely the axon's growth is dependent on the number of astrocytes and their processes. A lower amount of connective tissue in the cranial segment is responsible for the wider spread of optical fasciculi [16, 17, 19, 21–23]. A possible link between the fascicular reorganisation and the lower glial volume in the cranial segment may stem from the recomposition of optic fibres in the chiasma. Taking the A_{FS} and N_F in the cranial segment into consideration, a similar hypothesis may also be posited of that a significantly higher A_{FS} and lower N_F in the cranial segment may be the consequence of the lower number of fibrous astrocytes and the wider spread of the optic fibres. In addition, due to the fusion of the "small" fasciculi, their number decreases in the cranial segment [4, 18]. The final results suggest that the fusion of the "small" fasciculi begins from the orbital segment ($N_{F(orbital)} > N_{F(canalicular)}$; $A_{KS(orbital)} > A_{KS(canalicular)}$). In addition, fascicular and glial organisation in related nerve segements are followed with capilary rearrangement [24].

Having in mind the established fascicular nerve organisation, especially fascicular fusion, pathology and trauma of different segments would differ. Smaller injuries (fracture of the surrounding bones, or nerve contusion), or even lighter nerve compression (oedema and varoius types of haemorrhages) in cranial direction of the nerve can damage smaller number of fasciculi but with higher negative impact on eye sight.

Conclusion

The transversal surface of the optic nerve, as well as the entire fascicular surface grows from the orbital to the cranial segment. Conversely, the surface of the connective tissue and

blood vessels decreases upon reaching the chiasma, but not significantly.

The number of fasciculi decreases from the orbital to the cranial segment, while the surface of a single fasciculus increases in the same direction. There is probable a cause to believe that this may be due to fusion of the "small" fasciculi in the orbitocranial direction.

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Radical cystectomy in eldery

Radikalna cistektomija kod bolesnika u odmaklom životnom dobu

Vladimir Bančević*†, Predrag Aleksić*†, Novak Milović*†, Aleksandar Spasić*, Božidar Kovačević‡, Perica Toševski*, Zoran Čampara*, Radovan Milošević*†, Snežana Cerović†‡

***Clinic of Urology, ‡Institute of Pathology and Forensic Medicine, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy; University of Defence, Belgrade, Serbia**

Abstract

Background/Aim. Radical cystectomy is the method of choice for the treatment of muscle invasive bladder cancer. This major surgery is associated with many complications, especially in older patients. The aim of this study was to analyze preoperative comorbidity, and intraoperative and postoperative complicatons in patients older than 75 years. **Methods.** This clinical, retrospective study included 46 patients over 75 years, who underwent radical cystectomy. Indications for surgery, and complications during and after the surgery were followed up. **Results.** Preoperatively, anemia caused by hematuria was registered in 76% of the patients. In 52% of the patients urine derivation was performed by ileal conduit, in 35% by ureterocutaneostomy and in 13% orthotopic ileal neobladder was created. The average duration of surgery was 190 (120–300) min. A total of 76% of the patients were treated by blood supstitution intraoperatively, average 630 (310–1230) mL. Concerning pathological stage of transitional cell carcinoma of urinary bladder, 26% of the patients had T2, 4% T3a, 52% T3b, and 14% T4a stage. In one case, planocellular carcinoma was diagnosed by patohistological examination, and in 2 cases prostate carcinoma was incidentally found. The average duration of hospitalization was 16 (8–35) days. **Conclusion.** The main reason for cystectomy in patients over 70 and 80 years was gross hematuria caused by bladder cancer, with consecutive anemia which could not be solved using endoscopic treatment or blood supstitution. As expected, a prolonged stay in hospital after cystectomy, and a higher rate of complications were recorded in this population.

Key words:
urinary bladder neoplasms; cytectomy; aged; hematuria; comorbidity; postoperative complications.

Apstrakt

Uvod/Cilj. Radikalna cistektomija je metoda izbora za lečenje mišićnoinvazivnog karcinoma mokraćne bešike. Spada u grupu najvećih operacija u urologiji i povezana je sa brojnim komplikacijama, naročito kod starijih. Cilj ove studije bila je analiza preoperativnog komorbiditeta kao i intraoperativnih i postoperativnih komplikacija kod bolesnika starijih od 75 godina. **Metode.** U kliničku, retrospektivnu studiju bilo je uključeno 46 bolesnika starijih od 75 godina kojima je učinjena radikalna cistektomija. Praćene su indikacije za operaciju, kao i komplikacije tokom i nakon operacije**. Rezultati.** Preoperativno, 76% bolesnika imalo je anemiju uzrokovanu hematurijom. Kod 52% operisanih derivacija urina izvedena je ilealnim konduitom, kod 35% ureterokutaneostomijom, a kod 13% bolesnika kreirana je ortotopna ilealna neobešika. Prosečno vreme trajanja operacije iznosilo je 190 (120–300) min. Intraoperativno, 76% bolesnika primalo je transfuziju krvi, prosečno 630 (310–1230) mL. Kod 26% operisanih ustanovljen je tranzicioni ćelijski karcinom (TCC) mokraćne bešike u stadijumu T2, kod 4% u stadijumu T3a, kod 52% u stadijumu T3b, a 14% u stadijumu T4a. Kod jednog bolesnika radilo se o planocelularnom karcinomu, a kod dva bolesnika karcinom prostate dijagnostikovan je incidentalno. Prosečna dužina hospitalizacije nakon operacije iznosila je 16 (8–35) dana. **Zaključak.** Glavni razlog za cistektomiju kod bolesnika u osmoj i devetoj deceniji života bila je masivna hematurija uzrokovana TCC-om sa posledičnom anemijom, koji nisu mogli biti rešeni endoskopskim putem i transfuzijama krvi. U ovoj populaciji zabeležen je očekivano produžen boravak u bolnici nakon cistektomije, kao i veća stopa komplikacija.

Ključne reči:
mokraćna bešika, neoplazme; cistektomija; stare osobe; hematurija; komorbiditet; postoperativne komplikacije.

Correspondence to: Vladimir Bančević, Clinic of Urology, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 64 127 7350. E-mail: vladaban2004@yahoo.com

Introduction

Even today, radical cystectomy (RC) represents one of the most complex procedures in urologic surgery, connected with noumerous complications. The most common indication for performing RC is muscle invasive transitional cell carcinoma (TCC) of the urinary bladder [1]. Extention of life duration carries out the question of indications for RC in the population over 75 years, since this population is characterized by a number of comorbid conditions, and increased number of complications during extensive surgical procedures [2].

Methods

This clinical, retrospective study included 46 patients older than 75 years submitted to radical cystectomy in the Clinic of Urology, Military Medical Academy, Belgrade, during the period of 2003–2012. Indications for operation, comorbidity, the kind of applied urinary diversion, duration of surgical procedure, the need for blood supstitution before, during and after the surgery, postoperative duration of hospitalization, intraoperative and early postoperative complications, histopathological findings obtained after RC and kind of postoperative additional therapy were followed up. Criteria for blood supstitution were hematocrit below 27% or hemoglobin below 75 g/dL.

Results

A total of 26 (57%) male patients and 20 (43%) female underwent RC. The average age of patients was 78 (75–85) years. Pre-radical cystectomy treatment procedures are shown in Table 1.

Preoperatively, 22% of the patients had distant metastatic disease, the most common lung involvement, in 90%.

The average American Society of Anesthesologists (ASA) score for physical status classification was 2.46.

The average number od transurethral bladder tumor resections (TURBT) before RC was 2.9 (1–5), and the first TURBT was performed on the average in 11 months (1–96) before RC. Preoperatively, anemia, caused by hematuria, which needed blood supstitution, was registered in 76% of the patients. They were treated by blood supstitution intraoperatively, averagely 630 (310–1230) mL concerning the patients who underwent blood supstitution, and all the operated patients were given on average 512 (0–1230) mL.

The average duration of surgery was 190 (120–300) min. The type of applied urinary diursion are shown in Figure 1.

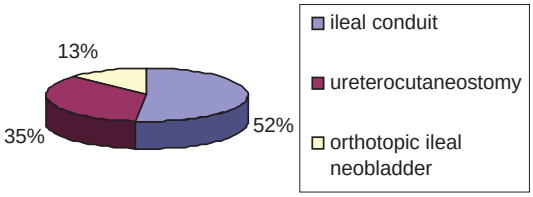

Fig. 1 – Type of the applied urinary diversion after radical cystectomy.

In 26% of the patients T2 stage of TCC of the urinary bladder was found, in 4% T3a stage, in 50% T3b stage and in 14% T4a stage. In one (2%) patients planocellular carcinoma was diagnosed and in 2 (4%) cases prostate carcinoma was incidentally found (Table 2).

Table 2
Histopathological findings obtained after radical cystectomy

Histopathological finding	Patients (%)
TCC stage	
T2	26
T3a	4
T3b	52
T4a	14
Planocellular carcinoma	2
Incidental prostate cancer	4
Metastases in the iliac and obturator lymph nodes	32

TCC – transitional cell carcinoma.

Table 1
Pre-radical cystectomy treatment procedures

PRC treatment procedure	Indication	Patients (%)	Time prior RC (years)
Neoadjuvant radiotherapy	Muscle invasive bladder TCC	9	5.1
Nephroureterectomy	TCC of pyelon	9	2.7
Partial cystectomy	Solitary. muscle invasive bladder TCC	7	2.4
Hysterectomy with bilateral adnexectomy	CaPVU	4	N/A
Hemicolectomy	Colon tumor	2	4.5
Neoadjuvant chemiotherapy: gemcitabin + cisplatina	Metastatic TCC	2	0.4

RC – radical cystectomy; TCC – transitional cell carcinoma; CaPVU – carcinoma of *portio vaginalis uteri*.

The average duration of hospitalization after RC was 16 (8–35) days. Two (2%) patients were on intensive care more than 24 hours. Postoperatively, 3 (7%) patients were febrile, 3 (7%) developed wound infection and dehiscence of which in 2 (4%) patients secondary suture was performed. Diarrheal syndrome was found in 2 (4%) patients postoperatively after RC. Two (4%) patients died in the early postoperative period, and one (2%) patient had a transient ischemic attack (TIA). Four (9%) patients were treated by chemotherapy according to the protocol gemcitabine + cisplatin during postoperative period.

Discussion

The risk of the occurrence of urothelial bladder cancer increases with age. However, the prolongation of life, but also the emergence of a number of comorbid conditions at the advanced age impose the question whether the performance of major surgery is indicated in eldery [3]. These patients are not only due to malignant disease, but also because of the general state of health in a significantly greater risk from anesthesiological complications and the intraoperative, as well as early and late postoperative complications [4]. Large studies show that cystectomy is still the method of choice in the treatment of muscle invasive bladder cancer, even in eldery, and especially if it causes anemic syndrome, the need for frequent blood transfusion or inability to control and stop active bleeding from bladder tumor [5]. In our study, even 76% of the patients who underwent cystectomy had anemia caused by hematuria, which required blood transfusion before surgery. It is an indicator of a poor general condition of patients, and significant comorbidity factor. Hematuria can occur suddenly, massively and cause a quick drop in the red blood elements and poor general condition of the patients. It, also, can be gradual, long-term, and patients for a long-time compensate chronic loss of red blood cells, slowly getting used to it. Their general condition was not so dramatic, although laboratory proof of a significant bleeding is present. In this second case, chronic and slow blood loss is present, not only because of the presence of a large tumor in the bladder, but also as a result of postirradiation cystitis, years after radiation. In our study, 4 patients had massive hematuria due to postirradiation cystitis with recurrence in urinary bladder. Although some authors present the experience with conservative ways of controlling massive hematuria by oral or intravenous use of conjugated estrogen using pentosan polysulfate or WF10 [6], in our series we had no experience with the use of these types of drugs. In our series, cystectomy was done only when even endoscopic procedures were not suitable to control bleeding from the bladder and threatened to lead to hemodynamic instability of the patient. Some authors state that regardless of the advanced age and the fact of a higher rate of complications and a small percentage of continent patients, in the selected cases, in those over 80, it is possible to perform orthotopic derivation of the urine with satisfactory results [7]. In reference to other studies, eldery patients often underwent ileal conduit diversion, while there are studies which report high percentage of patients who underwent ureterocutaneostomy, over 45% [8]. Here, as in our series, referring to patients with advanced disease, poor general state of health, with a short life expectancy the option was the simplest form of urinary diversion and maximum shortening the duration of surgery in 35% of the patients operated on. In the aforementioned study [8], the authors decided rarest for orthotopic derivation, although it was performed in 6.2% of operated patients. Our belief was reinforced by personal experience and the literature suggests that it is possible to do orthotopic derivation of the urine in selected cases in elderly patients appreciating their "biological" value rather than physical age, so we decided to create a neobladder in 13% of the treated patients. Chang et al. [9], in a series of over 300 middle-aged patients, came to the conclusion that 45% of patients had preoperative anemia. This percentage in our series is significantly higher, almost 76%, which in probably a consequence of several times unsuccessfully attempted endoscopic hemostasis. In younger patients, in better general condition, a large surgical intervention is more frequently chosen. Another reason is, that patients, often delay radical surgery until it can bocome life threatening, then there is certainly higher degree of anemia syndrome. This is illustrated by the average of 3 TURBT prior to cystectomy, while in younger patients after first TURBT, if there is present any of invasion of the muscular layer, we perform cystectomy [1]. In our series, the average volume of blood used for transfusion was higher than in the aforementioned series (600 : 630 mL), due to a larger number of patients with the signs of anemia preoperatively, but also because of the spreading of malignant disease in the pelvis. Bladder malignancy was confirmed by the fact 52% of the patients in the stage pT3b, and 14% in the stage pT4a, along with the fact that 32% of the operated on patients had the disease that spread to regional lymph nodes, and 22% had distant metastases at the time of surgery. Although it is known that positive lymph nodes and distant metastases are signs of poor prognosis for patients [10], in our series cystectomy was done not to improve "disease free" or "disease stabile" condition, but because of the vital indication at the time of decision making regarding operation. In this group of patients ureterocutaneostomy was most often created. In 7% of the patients before cystectomy, partial cystectomy was done, and in 9% radiation was conducted. These were patients in whom cystectomy was particularly difficult, due to these interventions. Considering that radiation was conducted on the average 5 years ago, and partial cystectomy on the average 2.7 years ago, maybe we should have been more rigorous before making decision to use these types of therapy, because during the years patients become significantly older, and the cystectomy significantly more difficult on the secondary field work. A Canadian study shows that patients with advanced age are at increased risk of developing neurovascular disease, but in the study a statistically significant difference in the mortality rate between younger patients and the elderly was not observed, which amounted to 0.9% and 2.3%, respectively [11]. In our study, perioperative mortality was 4%.

Four patients who had positive lymph nodes after the surgery, and who were in good general state and without significant comorbidities received postoperative chemotherapy according to the protocol gemcitabine + cisplatin.

Conclusion

The main reason for cystectomy in patients over 70 and 80 was hematuria caused by bladder cancer, with consecutive anemia which cannot be solved using endoscopic treatment or blood supstitution. As expected, a longer stay in

hospital after cystectomy, and a higher rate of complications was recorded in this population than in younger patients. We observed a significantly higher need for blood transfusion during surgery, and a higher rate of perioperative mortality. Most patients underwent urinary diversion with ileal conduit, and a significant number of patients, due to poor general condition or local findings, underwent ureterocutaneostomy. In the selected cases, the patients in good general condition underwent orthotopic diversion and a small number of patients received chemotherapy after surgery.

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Campylobacter jejuni infection and IgE sensitization in up to 2-year-old infants

Campylobacter jejuni infekcija i IgE senzibilizacija kod dece uzrasta do dve godine

Dara Jovanović*, Nevenka Ilić†, Biljana Miljković-Selimović‡, Dragoljub Djokić§, Tijana Relić†, Zoran Tambur‖, Radoje Doder¶, Gordana Kostić**

***City Institute of Public Health, Belgrade, Serbia; †Public Health Institute, Kragujevac, Serbia; ‡Reference Laboratory for *Campylobacter* and *Helicobacter*, Center for Microbiology, Institute of Public Health, Faculty of Medicine, University of Niš, Niš, Serbia; §Academy of Continuing Medical Education, Belgrade, Serbia; ‖Institute of Hygiene, ¶Clinic for Gastroenterology, Military Medical Academy, Belgrade, Serbia; **Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia**

Abstract

Background/Aim. The "hygiene hypothesis" addresses the correlation between the occurrence of atopy and the frequency of infections in the earliest age, explaining an increase in the incidence of atopic diseases by living in good, infection-free, hygienic conditions. The aim of our study was to determine the conection between atopy and *Campylobacter* infection, and to analyze the association between serum concentrations of total IgE and *Campylobacter* infection in relation to atopy in children up to two years. **Methods.** A case control study was conducted with the sample of 98 infants of the average age of 8 months. Total serum IgE and Phadiatop infant multi-test were determined on Immunocap-100 (Phadia AB, Uppsala, Sweden). The presence of atopy was determined by detection of serum-specific IgE ≥ 0.35 kUA/L (Phadiatop infant positive) and serum IgM, IgA, IgG levels against *C. jejuni* were determined by a quantitative immuno-enzyme test - SERION ELISA classic. **Results.** Total IgE cut-off values ≥ 15 kU/L point to atopy in infants, and tIgE cut-off values ≥ 8.1 kU/L pointed to a *C. jejuni* infection in infants. Within the group of atopic children, tIgE levels ≥ 29.8 kU/L point to *C. jejuni* infection, and within the group of non-atopic children, tIgE levels ≥ 5.9 kU/L point to infection. Enteritis is not a predictor of *C. jejuni* infection, because of a high frequency of asymptomatic cases of infection. The risk factors for *C. jejuni* infection are age and tIgE, and the protective factors are breastfeeding and atopy. **Conclusion.** *C. jejuni* infection increases the total serum IgE level, which is predictive of infection, regardless of the presence of atopy. The presence of symptomatic *C. jejuni* infection reduces the risk of atopy in a child of the age of 5–24 months by the factor of 10.

Key words:
campylobacter jejuni; child; hypersensitivity, immediate; immunoglobulins; immunoglobulin e; immunologic tests.

Apstrakt

Uvod/Cilj. Povezanost nastanka atopije i učestalosti infekcija u najranijem uzrastu tema je kojom se bavi „hipoteza higijene", objašnjavajući porast incidencije atopijskih bolesti činjenicom da se živi u dobrim higijenskim uslovima, bez infekcija. Cilj naše studije bio je da utvrdimo povezanost atopije i infekcije kampilobakterijom, kao i da analiziramo povezanost serumske koncentracije ukupnih IgE i infekcije kamlobakterijom u odnosu na atopiju kod dece uzrasta do dve godine. **Metode.** Sprovedena je studija praćenja ukupno 98 dece, srednjeg uzrasta osam meseci. Postojanje atopije utvrđeno je detekcijom serumskih specifičnih IgE kvalitatitvnim multitestom *Phadiatop infant*, a serumske koncentracije IgM, IgA, IgG na C. *jejuni* određivane su kvantitativnim imunoenzimskim testom – *SERION ELISA classic.* **Rezultati.** Vrednost ukupnih IgE ≥ 15 kU/L ukazuje na to da dete ima atopiju, a tIgE ≥ 8,1 kU/L da dete ima *C. jejuni* infekciju. U grupi dece sa atopijom serumska koncentracija tIgE ≥ 29,8 kU/L ukazuje na to da dete atopičar ima infekciju, a u grupi dece bez atopije koncentracija ukupnih IgE ≥ 5,9 kU/L ukazuje na to da dete bez atopije ima *C. jejuni* infekciju. Enteritis nije prediktor *C. jejuni* infekcije, zbog velike učestalosti asimptomatskih slučajeva infekcije. Faktori rizika za *C. jejuni* infekciju su uzrast i količina tIgE, a protektivni faktori dojenje i atopija. **Zaključak.** *C. jejuni* infekcija povećava serumski nivo tIgE koji predstavlja prediktivni faktor infekcije bez obzira na postojanje atopije. Postojanje simptomatske *C. jejuni* infekcije 10 puta smanjuje rizik od atopije kod deca uzrasta 5–24 meseca.

Ključne reči:
campylobacter jejuni; deca; hipersenzibilnost, rana; imunoglobulini; IgE; imunološki testovi.

Correspondence to: Nevenka Ilić, Public Health Institute, Atinska 14/18, 34 000 Kragujevac, Serbia. Phone: +381 34 341 272, E-mail: ilic.nena.nevenka@gmail.com

Introduction

The "hygiene hypothesis" addresses the correlation between the occurrence of atopy and the frequency of infections in the earliest age, explaining an increase in the incidence of atopic diseases by living in good, infection-free hygienic conditions [1]. The concept of controlling the balance of Th-1/Th-2 cell response, which is protective for the occurrence of an allergic reaction, happens directly through early exposure of infants to microbes through the gastrointestinal tract, leading to stimulation and development of Th-1 in the environment of the dominant Th-2 response, as physiologically dominant in the breastfeeding period [2, 3].

Early childhood is considered as the most important period for "educating" of the immune system, when it is not yet mature, and when the immune tolerance to food and microbiotic antigens develops [4, 5]. Incapability of atopic children to develop oral tolerance to antigens in food in the first several years of life can be the consequence of belated maturation of the immune system [6]. Investigations of the effects of infection on allergic sensitization show that microorganisms can have a potentially modulatory role in the etiology and pathogenesis of atopic diseases [2]. The microbiotic hypothesis explains that the composition of enteral microorganisms in the earliest age is the main source of immune stimulation and an important factor in the development of oral tolerance [7]. A Danish study shows that a combined seropositivity to *Clostridium difficile*, *Campylobacter jejuni* and *Yersinia enterocolitica* results in an increased incidence of atopy (OR 1.7; 95% CI, 1.2 – 2.6), and that hepatitis A virus, *Helicobacter pylori* and *Toxoplasma gondii*, as poor hygiene pathogens, are related to a low prevalence of atopy [8].

C. jejuni is a species of gram-negative bacteria, considered as the most common cause of acute diarrhea in children aged 0–4 years [9]. *Campylobacter* is a classic extracellular bacteria eliminated dominantly by the humoral immune response that provides neutralization, opsonization and lysis of bacteria by activation of the complement system. van Spreeuwel et al. [10] also describe the intracellular presence of *C. jejuni* in epithelial cells of intestinal mucosa in patients suffering from colitis caused by these specific bacteria. *Campylobacter*, as a gram-negative microorganism, with antigens recognised by the receptors for molecular patterns of microorganisms, such as toll-like receptors 4 (TLR-4) for lipopolysaccharides (LPS), and TLR-5 for flagellin, and TLR-2 and 6 for lipopeptides, which induce signalling predominantly through (NF)kB [11], and the production of proinflammatory cytokines in epithelial and dendritic cells [12]. High levels of transforming growth factor (TGF)-β in the digestive tract in the presence of proinflammatory cytokines, such as IL-1 and IL-6, lead to the differentiation of naive T-cells into the Th-17 subgroup, the activation of which leads to the neutrophil infiltration and increased intestinal peristalsis manifested as an inflammatory diarrhea. The synthesis of IgA and IgG2 antibodies is promoted in the digestive tract, particularly as the response to T-independent antigens, such as polysaccharides from the capsule of *Campylobacter* or lipopolysaccharides from the bacterial cell wall (LPS and lipopoligosaccharides – LOS) in the presence of a proliferation including ligand, B/cell activating factor (APRIL, BAFF) or TGF-β cytokines [13, 14]. Over a 24-hour period, a dendritic cell starts to produce IL-12 necessary for the differentiation of naive T-cells into the Th-1 subgroup. Th-1 cells produce INF-γ that helps macrophages eliminate the bacteria by a higher level of phagocytosis and microbicidal activity, and creates conditions for the maturation of affinities and changes in the antibody heavy chain in the B-cell from IgM to IgG, along with the inhibition of Th-2 response [13, 14].

Studies methodologically involving children with diarrhea and isolation of *Campylobacter* from feces show that the frequency of *Campylobacter* infections is very variable. World Health Organization (WHO) studies conducted on a global level helped in determining that the rate of isolation of *Campylobacter* from feces in children with diarrhea up to 2 years of age is 4–38.8% [15, 16], but this percentage can reach up to 66% at the age of 5 in Mexico [17]. The isolation rate of *Campylobacter* from feces in children up to two years of age is correlated with the humoral response to surface antigens of *C. jejuni* [18]. It is known that the development of immunity to *C. jejuni* antigens plays a vital role in the decrease in the disease incidence at an older age, in the manifestation of the clinical form and severity of the disease, and in the duration of the microbe excretion phase in the period of recovery [19]. The infants continuously exposed to these bacteria develop antibodies in serum very early in life, and the symptoms subside [20]. Even in cases when cultivation could not prove the presence of *Campylobacter*, the seroconversion of all the three classes of immunoglobulin to *Campylobacter* antigens was detected, causing the opinion that serology is a more sensitive diagnostic method than cultivation [9]. A study carried out by Strid et al. [21] on 210 subjects with *Campylobacter* infection detected in feces involved serological testing for the presence of all the classes of serum antibodies to *Campylobacter*. The testing showed that an acute *Campylobacter* infection can be proved by individual analysis of antibodies, namely: IgM with the specificity of 60%, IgA with the specificity of 80%, and IgG with the specificity of 71%; however, the analysis of all the three antibodies detected infection with the sensitivity of 92% on the day 35 after the infection, and 90% in 3 months after the infection.

C. jejuni infection can have significant effects on the functionality of intestinal epithelium as a barrier and on the normal microflora composition, and therefore on the development of the immune system in the earliest age, which is also important for the phenotype expression of atopy [22, 23]. Studies focused only on the clinical phenotype of an atopic disease can underestimate the correlation between intestinal infection and an atopy, that is, the effects of intestinal microorganisms on the occurrence of atopic phenotypes [24, 25].

The aim of our study was to determine the connection between atopy and *Campylobacter* infection, and to analyze the association between serum concentrations of the total IgE and *Campylobacter* infection in relation to atopy in children up to two years.

Methods

The study was carried out in the town of Kragujevac in the period 2009 – 2011. The inclusion criteria were children (n = 167) aged 5 – 24 months, in good health, whose parents gave a written consent for their inclusion into the study. Data on symptoms of a gastrointestinal disease – vomiting and diarrhea – were obtained from a non-standard questionnaire, and were complemented by data from the database maintained in the primary health care centers by following the diagnoses according to the International Classification of Diseases (ICD) from the group A – intestinal infections of unspecified origin, and the group K – intestinal diseases manifested by vomiting and diarrhea. The exclusion criteria were children with the diagnoses A00–A04 and A06–A07 (*Salmonella* spp., *Shigella* spp., *E.coli*, protozoans, etc.), surgical intestinal diseases, and children with a positive test result for an antibody, specifically of the IgG class at the age of 5 and 6 months due to possible transplacental transmission (n = 5) or the IgM class against C. jejuni (n = 64).

The definitive sample consisted of 98 infants, while the average period from the presence of enterocolitic symptoms to the moment of testing was 3 months.

The presence of atopy was determined by detection of serum-specific IgE using the qualitative Phadiatop infant multi-test (cut-off value ≥ 0.35 kUA/L). Allergens against which the presence of specific IgE is determined by the Phadiatop infant multi-test, are proteins: egg white, cow milk, peanuts, shrimps, cat and dog hair, mites, silver birch pollen, timothy grass, ambrosia and nettle [26] . The Phadiatop infant test was carried out *in vitro* by immunofluorescence (Fluorescent Immunoassay) on Immunocap-100 (Phadia AB, Uppsala, Sweden). Total serum IgE levels were determined by the same technique. The group of atopic children included those in which the specific IgE serum levels ≥ 0.35 kUA/L were determined (Phadiatop infant positive). The group of non-atopic children included those in which specific serum IgE antibodies were not detected (Phadiatop infant negative).

IgM, IgA, and IgG serum levels to *C. jejuni* were determined by quantitative immuno-enzyme assay - SERION ELISA classic (Institute Virion/Serion GmbH, Würzburg, Germany). For IgM, the samples were treated with a rheumatoid factor absorbent - SERION Rheumatoid FactorAbsor-bent. The serum levels of specific antibodies to C. *jejuni* were calculated in SERION easy base 4PL-Softwarey evaluate. Since the manufacturer's cut-off values of specific antibody levels to C. *jejuni* were not defined for children, in our study we took the cut-off results as positive for the following values: IgM > 40 U/mL, IgA > 20 U/mL, and IgG > 20 U/mL. The cut-off results were repeated twice, and in case of a repeated cut-off value, the result would be included in the study as positive, and in case of a negative finding – as negative. *C. jejuni* infection was defined as the presence of at least two classes of antibodies (IgG+IgA; IgG+IgM; IgM+IgA, or IgM+IgA+IgG) in the levels higher than the listed cut-off values (n = 35); the infants free from a *C. jejuni* infection were those without a positive antibody result (n = 63). The frequencies of combinations of the classes of specific antibodies to *C. jejuni* in the group of infected children were: IgM+IgG 68.6% (n = 24/35), IgM+IgA 8.6% (n = 3/35), and IgM+IgA+IgG 22.9% (n = 8/35).

The infants with symptomatic *C. jejuni* infection were those having at least two positive antibodies to *C. jejuni*, plus diarrhea and/or vomiting reported in the medical history or database of the primary health care center (n = 15). The children with asymptomatic *C. jejuni* infection were those with at least two positive antibodies to *C. jejuni*, but without diarrhea and/or vomiting reported in the medical history or database of the primary health care center (n = 20).

The obtained results were processed statistically using the commercial software package SPSS 13.0 for Windows. The differences in the frequency of *C. jejuni* infections with respect to atopy were tested using the $\chi 2$ test and Fisher's exact test. The correlation between continuous variables was determined using the correlation test (Spearman). The continuous variables between atopic categories and *C. jejuni* infections were compared using non-parametric tests – Mann Vitney and Kruskal Wallis. ROC curve was used to determine the cut-off tIgE values as markers of atopy and *C. jejuni* infection. The correlation models between a dependent variable and independent variables were determined by logistic regression. The logistic regression result was presented by odds ratio (OR) values and the confidence interval for the accuracy of statement of 95% (CI 95%). The statistical significance of the model is based on the difference between the model in block 0 (the expected results of the analysis without any independent variables of which the model is consisted of) and block 1 (the results of analysis which include the examined characteristics), and is defined by the values of $\chi 2$ – C2 in the number of degrees of freedom and the number of cases included in the model, as well as *p* significance. The differences were considered to be significant when $p < 0.05$.

Ethical principles

The test was carried out in accordance with the ethical standards of the Declaration of Helsinki adopted in 1975 and revised in 1983. The study was approved by the Ethical Committee at the Public Health Institute in Kragujevac, and the Ethical Committee at the Faculty of Medical Sciences in Kragujevac, within the plan for prevention of allergic diseases in children. The biological material (serum) was collected from children in a health care institution under pediatric control, and with a consent from the parents previously informed of the procedures and objectives of the study.

Results

The descriptive statistical parameters of the studied group are shown in Table 1. The atopic children (n = 22), when compared to the non-atopic ones (n = 76), had a lower IgM serum levels to *C. jejuni* (Md = 23.2 *vs* 34.0 U/mL, z = 2.3; $p = 0.022$), similar IgA levels to *C. jejuni* (Md = 6.68 *vs* 6.00 U/mL, z = 0.99 $p = 0.321$) and lower IgG serum levels to *C. jejuni* (Md = 5.4 vs. 8.83 U/mL, z = -1.62, $p = 0.106$).

The comparison of tIgE serum levels in children with *C. jejuni* infection (Md = 10.2 kU/L, n = 35) and those in

Table 1

Data among children with and without *C. jejuni* infection

Parameters	All children (98, 100%)	Children with *C. jejuni* infection (35, 35.7%)	Children without *C. jejuni* infection (63, 64.3%)	*p* value
Gender, n (%)				
male	55 (56.1)	14 (40)	41 (65.1)	0.014*
female	43 (43.9)	21 (60)	22 (34.9)	
Age (months), n (%)				
5–6	50 (51)	10 (28.6)	40 (63.5)	
7–12	35 (35.7)	12 (34.3)	23 (36.5)	0.000***
13–24	13 (13.3)	13 (37.1)	0 (0)	
Breastfeeding at the time of testing, n (%)				
yes	52 (53.1)	10 (28.6)	42 (66.7)	0.000***
no	46 (46.9)	25 (71.4)	21 (33.3)	
Atopia, n (%)				
atopic	22 (22.4)	6 (17.1)	16 (25.4)	0.348
nonatopic	76 (77.6)	29 (82.9)	47 (74.6)	
Enteritis, n (%)				
yes	29 (29.6)	15 (42.9)	14 (22.2)	0.032*
no	69 (70.4)	20 (57.1)	49 (77.8)	
tIgE (kU/L), mean ± SD (median)	37.2 ± 133 (6.1)	85.5 ± 214 (10.2)	10.3 ± 14.4 (5.4)	0.020*
Abs to *C. jejuni* (U/mL), mean ± SD (median)				
IgM	85.9 ± 120 (33)	196 ±147 (128)	24 ± 8.3 (24.1)	
IgA	8.7 ± 7.5 (6.0)	15.2 ± 8.7 (12.6)	5.0 ± 3.1 (4.95)	
IgG	18.0 ± 19.7 (7.8)	39 ±18.8 (36.3)	6.3 ± 4.9 (4.9)	

Note: *p*-values were calculated using χ^2 test (for categorial variables) or Mann-Witney (for continuous variables); **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

children without C. *jejuni* infection (Md = 5.4 kU/L, n = 63) determined a statistically significant difference (Mann Witney U = 788, z = 2.33, $p = 0.020$) with the cut-off value of tIgE ≥ 8.1 kU/L showing that a child had *C. jejuni* infection (sensitivity 60%, specificity 70%). In the group of atopic children the cut-off value of tIgE serum level ≥ 29.8 kU/L showed that an atopic child had *C. jejuni* infection (area = 0.917, sensitivity 83.3%, specificity 87.5%), and in the group of non-atopic children the cut-off value of tIgE ≥ 5.9 kU/L showed that a non-atopic child had a *C. jejuni* infection (area = 0.635, sensitivity 62%, specificity 68%). The cut-off values for tIgE distinguished atopic from non-atopic children (Table 2).

In order to study a predictive significance of the studied features for the manifestation of C. *jejuni* infection in infants aged 5–24 months, the model of logistic regression included: age (0 = 5–6 months, 1 = 7–12 months, 2 = 13–24 months), gender (0 = male, 1 = female), breastfeeding at the time of study (0 = no, 1 = yes), enteritis (0 = no, 1 = yes), tIgE serum levels on the basis of determined cut-off values (0 = ≤ 5.9 kU/L; 1 = 5.91 – 29.79 kU/L, 2 = ≥ 29.8 kU/L) and atopy (0 = Phadiatop infant negative, 1 = Phadiatop infant positive) (Table 3). The predictive factors that were particularly statistically conclusive of the manifestation of *C. jejuni* infection were age and tIgE, and breastfeeding at the time of the study and atopy had a protective role. An increase in age in each category increased the risk of the presence of infection by the factor of 3.8 compared to the age of 5–6 months. An increase in tIgE serum levels in each category increased the risk of the presence of infection by the factor of 4.5 compared to the children with tIgE ≤ 5.9 kU/L. Breastfeeding reduced the risk of the presence of

Table 2

Biomarker for atopy tIgE - depending on the category of children according to the presence of symptoms of enteritis and *C. jejuni* infection

Groups	Atopia	tIgE median (kU/L)	*p*	Area	Cut-off (kU/L) ≥	Sensitivity (%)	Specificity (%)
Total	Atopic (n = 22)	13.1	0.000***	0.769	15.0	50	80
	Nonatopic (n = 76)	5.4					
Enteritis							
without C. *jejuni* infection	Atopic (n = 4)	19.4	0.065	0.825	11.9	75	80
	Nonatopic (n = 10)	2.9					
with C. *jejuni i*nfection	Atopic (n = 2)	688.5	0.027*	1.000	86.9	100	92
	Nonatopic (n = 13)	10.6					
Without enteritis							
without C. *jejuni* infection	Atopic (n = 12)	7.7	0.013*	0.740	5.9	75	70
	Nonatopic (n = 37)	4.6					
with C. *jejuni* infection	Atopic (n = 4)	203.8	0.011*	0.922	33.7	75	94
	Nonatopic (n =16)	7.4					

Note: *p* values were calculated using Mann-Witney; **p* < 0.05; ***p* < 0.01; ****p* < 0.001.

Table 3

Logistic regression model that distinguishes children with *C. jejuni* infection

Phadiatop infant	Variable	B	S.E.	Wald	df	*p*	OR	CI 95%	
								lower	upper
Total	Age (kat)	1.33	0.42	10.22	1	0.001	3.78	1.67	8.55
	tIgE (kat)	1.50	0.48	9.71	1	0.002	4.48	1.74	11.51
Model	Breastfeeding	-1.24	0.58	4.65	1	0.031	0.29	0.09	0.89
c2 (6.98) = 46.4; $p = 0.000$	Atopy	-1.51	0.78	3.77	1	0.052	0.22	0.05	1.01
(37.7–51.8% variance)	Female	0.85	0.57	2.21	1	0.137	2.35	0.76	7.23
	Enteritis	0.56	0.63	0.81	1	0.367	1.76	0.52	6.00
	Constant	-2.24	0.68	10.88	1	0.001	0.11		
Non-atopic	Age (kat)	1.45	0.44	10.74	1	0.001	4.28	1.79	10.20
Model	tIgE (kat)	1.05	0.48	4.71	1	0.030	2.85	1.11	7.33
c2 (3.76) = 30.0. $p = 0.000$	Breastfeeding	-1.20	0.60	4.03	1	0.045	0.30	0.09	0.97
(32.6–44.4% variance)	Constant	-1.50	0.57	6.94	1	0.008	0.22		
Atopic	Age (kat)	2.11	1.32	2.54	1	0.111	8.24	0.62	109.9
Model	tIgE (kat)	4.10	1.92	4.57	1	0.033	60.7	1.40	2618.5
c2 (2.22) = 14.2. $p = 0.001$ (28.8–39.2% variance)	Constant	-8.36	3.78	4.88	1	0.027	0.000		

B – coeficient for usefulness of predictors; SE – standard error; W – Wald coeficient; OR – the ratio-change in the odds of the event of interest for a one-unit change in the predictor; CI 95% – confidience interval for 95%.

C. jejuni infection by the factor of 3.5, and atopy reduces the risk of the presence of infection by the factor of 4.5.

The model of logistic regression, differentiating the atopic children aged 5 – 24 months, revealed that an increase in tIgE serum level in each of the listed category raised the risk of the presence of atopy by the factor of 6.9, starting from tIgE serum levels ≤ 5.9 kU/L. The presence of *C. jejuni* infection gave a unique statistic predictor of the presence of atopy, reducing the risk by the factor of 5. The presence of symptomatic *C. jejuni* infection reduced the risk of the children aged 5 – 24 months being atopic by the factor of 10 (Table 4).

Table 4

Logistic regression model that distinguishes children with atopy

Phadiatop infant	Variable	B	S.E.	Wald	df	*p*	OR	CI 95%	
								lower	upper
Total	tIgE (kat)	1.93	0.50	14.80	1	0.000	6.89	2.58	18.40
	C. jejuni infection	-1.62	0.82	3.91	1	0.048	0.20	0.04	0.99
	Breastfeeding	0.36	0.60	0.35	1	0.554	1.43	0.44	4.66
Model	Enteritis	-0.23	0.65	0.13	1	0.719	0.79	0.22	2.81
c2 (6.98) = 22.0; $p = 0.001$	Age	0.05	0.49	0.01	1	0.919	1.05	0.40	2.75
(20.1–30.7% variance)	Female	-0.04	0.57	0.01	1	0.944	0.96	0.31	2.96
	Constant	-2.44	0.74	10.90	1	0.001	0.09		
Model	tIgE ≤ 5.9 kU/L			15.08	2	.001			
c2 (5.98) = 22.1. $p = 0.001$	tIgE 5.9–29.8 kU/L	1.73	0.66	6.89	1	0.009	5.63	1.55	20.45
(20.2–30.8% variance)	tIgE ≥ 29.8 kU/L	4.02	1.06	14.35	1	0.000	55.72	6.96	446.0
	No enteritis. No infection			5.53	3	0.137			
	Enteritis without infection	-0.00	0.77	0.00	1	0.997	0.98	0.22	4.50
	Asymptomatic infection	-1.63	.90	3.26	1	0.071	0.20	0.03	1.15
	Symptomatic infection	-2.32	1.13	4.22	1	0.040	.098	0.01	0.90
	Constant	-2.13	0.55	15.03	1	0.000	0.12		

B – coefficient for usefulness of predictors; SE – standard error; W – Wald coefficient; OR – the ratio-change in the odds of the event of interest for a one-unit change in the predictor; CI 95% – confidence interval for 95%.

Discussion

Humoral response in children in their first year of life shows the characteristics of its development that imply the following: the strongest is the IgM response and it reaches at the age of 12 months 75% of the levels of IgM response in adults; IgG synthesis exceeds the level of transplacentally transferred antibodies around the 4th month of age, reaching 60% of the serum levels in adults at the 12th month of age the IgA humoral response shows the slowest development [14, 21]. IgM production is dominant in the primary immune response to protein antigens, while the formation of other antibody isotypes at the larger extent is the characteristic of the secondary immune response [13]. In our study group, 68.6% of the children with *C. jejuni* infection had a combination of IgM+IgG classes, and in all combinations of antibodies the IgM class was always present. Lower IgM serum levels against *C. jejuni* detected in the atopic children can indicate a weaker immune response which does not correlate with the TH-1/TH-2 ratio.

Atopy is a subgroup of allergic hypersensitivities and is defined as a genetic predisposition for IgE production in response to exposure to allergens. Occurrence of specific IgE antibodies to allergens lies in the basis of the development of a clinical disorder (phenotype) of an atopic disease [27, 28]. In several studies the tIgE serum level is described as the marker of atopy, now widely used in the diagnosis of allergic diseases in children [29, 30]. Several studies determined increased levels of the total IgE in a group of sensitized children, but the cut-off values of the total IgE implying the presence of atopy in early childhood varied, ranging from 15.15 kU/L to 106 kU/L [29, 30]. In this study, tIgE was the marker of atopy with the cut-off value of tIgE ≥ 15 kU/L (sensitivity 50%, specificity 80.3%). Infection can have a role in a higher production of IgE during exposure to immunostimulants of bacterial origin [31]. Our study determined that a higher tIgE level can be a marker of the presence of *C. jejuni* infection in children aged 5–24 months, with the cut-off value ≥ 8.1 kU/L (60% sensitivity, 70% specificity). Th-2 response physiologically present in infancy also causes an increase in tIgE level during infection with pathogenic microorganisms, regardless of the presence of atopy. Reacting to antigenic stimulation, T-cells from the thymus (that reaches its highest cellularity at the age of 6-12 months) primarily differentiate into Th-2 producing IL-4 and IL-13. Primarily lower Th-1 cell response in infants is interpreted by lower IL-12 production from dendritic cells in response to LPS, lower expression of CD40-ligand on CD4+ cells after activation (which additionally reduces IL-12 expression in dendritic cells), lower expression of STAT4 transcription factor and higher gene methylation for INF-γ [32]. The possibility for Th-1 response during bacterial infections to be responsible for the growth of tIgE antibodies is excluded, and only TH-2 helper cells participate in this process [33]. According to our results, serum levels of tIgE < 5.9 kU/L show that a child has neither an infection nor atopy, whereas tIgE ≥ 29.8 kU/L shows that a child has both atopy and infection. Proper interpretation of tIgE serum levels in this age is additionally complicated by the fact that a *C. jejuni* infection can also be asymptomatic by itself. Namely, if a child has no enteritis symptoms, it can be atopic even with the levels of tIgE ≥ 5.9 kU/L in the case of absence of infection, and if a child has a asymptomatic *C. jejuni* infection, the serum level of tIgE ≥ 33.7 kU/L can imply that a child is atopic. If an atopic child aged 5–24 months has enteritis, the symptoms can be the consequence of food allergy only (cut-off value of tIgE ≥ 11.9 kU/L) or can be an intestinal infection on the ground of an Th-2 inflammation already present in the intestines (cut-off value of tIgE ≥ 86.9 kU/L), implying that *C. jejuni* infection in an atopic child strongly stimulates Th-2 response. Therefore, the tIgE serum level range 5.9 -33.7 kU/L in children without gastrointestinal symptoms, and the range 11.9 – 86.9 kU/L in children who had enteritis , are the "grey zones" where it is always necessary to test both for atopy and an infection. If an infant up to two years of age has extremely high levels of tIgE, there is a danger for a diagnostician to focus his attention on atopy, leaving the infection unnoticed. On the other hand, tIgE reference levels in atopic children without an infection imply the danger of not noticing atopy. tIgE serum level cannot be a reliable marker of atopy in infants up to two years of age, unless this is considered in the context of infection.

In our study, enteritis symptoms did not have a predictive significance for *C. jejuni* infection, because of a large number of asymptomatic cases. Tenkate and Stafford [34] indicate a decreasing rate of symptomatic infections during the first two years of life. New conclusions show that *C. jejuni* colonization is most often asymptomatic, but clinical manifestations also depend on the host-specific factors, such as: age, immune competence and health condition [35].

In our territory, the gender-specific differences in illness caused by *C. jejuni* infection in children are related to a higher frequency of breastfeeding of male children. Diarrhea caused by *C. jejuni* is less frequently and less intensively manifested in breastfed children [34.] Heresi et al. [35] stated that breastfeeding reduces the frequency of symptomatic campylobacteriosis, but does not reduce the colonization with these bacteria. In addition to the lysis of bacteria, lactoferrin in mother's milk has a role in the reduction of inflammatory response by immature enterocytes, and the interraction between glycans from mother's milk, microflora and glycans in mucin from the intestinal epithelium assist the development of mucosal immunity and protect an infant from infection and inflammatory intestinal diseases. A mother's exposure to *Campylobacter* will activate specific clones of T- and B-cells to these bacteria, and they will reach the breast tissue causing mother's milk to contain immunoglobulins IgA, but also IgG and IgM. Titres of secretory antibodies to surface *C. jejuni* antigens are the highest in colostrum, but persist through the whole period of lactation [34]. Significant quantities of immunoregulatory cytokines, such as TGF-β, IL-10, erythropoietin and lactoferrin, reduce excessive inflammatory response in the intestines of an infant [13, 14].

Even though the socioepidemiologic indicators of infections suggest an inverse correlation with atopy [36], immunopathogenic studies on the correlation between bacterial infections and allergies are less consistent [37]. It is known that infection cannot generate an atopic condition, and some microbes manifest antagonistic activity to the development of atopy, as well as the normal flora in the gastrointestinal tract necessary for the development of oral tolerance to antigens/allergens [38, 39]. Our study shows that atopy points to a lower probability of the presence of *C. jejuni* infection, which is in line with the opinion that atopy protects a child from developing gastrointestinal infections at the earliest age [6, 40]. In our study, however, most children with infection had a positive result for the IgM+IgG combination of antibodies to C. *jejuni*, whose antibodies are predominantly produced in Th-1 immune response. Furthermore, the result showing that symptomatic *C. jejuni* infection reduces the risk of atopy in a child is interpreted by a lower probability that an atopic child will develop a significant neutrophil inflammation dependent on Th-17 response that is in synergy with Th-1 immune response. Atopic children have a lower immune response regulation function (TGF- beta and IL-10), along with genetically conditioned mechanisms for the de-

velopment of Th-2 response. Weaker immune response regulation, with lower TGF-β at the beginning of infection, leads to a reduced joint effect of this cytokine with IL-1 and IL-6 in the production of Th-17 cells, and a lower development of neutrophil inflammation in atopic children [14]. However, lower TGF-β can result in the lack of the immunosupressive role both to Th-1 and Th-2 response in infection in inplants. *Campylobacter* with its antigens (primarily lipopolysaccharides) causes primarily Th-1/Th-17 immune response, but in atopic children the immune response to these bacteria is directed to Th-2 response, which is also indicated by a high tIgE level, as an indicator of a strong Th-2 immune response correlated with the severity of infection. Namely, an increase of tIgE level in atopic patients within the defined categories raises the risk of an infection by the factor of 60, and an increase of tIgE in non-atopic children can point to a risk of infection higher only by the factor of 2.8. Prescott et al. [41] showed that the development of allergy is correlated with the continuation of Th-2 response (Il-4, Il-13) and a reduced capacity for Th-1 response (INF-γ) to allergens, while non-atopic patients showed a strong Th-2 response only at birth, after which it decreased and the Th-1 response increased over the first six months of life.

The Th-1/Th-2 cell response balance is undoubtedly significant for the development of allergy, but the establishment of this balance is increasingly under consideration from the aspect of variability of the inborn immunity function, and the effector functions of T-cell immunity and regulatory T-lymphocytes, which may be compromised in the earliest age [2]. Nowadays efforts in overcoming the problem of non-compliant results direct to more sophisticated methods that could, in the future, enable studies of genomes of the normal intestinal flora and its influence on the development of immune response correlated with the individual genetic predisposition [2].

Conclusion

C. jejuni infection increases the total serum IgE level, which is predictive of infection, regardless of the presence of atopy. The presence of symptomatic *C. jejuni* infection reduces the risk of atopy in a child of the age of 5–24 months by the factor of 10.

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Social participation of women with breast cancer

Uključivanje u društvo žena obolelih od karcinoma dojke

Snežana Nikolić*, Danijela Ilić-Stošović*, Ivan Kolarević†, Ana Djurdjević‡, Snežana Ilić*, Milica Djuričić*

***Faculty of Special Education and Rehabilitation, University of Belgrade, Belgrade, Serbia; †Office for Youth, Palilula, Belgrade, Serbia; ‡Institute of Oncology and Radiology of Serbia, Belgrade, Serbia**

Abstract

Background/Aim. The general problems of persons with malignant diseases (stages of asthenia, chronic fatigue and exhaustion, followed by depression and anxiety) lead to a decrease in functional abilities and a declining quality of life. The aim of this study was to determine the level of difficulty, the type of required assistance and the level of satisfaction that derives from maintaining life habits. The study also examined the correlation between the level of accomplishment of life habits and the level of satisfaction with how they are maintained. **Methods.** The research was conducted at the Military Medical Academy in Belgrade and in the "Get Together" Association of Women with Breast Cancer from June to September 2012 on a sample of 30 women. A standardised questionnaire, Assessment of Life Habits – LIFE-H v.3.0, was administered. **Results.** The lowest level of maintaining normal activities was related to education, housing and recreation. The greatest need for support to maintain normal activities was in the domains of housing, interpersonal relationships and employment. The greatest satisfaction in the accomplishment of normal activities was observed in the domains of mobility, nutrition and housing, and the lowest level of satisfaction was in the domains of recreation, communication and interpersonal relationships. The correlation between the level of accomplishment of normal activities and the level of satisfaction was the highest in the domains of general physical activity, responsibility and life in a community; the lowest level was in the domains of personal hygiene, housing, mobility, employment and recreation ($p < 0.001$). **Conclusion.** The results indicate that research participants found it more difficult to maintain their social activities than their everyday activities. This clearly indicates the necessity to develop and implement special advisory and educational programs aimed at preventing social exclusion and to strengthen and support personal resources in the area of the social roles of women with breast cancer.

Key words:
breast neoplasms; women; quality of life; questionnaires.

Apstrakt

Uvod/Cilj. Najčešći problemi osoba sa malignim bolestima (astenija, hronični umor i iscrpljenost, depresija, anksioznost) dovode do sniženja funkcionalnih sposobnosti i opadanja kvaliteta života. Cilj ovog istraživanja bio je utvrđivanje nivoa teškoća, vrste potrebne pomoći i stepena zadovoljstva realizacijom životnih navika, kao i usaglašenost nivoa realizacije životnih navika i stepena zadovoljstva sa realizacijom istih. **Metode.** Istraživanje je obavljeno u Vojnomedicinskoj akademiji u Beogradu i u Udruženju žena obolelih i lečenih od raka dojke „Budimo zajedno", u periodu jun–septembar 2012. godine, na uzorku od 30 osoba. Instrument procene bio je standardizovani upitnik za procenu životnih navika – *Assessment of life habits* – LIFE-H v.3.0. **Rezultati.** Najniže upražnavanje životnih navika prisutno je u obrazovanju, stanovanju i rekreaciji. Najveća pomoć u realizaciji životnih navika potrebna je u oblastima stanovanja, međuljudskih odnosa i zaposlenja. Najveće zadovoljstvo pokazano je realizacijom životnih navika u oblasti pokretljivosti, ishrane i stanovanja, a najmanje realizacijom životnih navika u oblasti rekreacije, komunikacije i međuljudskih odnosa. Najveća saglasnost između realizacije i nivoa zadovoljstva realizacijom životnih navika utvrđena je u oblasti opšte fizičke sposobnosti, komunikacija, odgovornosti i života u zajednici, a najniža u oblasti lične higijene, stanovanja, pokretljivosti, zaposlenja i rekreacije ($p < 0.001$). **Zaključak.** Rezultati ove studije ukazuju na to da ispitanice imaju veće teškoće u ostvarenju svojih društvenih uloga, nego u vršenju svakodnevnih aktivnosti. Ovo jasno ukazuje na potrebu izrade i primene posebnih savetodavnih i obrazovnih programa za sprečavanje socijalne isključenosti, ali i za jačanje i podršku ličnih mogućnosti u oblasti društvene uloge žena lečenih od karcinoma dojke.

Ključne reči:
dojka, neoplazme; žene; kvalitet života; upitnici.

Correspondence to: Snežana Nikolić, Faculty of Special Education and Rehabilitation, University of Belgrade, Visokog Stevana 2, 11 000 Belgrade, Serbia. Phone: +381 11 2183 036. E-mail: coan@open.telekom.rs

Introduction

The roles of medical care, special education, psychological support and social practice in the rehabilitation of persons with malignant diseases are of great importance. Every day, professionals all over the world strive to decrease the incidence of malignant diseases by methods of prevention and to increase the percentage of successful treatment of existing malignant diseases and improve cancer patients' quality of life [1]. The terms "quality of life" and "health-related quality of life" in particular refer to the physical, psychological and social domains of health, observed as distinct areas influenced by a person's experiences, beliefs, expectations and perceptions [2].

The general problems of persons with malignant diseases (stages of asthenia, chronic fatigue and exhaustion, followed by depression and anxiety) lead to a decrease in functional abilities and a declining quality of life [3]. Malignant diseases pose a threat to survival, physical integrity, autonomy, intimacy, self-control and self-esteem; delay or cancel life plans; disturb relationships with family, friends and co-workers; and endanger professional careers and financial situations [4].

Generally speaking, social expectations can affect daily life activities and social roles that should be adapted to surroundings. Life habits are related to the activities of daily living and the social roles that ensure survival and the lifespan development of an individual in society [5]. A person who deviates from such expectations has been 'labelled' as 'different' from the majority; possible consequences include discrimination, social isolation and the devaluation of one's abilities that affect the security and welfare of an ill person [6].

The consequences of malignant diseases and of specific oncologic treatments may have a great influence on one's functional abilities in all life domains. From the point of view of education and rehabilitation, a person with a malignant disease does not necessarily have to be prevented from accomplishing life habits; what the person can do depends on the interaction between the individual and environmental factors [7]. The main challenge to full social participation of persons with this disease is related to the lack of support programs and services, social measurements, values and societal attitudes, ecological factors and the technological progress of society [8].

The profile of life habits accomplishment in persons with malignant diseases as the correlation between the level of their accomplishment and level of their satisfaction with their accomplishments indicates the guidelines for the definition of specific goals and a plan for professional intervention to improve social participation and to change patients' personal perception of reality [9].

The prolonged life cycle of these patients reveals a new need for more complex rehabilitation of persons with malignant diseases. A valid assessment of the possible implications of cancer on everyday living and social participation is an important component of rehabilitation. Social participation is understood to be the complete accomplishment of life habits resulting from the interaction between the personal factors of an individual (the ensured integrity of the organ system and abilities) and different environmental factors (stimulating or non-stimulating).

The aim of this fundamentally descriptive study was to provide insight into the social participation of women with breast cancer as well as to assess the level of difficulty in accomplishing life habits, types of required assistance and level of satisfaction with the accomplishment of life habits, to assess the role of specific oncological treatments at the level of life habits accomplishment, and to analyse the correlation between the level of life habits accomplishment and the level of satisfaction with how the life habits were accomplished.

Methods

Thirty women with breast cancer disease participated in this study. The criteria for participants were as follows: age 20–65 years; minimum level of education – primary school; verified diagnosis of a malignant disease by histopathological results; localised stage of the disease; surgical intervention followed by radio- and chemotherapy; absence of physical, sensory or mental illnesses and conditions not connected to the malignant disease that would have a possible significant effect on life habits; patient's awareness of the diagnosis; agreement of the participants to participate in the study.

After a review of medical records, the patients who met the sampling criteria were chosen for the study. These patients were offered the opportunity to participate in the research, and the final sample comprised those patients who agreed to participate (Table 1).

Table 1

Patient (n = 30) characteristics

Parameters	Number of patients
Age (years)	
20–35	2
36–50	10
51–65	18
Type of oncology therapy	
chemotherapy	11
radiotherapy	2
chemo-and radiotherapy	17
Educational level	
low	2
middle	17
higher	9
high	2
Employment	
employed	4
unemployed	11
student	0
retired	15

The majority of the women were 51–60 years of age (n = 18) and had a high school education (n = 17). All of the participants were treated by surgical intervention, 17 of them had additional radio- and chemotherapy, 11 women had only chemotherapy and two of them were treated by radiotherapy only. Regarding their employment status, half of the partici-

pants (n = 15) were retired (Table 1). The research was conducted at the Military Medical Academy in Belgrade (n = 17) and the „Get Together" Association of Women with Breast Cancer (n = 13) from June to September 2012.

For the purpose of the research, the originally compiled questionnaire was utilised to obtain data regarding sex, age, education, employment status, type of therapy, etc. The Standardised Questionnaire for Assessment of Life Habits (Assessment of Life Habits – Life-H v.3.0) was also applied.

The LIFE-H assesses the accomplishment of life habits and the patients' satisfaction with how the life habits are accomplished (Table 2). The accomplishment scale of the LIFE-H covers all 12 domains of life habits proposed by the Disability Creation Process (DCP) model. The first six domains are related to activities of daily living (ADL): nutrition, fitness, personal care, communication, housing and mobility. The remaining domains are related to social roles: responsibilities, interpersonal relationships, life in a community, education, employment and recreation [10]. For each item on the accomplishment scale, the participants were asked about a perceived difficulty in performing a life habit (Table 3) and the type of assistance required to perform it. When a particular life habit was not part of the person's daily life, it was considered a non-applicable item [5, 8]. Satisfaction with each item was rated on a 5-point Likert scale ranging from 1 (very dissatisfied) to 5 (very satisfied).

The Assessment of Life Habits was developed to assess the quality of social participation of people with disabilities by estimating how a client accomplishes activities of daily living and fulfils social roles [8]. The questionnaire was standardised and validated in Serbian language and translated in two directions with the approval of the authors.

The participants were requested to answer two questions for each life habit. Question 1 determines, for each person`s life habit, the level of accomplishment (A) and the type of assistance required to accomplish it (B). Question 2 determines the level of satisfaction with the level of accomplishment for each of the person`s life habits (Tables 2 and 3).

The formula for the level of accomplishment (the weighted score) and the score transformation is presented below:

$$\sum \text{scores} \times 10 / \text{Number of Applicable Life Habits} \times 9$$

The mean values of 12 life habits accomplishment were weighted by the displayed formula.

Relevant parameters were described by the methods of descriptive statistics; correlations among variables were examined using ANOVA, Student-s *t*-test of arithmetic means for small samples and an Intraclass Coefficient Correlation (ICC) test.

Table 2

Questions and the format of the Questionnaire [10]

Live habits	Question 1		Question 2
	A Level of accomplishment	B Type of Assistance	Level of Satisfaction
Daily activities	No difficulty	No assistance	Very dissatisfied
communication	With difficulty	Assistive device	Dissatisfied
mobility	Accomplished by a	Adaptation	More or less satisfied
nutrition	proxy	Human assistance	Very satisfied
personal care	Not accomplished		
fitness	Not applicable		
housing			
Social roles			
responsibility			
interpersonal relationships			
community life			
education			
employment			
recreation			

Table 3

Description of the scale of accomplishment in the performance of life habits[11]

Score	Level of difficulty	Type of assistance
9	Performed with no difficulty	No assistance
8	Performed with no difficulty	Tehnical aid (or adaptation)
7	Performed with difficulty	No assistance
6	Performed with difficulty	Tehnical aid (or adaptation)
5	Performed with no difficulty	Human assistance
4	Performed with no difficulty	Tehnical aid (or adaptation) and human assistance
3	Performed with difficulty	Human assistance
2	Performed with difficulty	Tehnical aid (or adaptation) and human assistance
1	Performed by substitute	
0	Not performed	
NA	Not applicable	

Results

The results of the investigation (Figure 1) indicate the level at which women with breast disease accomplished 12 life habits and their level of satisfaction with how the life habits were accomplished. The type of assistance required to maintain daily activities was presented in a descriptive manner.

For five of the participants, communication (mean score 8.47) did not include using a computer; for two of them, this way of communication was not possible; and in two cases, this life habit was accomplished with human assistance. Seven participants experienced difficulties in communication, and 10 of them required technical aids to read and understand written information.

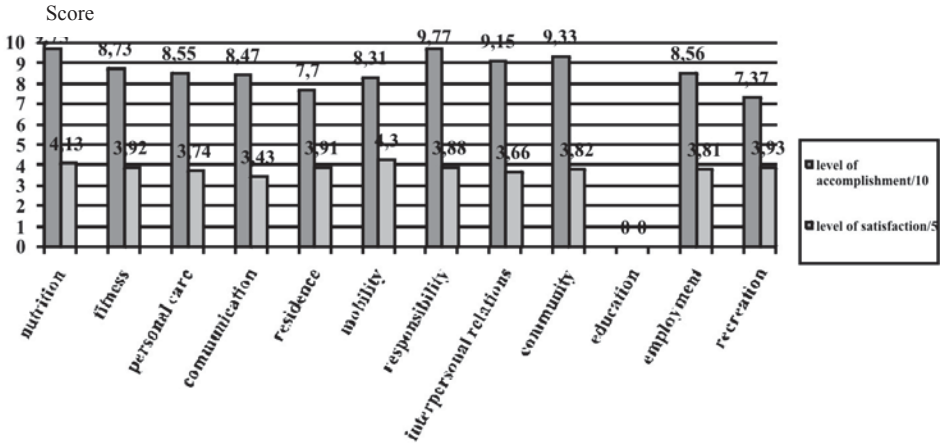

Fig. 1 – Level of accomplishing life habits and the level of satisfaction.

The ability to maintain nutrition (mean score 9.75) was significantly affected by the possibility of using restaurant services (three participants were not able to eat in restaurants and three did not); the greatest difficulties in this domain of life habits were related to preparing meals (three participants required some type of technical aid and human assistance). Although the level of accomplishment was high, the level of satisfaction with how the activity was accomplished (mean score 4.13) was lowest in the domain of selection of materials for food preparation and highest in the domain of using dishes and cutlery.

Regarding the ability to maintain fitness (mean score 8.73), one participant did not perform any physical activities, and two participants had no opportunity to perform this life habit to sustain and improve their health and physical condition. Eight participants did not practice relaxation exercises to improve their mental health whereas seven of them had no opportunity to practice yoga, meditation, chess, etc.

Regarding sleeping, 10 participants had some difficulty; however, only two spoke about technical aids in this domain. The women were generally satisfied with this life habit accomplishment (mean score 3.92); the lowest level of satisfaction was associated with the quality of sleep (comfort, sleep duration, depth of dreams, etc.).

Regarding personal care (mean score 8.55), 11 participants indicated that habits such as putting on, removing on and taking care of prosthetic aids were non applicable. Regardless of the difficulties in all of the aspects of this life experience, only three of the participants utilised technical aids in this domain. By assessing the level of satisfaction with how this life habit was accomplished (mean score 3.74), health care was at the highest level of satisfaction and using bathrooms and toilets out of home was at the lowest level.

The level of satisfaction with how this life habit was accomplished (mean score 3.43) was the highest in the domain of using a telephone (at home and at work) and lowest in the domain of using a computer.

In the domain of housing, housekeeping (mean score 7.70) was not available to 16 participants. Choosing an available house or a flat according to the specific needs of an ill person was a non-applicable habit for five participants and not possible for three participants. Difficult housekeeping tasks were a non-applicable habit for 11 participants, and for four of them, difficult housekeeping tasks were an unaccomplished habit; seven participants required human assistance with housekeeping activities. The level of satisfaction with how life habits in the domain of housing were accomplished (mean score 3.91) was reasonable; however, there were difficulties (the highest level of difficulty was in the domain of mobility at home, and the lowest level was in the domain of performing difficult housekeeping activities).

Mobility (mean score 8.31) by bicycle was an unaccomplished activity for 10 participants, and for 10 participants it was non-applicable. Driving a car was non-applicable for 20 participants, and for three it was an unaccomplished habit; only two participants were independent in performing this daily activity without difficulty or human assistance. The highest level of satisfaction (mean score 4.30) was in the domain of mobility on foot, and the lowest level was in the domain of driving a car.

In the domain of family and personal responsibility (mean score 9.77), three participants required human assistance, and the same number required technical aids. In five cases, using a bankcard was a non-applicable habit, and 10 participants did not support the education of their children. The level of satisfaction with how this life habit was accom-

plished (mean score 3.88) was the highest in using an automated teller machine (ATM) and the lowest in the domain of planning budgets and financial transactions.

Social support is a multi-factored concept that includes a number of interpersonal relationships and the quality of social relationships. Social support addresses care and empathy as well as obtaining goods, services and information. The support is provided by family, friends, health professionals, the religious community and other people in an identical life position [12].

Regarding interpersonal relationships (mean score 9.15), safe, healthy sex life was a non-applicable habit for eight participants; four participants had unaccomplished habits in this domain whereas five participants spoke regarding the need to accommodate sex life. Close relationships with children, parents, family members, friends and social connections were perceived as being conducted with difficulty in more than 10 cases. The life habits related to interpersonal relationships had a low mean score (3.66) on the subscale of satisfaction with how the relationships were accomplished. The highest level of dissatisfaction was with the participants' sex life (reducing or stopping sexual activities) and decreasing the level of close relationships with family members. The highest level of satisfaction was in the domain of close relationships with children. A malignant disease *per se*, the effects of therapy, negative effects from medications as well as aging, general health conditions, etc, could be factors in sexual dysfunction, which may also be explained by the lack of open communication between partners [13] regarding sexual problems.

Education in terms of professional training (high school level), college and university education, attending different training courses, craft and art education or professional and scientific work were activities that were non-applicable to all participants, indicating that education was the most neglected life habit.

In the domain of employment (mean score 8.56), four participants had no difficulties in choosing their jobs and professional careers, whereas for 13 participants, it was a non-accomplished habit; 30 women required assistance in looking for a job, and five participants were housewives who required help with housekeeping activities. The level of satisfaction (mean score 3.81) was the highest in the domain of "entrance and mobility at the workplace", and the lowest level was in the domain of looking for a job or choosing a job and career.

Quality of recreation activities (mean score 7.37) was mostly affected by attending sporting events; 23 participants did not accomplish this life habit whereas seven of the women participated in no outdoor activities (hiking, mountain climbing, camping, etc.) and did not use local recreation services. The highest level of dissatisfaction regarding how this habit was accomplished (mean score 3.93) was in the domain of travelling, using local tourist services and camping whereas the highest level of satisfaction was in the domain of manual jobs and handicrafts.

The type of oncologic therapy had a significant effect on life habits accomplishment in any of the assessment domains (Table 4).

Table 4

Correlation analysis between the type of oncology therapy and accomplishment of life habits

Parameters	The level of satisfaction with how life habits were accomplished and type of oncologic therapy		The level of accomplishing life habits and the type of oncologic therapy	
	F	Sig.	F	Sig.
Nutrition	1.479	0.246	0.379	0.688
Fitness	1.004	0.380	0.668	0.521
Personal care	0.515	0.604	1.354	0.275
Communication	1.013	0.377	0.384	0.685
Housing – Housekeeping	1.682	0.205	2.722	0.084
Mobility	0.248	0.782	2.680	0.087
Family and personal responsibility	1.985	0.157	0.073	0.930
Interpersonal relationships	0.632	0.539	0.364	0.699
Community life	0.170	0.845	0.901	0.418
Employment	0.445	0.649	1.460	0.250
Recreation	0.598	0.561	0.396	0.677

In the domain of community life (mean score 9.33), five of examined women did not participate in social, religious or spiritual groups or their events, and the participants did not require technical aids or human assistance for this life habit accomplishment. The level of satisfaction with how community life was accomplished (mean score 3.82) was the highest in the domain of "entrance into public institutions and just walking around" whereas the lowest level was related to participation in spiritual and religious events.

The correlation between the level of life habits accomplishment and the level of satisfaction with how life habits were accomplished was the highest in the domains of fitness, communication, responsibility and community life. The level of life habits accomplishment in the domains of nutrition and interpersonal relationships was not significantly correlated with the level of satisfaction (Table 5). Statistically significant correlations ($p < 0.001$) were observed between the level of dissatisfaction and life habits accomplishment in the domains of personal care, housing, mobility, employment and recreation.

Table 5

Relationship between the level of accomplishment and the level of satisfaction

Category of life habits	Level of accomplishment/10 (range 0–1)	Level of satisfaction/5 (range: 0–1)	Intraclass coefficient correlation
Nutrition	0.98	0.83	0.90
Fitness	0.87	0.78	0.93
Personal care	0.86	0.75	0.68
Communication	0.85	0.69	0.98
Housing	0.77	0.78	1
Mobility	0.83	0.86	0.89
Responsibility	0.98	0.78	0.87
Interpersonal relations	0.92	0.73	1
Community	0.93	0.76	0.50
Education	/	/	/
Employment	0.86	0.76	0.92
Recreation	0.74	0.78	0.99

Discussion

The aim of this study was to determine the level of difficulty, the type of required assistance and the correlation between life habits accomplishment and the level of satisfaction with how they are accomplished.

This study was conducted on a small sample (n = 30), thus, completely reliable conclusions cannot be derived. In addition, the sample included a wide age range of participants, a significant number of whom were retired; thus, the results related to life habits accomplishment in the domains of employment, education and child care may not be fully representative of all women with breast cancer.

Nevertheless, the study can help us understand the variations in life habits accomplishment and satisfaction with the activities' accomplishment in women with breast cancer at different ages. In addition, the study provides an overview of the accomplishment of 12 life habits and satisfaction with the accomplishment, which can be a strong basis for creating high-quality counselling programs and psychosocial education in the area of rehabilitation.

Life habits accomplishment in persons with malignant diseases has been studied by many researchers. A study of the quality of life and the psychosocial adjustment of women aged 65+ in the 15 months after being diagnosed with breast cancer [14] suggests a high level of satisfaction with physical and emotional functionality in the three months after the breast cancer surgery; however, contrary to other findings, this study showed a significant deterioration after that. Further, the deterioration was much greater in women who had breast cancer surgery (without additional radiotherapy) than in women who had radiotherapy only. This finding was explained by the number of comorbidity factors and chemotherapy treatment.

An investigation of the effect of psychosocial education in life adjustment of women after breast cancer treatment[15] observed that women who have had mastectomies show lower achievement in the domain of physical functionality than women in general population.

The first study in our country on the level of life habits accomplishment and quality of life in persons with malignant diseases [7] showed that there was no full social participation in any domain of life habits. Investigations on the level of life habits accomplishment in 100 participants with solid malignant tumours and hematologic malignancies showed that the participants were the most deprived of performing social roles in the domains of education, recreation and employment. Required assistance, especially human assistance in maintaining the activities of responsibility, community life, employment and recreation, had a great effect on decreasing the level of social integration. The results related to the correlation between life habits accomplishment and the level of satisfaction with how activities are accomplished may be summarised as follows: in seven of the categories of life habits (fitness, personal care, communications, mobility, responsibility, interpersonal relationships and community life), the level of accomplishment was higher than the level of satisfaction. In the other five domains (nutrition, housing, education, employment and recreation), the level of satisfaction was higher than the level of real life habits accomplishment. The highest correlations were in the domains of mobility and housing, and the lowest correlation was in the domain of communication.

Systematic education can be a strong supporting model for persons with malignant diseases. By actively learning about the disease, treatment and strategies of copying with malignancy, cancer patients acquire new tools in the struggle for a better quality of life (adapting to the new experience, overcoming the feelings of fear and insecurity connected to the disease and therapy). Educational programs should be created from the patient's perspective on the basis of evaluation of previous knowledge, actual needs, specific wishes, requirements and interests because full understanding as well as usefulness of information always depend on the capacity of individual people [16].

Conclusion

The expected benefits of the study were related to noting the importance of social participation (by life habits accomplishment) in women with breast cancer as well as emphasising the need for education and rehabilitation in oncology. The results indicate the social difficulties in life habits accomplishment in persons with malignant diseases, and also

directions for possible intervention in the course of this process facilitation.

The results of our study show a great number of unaccomplished life habits associated with social roles accomplishment (education, recreation and employment); life habits associated with everyday life activities (nutrition, personal care, communication, mobility, responsibility) were accomplished to a greater extent.

The highest levels of satisfaction with how life habits were accomplished were in the domains of mobility, nutrition and housing, and the lowest levels of satisfaction were in the domains of recreation, communication and interpersonal relationships. According to the obtained results, intraclass coeficient correlation analysis indicates the highest correlations between the level of life habits accomplishment and the level of satisfaction in the domains of fitness, communication, responsibility, interpersonal relationships and community life and the lowest level in the domains of personal care, housing, mobility, employment and recreation. It was not shown that the type of oncology therapy had a significant effect on life habits accomplishment in any domain of assessment.

The results obtained in this study clearly indicate the necessity of developing and implementing special advisory and educational programs aimed at not only preventing social exclusion but also strengthening and supporting personal resources in the area of social roles of women with breast cancer.

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Estimating disability and quality of life after different degrees of hand and forearm trauma

Procena onesposobljenosti i kvaliteta života posle povreda šake i podlaktice različitog stepena

Marija Marinković, Zlata Janjić, Jelena Nikolić

Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, Novi Sad, Serbia

Abstract

Background/Aim. Hand injuries comprise up to one fourth of all injuries and require excellent skills and aggressive physical therapy with still a high potential to cause long term physical and functional disability which affects one's quality of life. The aim of this study was to evaluate disability and quality of life in patients with different degrees of hand and forearm injuries using the two different scoring sistems and to examine the correlation between them. **Methods.** This retrospective study was performed among patients operated on at our clinic due to acute hand and forearm trauma during the period of two years. Four groups of patients were made according to the Modified Hand Injury Severity Score (MHISS). One year after the treatment, phone interviews were made with those patients to answer to the Disability of Arm Shoulder and Hand (quick-DASH) score for estimating disability and to the World Health Organization Quality of Life BREF (WHOQoL-BREF) score to estimate the quality of life regerding four domains: physical, social, environmental and psychological. **Results.** Out of 182 patients who satisfied the inclusion criteria, only 60 completely answered to the questionnaires, 46 (17%) men and 14 (23%) women. Most of the patients were in the group with moderate injuries according to the MHISS, followed by the group with major and severe injuries. A weak correlation was found between the MHISS and quick DASH score in the group with minor injuries, compared to no correlation between these parameters in other groups. The lowest quality of life was registered in the physical domain, while the highest in the social one. A negative correlation was found among the four domains of the WHOQoL BREF score and quick-DASH score in all the groups. **Conclusion.** Severity of hand and forearm injuries does not necessarily correlate with patient's perception of disability. The quality of life was less affected by severity of injury than by the patient's perception of disability.

Key words:
hand injuries; quality of life; disability evaluation; questionnaires.

Apstrakt

Uvod/Cilj. Povrede šake obuhvataju skoro jednu četvrtinu svih povreda, zahtevaju odličnu hiruršku tehniku i upornu fizikalnu terapiju, sa i dalje visokim potencijalom da dovedu do dugotrajnih psihofizičkih posledica koje utiču na kvalitet života pojedinca. Cilj rada bio je procena onesposobljenosti i kvaliteta života nakon povreda šake i podlaktice različite težine koristeći dva različita sistema bodovanja, kao i upoređivanje korelacije rezultata između njih. **Metode.** Ova retrospektivna analiza sprovedena je kod bolesnika operisanih na našoj klinici zbog povrede šake i podlaktice tokom dvogodišnjeg perioda. Bolesnici su bili podeljeni u četiri grupe prema težini povrede, odnosno prema sistemu bodovanja *Modified Hand Injury Severity Score* (MHISS). Godinu dana nakon završenog lečenja, bolesnici su intervjuisani telefonom, i odgovarali su na upitnik *Disability of Arm Shoulder and Hand* (quick-DASH) koji procenjuje invalidnost i upitnik *World Health Organisation Quality of Life BREF* (WHOQoL-BREF) koji procenjuje kvalitet života kroz četiri domena: fizički, socijalni, psihološki i efekat sredine. **Rezultati.** Od ukupno 182 bolesnika koji su zadovoljili kriterijum za uključivanje u ispitivanje, samo 60 je završilo studiju, 46 (17%) muškaraca i 14 (23%) žena. Najveći broj bolesnika (46.7%) našao se u grupi sa srednje teškim povredama prema sistemu za bodovanje MHISS, pa u grupi sa teškim i najtežim povredama. Utvrđena je slaba korelacija između sistema za bodovanje MHISS i quick-DASH u grupi sa povredama minimalne težine, ali nije nađena korelacija između MHISS i quick-DASH u ostalim grupama. Najniži kvalitet života zabeležen je u fizičkom, a najviši u socijalnom domenu. Negativna korelacija ustanovljena je između vrednosti četiri domena sistema WHOQoL-BREF i quick-DASH u svakoj grupi. **Zaključak.** Težina povrede šake i podlaktice ne mora uvek da bude povezano sa bolesnikovim poimanjem onesposobljenosti. Kod većine bolesnika utvrđen je slab uticaj težine povrede šake i podlaktice na kvalitet života. Na kvalitet života više utiče bolesnikovo shvatanje onesposobljenosti.

Ključne reči:
ruka, povrede; kvalitet života; sposobnost, ocena; upitnici.

Correspondence to: Marija Marinković, Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina, 21 000 Novi Sad, Serbia. Phone: +381 62 256 225. E-mail: mmarinkovic.marija@gmail.com

Introduction

Hand injuries comprise between 6.6% and 28.6% of all injuries and have the potential to cause a long-term physical and functional disability [1], as well as emotional impairment [2]. Hand injuries are the main cause of work-related disability in young adults [3]. Furthermore, a high incidence of hand traumatism in young adults is found in Vojvodina, which is an agricultural region with the city of Novi Sad as a regional center. Most injuries are the consequence of dealing with agricultural machinery without proper training [4]. In adults, hand injuries mean lasting absence from the workplace with a probable invalidity and the need for professional reorientation which is a serious social and economic problem.

However, not every hand trauma results in disability; it certainly depends on the extent of injury. Nowadays, the Hand Injury Severity Score (HISS) is used for estimating the seriousness of hand trauma. HISS score also identifies those patients who would return to workplace soon after injury and who would probably need some aspect of professional reorientation [5]. Recently, the Modified Hand Injury Severity Score (MHISS) has been designed in order to expand HISS score from only hand to also carpus and forearm. According to Urso Baiarda, et al. [2] only 60% of those with major hand injuries defined by MHISS return to work.

Treatment and recovery from hand injury does not rely only on technical skills of surgeon but also on aggressive physical therapy and patient's compliance. Effectiveness of the treatment can be estimated through objective tests of hand function (like range of motion, strength, etc.). Those tests reflect some level of one's disability but can often differ from subjective perception of one's insufficiency. That is why different questionnaires were formulated in order to measure one's perception of disability. One of the most frequently used one is Disability of Arm, Shoulder and Hand (DASH) questionnaire which is validated many times [6–8]. Wong et al. [8] showed a high efficiency of DASH score in acute hand injuries, but they also recommend that DASH score should not be the only tool for assessing treatment effectiveness.

Furthermore, modern treatment options are focused not only on short morbidity but also on long term functioning, wellbeing, early returning to work, low costs and quality of life. Concerns about "the quality of life" remain since the 4th century BC, when great philosophers Plato and Aristotle used the term "good life" to describe both an internal and external state of living. However, not until 1960's was "Health related quality of life" found in medical literature [9]. Today, World Health Organization (WHO) defines Quality of Life (QoL) as "perception by individuals of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [10].

The aim of this study was to evaluate disability, through the quick-DASH questionnaire, and quality of life, through WHOQoL-BREF score, in patients with different levels of severity of hand and forearm injuries. Since we assumed that higher disability would induce lower quality of life, our aim was also to examine the correlation between these two tests for each level of severity of injury.

Methods

This study was conducted as a prospective enquiry at the Clinic for Plastic and Reconstructive Surgery, Clinical Center of Vojvodina in Novi Sad, Serbia. We selected only the patients operated on at our clinic in 2008 and 2009 due to hand or forearm trauma or both, and in whom a year passed after completing the treatment (surgery and physical therapy). Patients with isolated bone fractures of hand and forearm were not included in the study.

Demographic data and the precise diagnosis were taken from the patients records of the selected patients. According to their diagnosis and MHISS, the patients were divided into four groups, starting from the group 1 with minor injuries to the group 4 with severe injuries. Furthermore, telephone interviews were conducted among the patients when they were asked to answer to the short version of DASH questionnaire (quick-DASH) and QoL score designed by WHO (WHO-QoL-BREF questionnaire). Three call attempts were made for contacting patients.

Assessment instruments

The MHISS score was designed by Urso-Bairada et al. [2] in 2008 as a modification of HISS designed by Cempbell and Kay [5] in 1996. The modified score was extended to include not only hand injuries as in the HISS score, but also wrist and forearm injuries, as well. It is validated by its designers to be a good predictor in returning to workplace (Urso). In each injury, the integument, bones, tendons and muscles and the neurovascular structures are evaluated separately and the scores are calculated for each of these components. The overall MHISS score is the total of the scores for each component. The MHISS score is grouped into four categories: minor (< 20), moderate (21–50), severe (51–100) and major (> 101).

The DASH questionnaire was formulated in 1996 at the Institute for Work and Health in Toronto, Canada [6]. It examines symptoms after upper extremity injury and the ability to do specific actions. It is one of the most commonly used measurements for upper extremity function. The DASH score showed good competence not only in degenerative diseases of the upper extremity but also in acute trauma, as well [8, 11]. The original DASH score consists of 30 questions and its shorter version – quick-DASHof only questions [11]. Both DASH and quick DASH showed effectiveness of using self-reported functional assessment. DASH has been shown to correlate with health status, injury severity and function [8]. We used the quick DASH questionnaire in our research which has two components: the first one estimates invalidity and measures symptoms, and the second one, which is not obligatory, assesses high competence in everyday life like playing instruments and doing sports. At least 10 out of 11 questions have to be answered in order to calculate the score. The DASH score values range from 0 which indicates absence of disability, till 100, which signifies the highest disability.

The WHOQoL-BREF questionnaire was formulated by WHO in 1991 [10] as an international cross-culturally comparable quality of life assessment instrument and has already been translated into multiple languages, including Serbian. It measures a person's subjective perception about their life according to their goals, concerns and satisfaction. WHOQOL BREF is constructed of 26 questions which are divided in four domains, representing one's physical health, psychological health, social relationships and their environment. Each domain scores numeric values so that a higher score represents higher quality of life.

Statistical analysis

Collected data were organized in Word Excel spread sheets. The statistical package SPSS for Windows (ver. 16) was used for statistical analysis. The most important results were highlighted through tables and graphs. To measure the strength of the relationship between the quick-DASH and WHOQoL-BREF results for each group, correlation coefficient "r" was used. The correlation is considered moderate when r is in the range from 0.5 to 0.75 or –0.5 to –0.75 and strong when r ranges from 0.75 to1 or –0.75 to -1. Positive values indicate that when values of one score increase the values of the other score decrease, while negative values indicate that decreasing of one score will lead to increase of the other.

Results

According to our inclusion criteria, 182 patients were operated on at our clinic due to hand and forearm trauma. However, only 60 patients fulfilled the rest of inclusion criteria (a 1-year period after finishing physical therapy), were reached over the telephone, agreed to answer the questionnaires and managed to complete them. Among them 46 (77%) were male and 14 (23%) female. The patients were 45.8 (SD = 14.3) years old, on the average for the men 46.5, while for the woman it was a bit less, 43.3 years.

The sides were equally injured, 28 patients had right- and 28 left- side injuries, while two patients had injuries on both sides. The forearm was injured in 26.7% of the patients, the hand was injured in 63.3% of the patients and the rest (10%) had combined hand and forearm injuries.

The median MHISS score was 51.5 (range 6–270). According to the values of MHISS, four groups of the patients were made: group 1 (minor severity of injury) of 8 (13.3%) patients with the average MHISS of 11.5 ± 4.9; group 2 (moderate severity of injury) of 22 (46.7%) patients and the average MHISS of 34.04 ± 9.01; group 3 (severe injuries) of 17 (28.3%) patients and the average MHISS of 17.3 ± 1; and group 4 (major severity of injury) of 13 (21.7%) patients, with the average MHISS of 194.6 ± 43 (Table 1).

The results of the quick-DASH score in all four groups are shown in Figure 1. The average quick-DASH score in the group 1 was 12.8, in the group 2–22, in the group 3–17 and in the group 4–46.2. The statistical significance ($p < 0.05$) was found between the groups 1 and 2 quick-DASH values and between the groups 2 and 3 quick-DASH values ($p = 0.04$), and a high statistical significance ($p < 0.005$) between the groups 3 and 4 quick-DASH values ($p = 0.0009$).

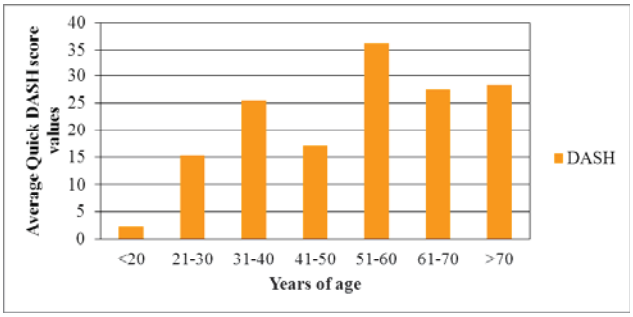

Fig. 1 – Results of Disabillity of Arm Shoulder and Hand (DASH) score in respect to age distribution.

A minor correlation was found between the values of MHISS score in minor injuries and a corresponding quick-DASH score. There was no other correlation found among these parameters in other groups. This means that severe injury does not have to lead to the highest disability since good surgical treatment and physical therapy with patient compliance can have excellent results.

The quality of life estimated through WHOQoL-BREF was represented through four, aforementioned domains: physical, psychological, social and environmental. The highest quality of life was found in the social domain, while the lowest was recorded in the physical domain in all four groups of patients (Figure 2). Furthermore, the results

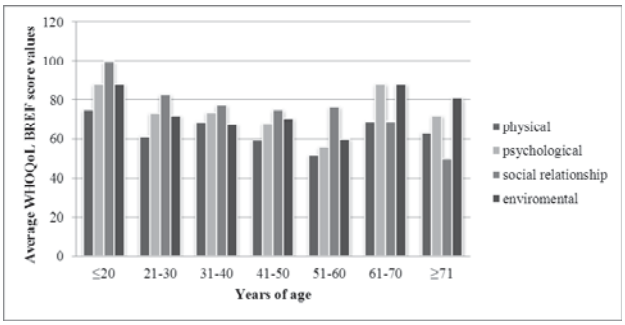

Fig. 2 – Results of World Health Organisation Quality of Life (WHOQoL)-BREF score in respect to age distribution.

of physical, physiological and environmental health showed a steady decrease as injuries got more severe. Only domain showing improvement with severity of injury was the domain of social relations.

Table 1

Results of Quality of life (QoL) – BREF Questionnare in respect to gender distribution

Gender	QoL domains				
	physical	psychological	social	environmental	average
Men	62.13	70.83	78.26	72.17	70.8
Women	52.86	57.14	67.86	58.14	59
All patients	59.97	67.63	75.83	68.9	64.9

The correlation between quick-DASH scores and WHOQoL-BREF scores was analyzed. The moderate and strong correlations were found between the quick-DASH score and all four domains in the group 1. A negative moderate correlation (r = -0.7) was found between environmental health domains and corresponding quick-DASH scores in the groups 2, 3, and 4. There were no other correlations found (Table 2).

Table 2

Correlation between the quick-Disabillity of Arm Shoulder and Hand (DASH) score of each age group and each domain of Quality of Life (QoL) in corresponding age group

QoL domains	Coefficient of correlation (r)
Physical	-0,62
Physhotogical	-0.58
Social	-0.7
Environmental	-0.48

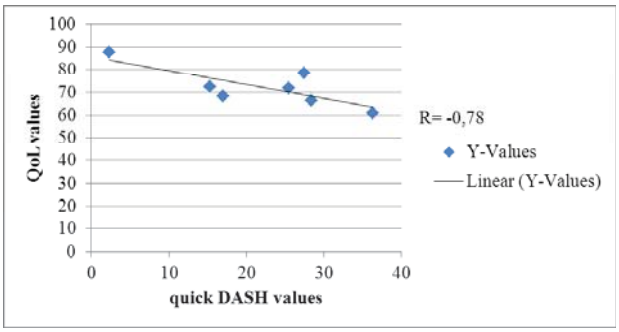

Fig. 3 – Correlation between the quick-Disabillity of Arm Shoulder and Hand (DASH) score and assembled Quality of Life (QoL) scores for every age group.

Discussion

Different instruments are in use today for estimating outcomes of hand trauma. In the last couple of decades, the impact of trauma and its short and long-term consequences are especially emphasized as they often enlarge special needs for patients, enlarge economical expenses while lowering the quality of life [2, 7, 12].

In our study only 60 patients fulfilled inclusion criteria and finished all questionnaires compared to 182 patients operated on at our clinic in the observed period. This low response rate of 32.9% was close to the response rate of 40.3% reported by Kovacs et al. [9]. It is known that this phenomenon is common in self-administered questionnaires.

The patients examined in this study were 46 years old. In the average compared to the mean age of 35 years reported by Kovasc et al. [9] and 38.2 years reported by Chan et al. [1], who also examined patients with acute hand trauma at their clinics. We have no other explanation for higher average age in our study but to assume that older people are still very active and working in our living area.

Isolated hand injuries were present in more than 60% of the cases, isolated forearm injuries in 26%, while combined injuries of the hand and forearm were present in 10%. That is why we decided to use MHISS instead of HISS score. The main advantage of the MHISS score is the fact that it includes injuries of the forearm, as well. Most patients had moderate injuries followed by severe and major injuries, respectively. The lowest number of patients were found in the group with minor injuries, which is probably due to the fact that most of minor injuries are treated ambulatory in local anaesthesia and were, therefore, not included in this study.

In this research a steady linear incline was registered in the quick-DASH results with increasing severity of hand trauma. A discrepancy was noted between the groups 2 and 3, where the group 3 should have had higher results instead of the group 2, as was found in our results. This is probably the consequence of a small number of patients in each group. Nevertheless, a statistical significance was found between the quick-DASH of each group. The average quick-DASH score in the groups 3 and 4 was 47.3. This result is much higher compared to the results shown by Kovacs et al. [9] who measured the quality of life in major and sever hand injuries and whose average DASH score was 28.7 in less than 3 years after finishing the treatment.

A weak correlation was found between the values of quick-DASH and MHISS which corresponds to the previous results shown between HISS score and DASH by Kovacs et al. [9].

All four domains of WHOQoL-BREF showed similar distribution in all the examined groups except in the group 4 with the rise in the social domain, while physical, psychological and environmental domains were decreased. The lowest quality of life was registered in physical and the highest in social domain in all four groups. This means that the patients were satisfied with social support they received but were unhappy with physical status as was expected. These results correspond with the results shown by van Delft-Schreurs et al. [13], who also documented that QoL depends more on sociodemographic factors (as living alone…) rather than on rehabilitation time after the accident or the severity of injury or injured body area [14].

Our assumption was that higher disability would induce lower quality of life [14, 15], meaning that the results of quick-DASH would have negative correlation with the results of WHOQoL-BREF. However, analyses were not persuasive. A negative correlation was registered in environmental and most of physical and psychological domains but with a moderate to low statistical significance. It is interesting that a positive correlation was registered, mostly in the social domain.

The study had a few limitations. Despite the fact that the whole number of patients was 60, when they were divided into 4 groups according to the MHISS, those groups appeared to be small for representative statistical analysis.

Conclusion

With the increasing severity of the injury of hand and forearm, the results of the quick-DASH questionnaire showed a rising disability. Therefore, we think that the quick DASH is a fast and good test for estimating the perception of disability by patients. Even though physical, psychological and environmental domains of WHOQoL-BREF score do

decrease with more severe injuries, implying lower quality of life in those domains, it appears that the quality of life was little affected by the severity of hand and forearm injuries in the majority of patients. Social aspect of the quality of life showed improvement as injuries got worse. A negative correlation with moderate or no statistical significance was found between the quick-DASH and WHOQoL-BREF in the patients with moderate, severe and major injuries. This means that higher disability can, but not necessarily, lead to lower quality of life. Interestingly, a high correlation between these two tests was found in patients with minor injuries. Further research on a larger sample of patients is needed to confirm these results and also to identify factors that affect one's perception of disability.

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Continuing medical education in Serbia with particular reference to the Faculty of Medicine, Belgrade

Kontinuirana medicinska edukacija u Srbiji sa posebnim osvrtom na Medicinski fakultet u Beogradu

Vesna Bjegović-Mikanović*, Nebojša Lalić*, Helmut Wenzel†, Ružica Nikolić-Mandić*, Ulrich Laaser‡

***Faculty of Medicine, University of Belgrade, Belgrade, Serbia; †Independent Consultant, D-78464 Konstanz, Germany; ‡Faculty of Health Sciences, University of Bielefeld, Bielefeld, Germany**

Abstract

Background/Aim. Continuing Medical Education (CME), conceptualised as lifelong learning (LLL) aims at improving human resources and continuing professional development. Various documents of European institutions underline its key importance. This paper therefore tries to analyse the current status of CME and the main deficits in the delivery of LLL courses at medical faculties in Serbia with special consideration of the Faculty of Medicine in Belgrade with detailed financial data available. **Methods**. Data of 2,265 medical courses submitted in 2011 and 2012 for accreditation were made available, thereof 403 courses submitted by 4 medical faculties in Serbia (Belgrade, Kragujevac, Niš, Novi Sad). A subset of more detailed information on 88 delivered courses with 5,600 participants has been provided by the Faculty of Medicine, Belgrade. All data were transferred into an Excel file and analysed with XLSTAT 2009. To reduce the complexity and possible redundancy we performed a principal component analysis (PCA). Correlated component regression (CCR) models were used to identify determinants of course participation. **Results.** During the 2-year period 12.9% of all courses were submitted on pre-clinical and 62.4% on clinical topics, 12.2% on public health, while 61.5% of all took place in Belgrade. The subset of the Faculty of Medicine, Belgrade comprised 3,471 participants registered with 51 courses accredited and delivered in 2011 and 2,129 participants with 37 courses accredited and delivered in 2012. The median number of participants per course for the entire period was 45; the median fee rates for participants were 5,000 dinars in 2011 and 8,000 in 2012, resulting together with donations in a total income for both years together of 16,126,495.00 dinar or almost 144,000.00 euro. This allowed for a median payment of approximately 90 eur per hour lectured in 2011 and 49 euro in 2012. The 2 factors, D1 (performance) and D2 (attractiveness), identified in the PCA for Medical Faculties in Serbia, explain 71.8% of the variance. Most relevant are the duration of the courses, credit points, and hours per credit point gained by lecturers and participants respectively. In the PCA for Belgrade D1 and D2 explain 40.7% of the total variance. The CCR on the number of participants reveals the highest positive impact from the number of lecturers per course and the expenditure on amenities, the highest negative impact from the total income collected per participant. **Conclusion.** The faculties of medicine in Serbia should reconsider the entire structure of their organisation of CME, especially to improve the quantity and quality of registration limit the course fee rates per hour and reduce administrative and other costs request lecturing in CME programmes as obligatory for academic promotion and organise a focussed marketing.

Key words:
education, medical, continuing; serbia; factor analysis, statistical; economics.

Apstrakt

Uvod/Cilj. Kontinuirana medicinska edukacija (KME), sa planom doživotnog učenja (*lifelong learning* – LLL), ima za cilj unapređenje ljudskih resursa i stalni profesionalni razvoj. Njen ključni značaj naglašen je i u različitim dokumentima evropskih institucija. Stoga, u ovom radu analizira se sadašnja situacija KME i osnovne slabosti u pružanju usluga LLL na medicinskim fakultetima u Srbiji sa naročitim razmatranjem Medicinskog fakulteta u Beogradu gde su bili dostupni detaljni finansijski podaci. **Metode.** Korišćeni su podaci o 2,265 medicinskih kurseva koji su podneti za akreditaciju u 2011. i 2012, među kojima 403 kursa podnela su četiri medicinska fakulteta u Srbiji (Beograd, Kragujevac, Niš, Novi Sad). Medicinski fakultet u Beogradu pružio je i podskup detaljnijih informacija o 88 izvedenih kurseva sa 5 600 pola-

Correspondence to: Vesna Bjegović-Mikanović, Faculty of Medicine, University of Belgrade, Dr Subotića, 11 000 Belgrade, Serbia.
E-mail: bjegov@md.bg.ac.rs

znika. Svi podaci uneseni su u *Excel* bazu i analizirani pomoću programa XLSTAT 2009. Da bi se snizila složenost i moguća ponavljanja izveli smo analizu glavnih komponenti (PCA). Modeli regresije korelisanih komponenti (CCR) korišćeni su za identifikaciju determinanti učešća u kursevima. **Rezultati.** Tokom dvogodišnjeg perioda 12,9% kurseva koji su podneti za akreditaciju bili su u prekliničkim, 62,4% u kliničkim i 12,2% u javnozdravstvenim oblastima, a za 61,5% planirano je da se izvedu u Beogradu. Podskup Medicinskog fakulteta u Beogradu činio je 51 kurs akreditovan i izveden u 2011. godini sa 3 471 učesnikom, kao i 37 kurseva akreditovanih i izvedenih u 2012. sa ukupno 2 129 učesnika. Za ceo period prosečan broj učesnika po kursu bio je 45; u proseku učešće u troškovima iznosilo je 5 000 dinara u 2011. godini i 8 000 dinara u 2012, tako da je ukupni prihod sa donacijama za dve godine bio 16 126 495,00 dinara ili gotovo 144 000,00 evra. Ovo je omogućilo prosečnu stimulaciju od približno 90 evra po času predavanja u 2011. godini i 49 evra u 2012. Dva faktora, D1 (izvršenje) i D2 (atraktivnost), identifikovana za medicinske fakultete u Srbiji primenom PCA, objašnjavaju 71,8% razlike. Najvažnija obeležja bila su dužina kursa, broj bodova i časova edukacije po bodu za predavače i za učesnike. Nakon PCA za Medicinski fakultet u Beogradu, D1 i D2 objašnjavaju 40,7% ukupnog variranja. U CCR modelu najveće pozitivno delovanje na broj učesnika imali su broj predavača po kursu i troškovi organizacije, dok je najveći negativni uticaj imao ukupni prihod po učesniku. **Zaključak.** Medicinski fakulteti u Srbiji trebalo bi da preispitaju celokupnu organizaciju KME, a posebno da unaprede kvalitet i kvantitet registracije učesnika, ograniče učešće po času edukacije i snize administrativne i druge troškove, preporuče da učestvovanje predavača u KME bude kriterijum za akademsko unapređivanje i da organizuju usresređenu propagandu.

Ključne reči:
obrazovanje, medicinsko, kontinuirano; srbija; statistička analiza faktora; ekonomski faktori.

Introduction

Continuing Medical Education (CME) is probably the most developed field of lifelong learning (LLL), increasingly also termed continuing professional development (CPD); the variant terminology has been discussed in extenso, e.g. by Aspin and Chapman, 2007 [1]. The concept is linked to the idea of improving human resources in the field of professional competences and securing professional development, which will lead to better and accountable performance. It is generally accepted that LLL is an imperative for individuals and professional groups in a knowledge-intensive society and that it has far-reaching positive effects that go beyond simple economic issues [2, 3].

Various documents of European institutions underline the growing importance of LLL since the early 2000s (e.g. European Parliament and the Council, 2006 [4]). Universities of Europe are strongly encouraged to develop a lifelong learning approach to education. This is further supported by the endorsement of the "European Universities' Charter on Lifelong Learn-ing" in 2008 [5]. In March 2010 the European Ministries of Education have adopted the Budapest-Vienna Declaration on the European Higher Education Area [6]. Among the priorities of higher education in the decades to come, LLL is listed there as the second priority after equal access to and completion of education. In the same line are all actions of the European Union (EU) in the field of higher education, starting from the Lisbon Strategy and "The role of education in a fully-functioning knowledge triangle" [7]. Among the priorities listed are of special relevance: "Partnership between universities and business and other relevant stakeholders" as well as "Creating incentives for universities to develop transferable knowledge". The "Strategic framework for European cooperation in education and training" [8] calls for "Making Lifelong Learning and mobility a reality" and out of the five European benchmarks Adult participation in LLL is targeted as follows: "By 2020, an average of at least 15% of adults (25–64) should participate in lifelong learning" and "By 2020, the share of 30–34 year olds with tertiary educational attainment should be at least 40%".

The movement for LLL is also presented in a Green Paper from the EU Commission calling for bigger investment in workforce planning and training whilst the EU Council has called for greater priority to be given to LLL as 'a basic component of the European social model' [9]. The European universities are reporting on their organization of LLL under the umbrella of higher education institutions [7]. Despite recognition of LLL as one of the most important activities safeguarding the future of European universities, progress in the delivery of CPD is still not satisfactory (35% of educational institutions had strategies for development of LLL in 2003 with only a slight improvement in 2010 – 39%).

In Serbia as well as in the other successor states of the former Yugoslavia, publications on the organisation and management of CME are still rare, usually case studies respectively be-fore/after evaluation of specific courses [10–12].

In the light of the European development even less has been published [13]. Nevertheless, following the Bologna process and the new Law on Higher Education in Serbia [14], during the last years important strategies in support to LLL are developed and endorsed, such as the Na-tional Strategy for Development of Adult Education [15].

Considerable efforts have been invested during the first decade of the 21st century in order to implement in Serbia the Bologna principles in academic education and training at the level of bachelor, master and doctoral studies, less has been done in relation to continuing education in all fields. However, to support CPD, in 2007 the Ministry of Health introduced by-laws on CME based on the systems' laws such as the Law on Chambers of the Health Workforce and the Law on Health Care [16, 17], prescribing, among other conditions, the types of courses and the related credit points of CME. The legislation on the health professional chambers16 is supporting further development of LLL by imposing obligatory relicensing every seven years, requesting a min imum number of CME credits. These changes open an at-

tractive market for many providers of educational services. Since both private and public providers compete for customers with a broad spectrum of different types of CME.

Following the new trends, medical faculties in Serbia are also engaged in the organisation of LLL. Particularly the Faculty of Medicine, Belgrade (FMB) has a long tradition in leading CME [13]. Between 2003 and 2010, FMB alone delivered 492 courses [18]. The University of Bel-grade permanently offers favourable conditions for the improvement of LLL including a re-cently endorsed Strategy for development of LLL [19]. The aim of this strategy is to promote a culture of education and training, to strengthen cooperation and networking at a national and international level, to develop generic competences as preconditions for contemporary literacy, and to support social development and decrease unemployment by a flexible and acces-sible environment for education and training. Nevertheless, since the establishment of a na-tional accreditation system by the Health Council of Serbia in 2009 [20] and the appearance of a competitive market, reorganization of CME and adaptation to the new situation became man-datory if stagnation and outclassing of the medical faculties should be avoided.

Not only the Faculty of Medicine, University of Belgrade, but all higher academic institutions in Serbia and in the South-Eastern European Region are to revisit their LLL activities in order to take the chance of offering competitive programmes for a wider audience in national language and based on the standards according to the Bologna process. In addition the offer of programmes in English for a European and global audience has been considered, supported by distance learning formats. This paper therefore tries to analyse the present status of CME and the main deficits in the delivery of LLL courses at medical faculties in Serbia with special consideration of the FMB where detailed financial data are available.

Methods

Data of 2,265 courses for CME, submitted in 2011 and 2012, have been analysed on the basis of the documentation provided by the accrediting authority, the Health Council of Serbia [21]. Thereof 403 courses were offered by 4 medical faculties in Serbia: Belgrade, Kragujevac, Niš, and Novi Sad. The Medical Faculty in Kosovska Mitrovica did not accredit any course during the period under consideration while the Faculty of Medicine the Military Medical Academy did not apply for accreditation as an independent higher education institution [22]. A subset of courses actually accredited and delivered in the same year by the FMB could be analysed in more detail on the basis of the documentation provided by the administrative office of the Faculty: 51 course sheets were collected for courses delivered in 2011 and 37 for courses in 2012, together 88 courses. The database for Serbia comprised 26 variables, the subset for Belgrade 26 partly different variables of together 5,600 participants in 2011 and 2012.

The basic analyses have been performed with XLSTAT 2009. For the description median and inter-quartile-range (IQR, the distance between the 25th and the 75th percentile) were preferred because of the heterogeneity of the datasets. As there were many lecturers reading repeatedly we counted the number of lecturers *per* course but sum-up across all courses as "lec-torates". As of 1 January 2013 the national currency of dinars is traded against the euro at a rate of 112 dinars/euro [23].

For the analysis we used a two-step approach. First, we conducted principal component analysis (PCA) in order to reduce the number of variables without giving up relevant information. PCA is especially recommended when planning regression analysis where the number of independent variables is large relative to the number of observations, or, if it can be assumed that the independent variables are highly correlated [24]. Employing PCA for our dataset allowed to reduce the number of independent variables and to replace highly inter-correlated variables by fewer and independent factors. In the second step we calculated the actual regression model to identify the determinants of course participation. We applied a relatively new approach – correlated component regression (CCR) – which takes into account still remaining multicollinearity [25, 26]. Remaining multicollinearity would have increased the standard errors of the correlation coefficients and led to false interpretation by missing significant differences.

Results

Table 1 shows the basic composition of the data according to organisers and classification of CME. A total of 2,265 courses were submitted for accreditation in 2011 and 2012 together and almost all certified (98.6%), which does not imply that they were also delivered in the year of accreditation or even later. Almost two thirds of the submitted programmes were in the field of clinical medicine (62.4%) and likewise almost two thirds came from organisers in Belgrade (61.5%). The majority of programmes, i.e. 57.3%, were offered by state institutions and 35.7% by non-governmental organisations (NGO). The four medical faculties, in Belgrade, Kragujevac, Niš, and Novi Sad together offered 403 courses or 17.8%, there of the FMB the largest part with 169 submissions or 41.9%. There were two other medical faculties: in Belgrade under the Ministry of Defence, within the Military Medical Academy (MMA), and in Kosovska Mitrovica. Whereas potential submissions from Kosovska Mitrovica could be clearly excluded, the Faculty of Medicine of the MMA accounts for only 1 submission out of 80 courses submitted by other MMA institutes. In addition the code "Other faculty or educational institution" accounts for only 5 programmes in 2011 and 15 in 2012.

Characteristic details of continuing medical education for all 2,265 programmes submitted for accreditation in Serbia during 2011 and 2012 and for all four identified medical faculties together (Belgrade, Kragujevac, Niš, Novi Sad) are summarised in the Addenda, Tables A1 and A2. Moreover, the 88 course sheets (37 in 2012 and 51 in 2011) from programmes actually delivered at the Faculty of Medicine in Belgrade were analysed in more detail Table A3, especially including financial parameters.

Table 1

Continuing medical education in Serbia, overview of all courses submitted in 2011/12

Field of continuing medical education (CME)	Faculty of Medicine, Belgrade (FMB)	Medical faculties incl. FMB	All other organisers	Total number (%)
2011				
Preclinical	19	41	87	128 (10.7)
Clinical	58	136	619	755 (63.1)
Public Health	13	27	149	176 (14.7)
Mixed/unspecified topics	4	18	120	138 (11.5)
Total	94	222	975	1197 (100)
2012				
Preclinical	22	40	125	165 (15.4)
Clinical	43	117	542	659 (61.7)
Public Health	5	9	92	101 (9.5)
Mixed/unspecified topics	5	15	128	143 (13.4)
Total	75	181	887	1,068 (100)
Total 2011/12	169	403	1862	2,265 (100)

80 submissions with missing values excluded

The median duration of all courses in Serbia was 6 hours, the median number of credit points for lecturers 10 and for participants 5. *Per* credit point a lecturer reads 0.67 hours, a participant attends for 1.33 hours; this is not very different between Serbia in general, medical faculties alone and the FMB specifically. Likewise the average lecturing time *per* domestic lecturer is 2 hours for all courses in Serbia and not much higher, e.g. for the FMB with 3 hours. However, the rates for participants differ considerably, between 1,500 dinar in Serbia overall, 4,000 for medical faculties and even 5,000 in Belgrade with broad interquartile ranges (IQR). Correspondingly, the rates *per* hour and *per* credit point are higher in the programmes of medical faculties.

For the subset of Belgrade with 88 course sheets collected all together 3,471 participants registered in 2011 with a median of 51 *per* course, and 2,129 in 2012 with a median of 39. *Per* course a median of 6 lecturers is counted, equivalent to a total of 665 "lectorates" in both years together. The median fee rates for participants (partly supported directly by sponsors) were 5,000 dinars in 2011 and 8,000 in 2012 resulting, together with donations, in a total income of 11,463,122.00 dinar in 2011 and 4,663,373.00 in 2012, which is 16,126,495.00 dinar for both years together or equivalent to 143,987.00. In fact only 89.7% of the total charges due have been collected. The reduction of income in 2012 is owed to the reduced number of participants whereas the median income rate per participant (including donations) remained stable between 4,086 and 4,284 dinars. The median rates *per* hour and *per* credit point oscillate between 417 and 769 dinar.

The FMB charged 10.0% as a special charge on CME and 13.0% on administration by the Faculty, together 23.0% of the total income, or 33.5% of all expenses in 2011 and 40.6% in 2012. The next highest position is the cost of certificates produced by the faculty with 24.5% of the total expenses in 2011 and 32.0% in 2012. The sur-plus after deduction of all expenses allowed for a median payment of 10,101 dinars or 90 euro *per* hour lectured in 2011 and 5,492 dinars or 49 euros in 2012.

The classification of the variables of main interest, i.e. the number of participants, faculty earnings, and surplus *per* lecturer according to preclinical courses, clinical courses, courses in public health, and courses of other types indicates a considerable variance between less attended preclinical programmes (median 5.5) and a quite numerous participation in the clinical (median 85) and public health (median 24) courses. Nevertheless, the surplus *per* lecturer after deduction of all expenditures is quite similar across all programmes (median overall 12,639.00 dinar or 113 euros) with the exception of the preclinical courses (2.506.00 dinar). Faculty earnings, however, vary much more (overall median 36,527.00 - IQR 297,031.00 dinar).

For the year 2012 also 779 participant's evaluation forms from 19 courses in Belgrade were available. The average ranking of the 19 courses was between 4.47 and 5.00 (from a scale ranging from 1 to 5, the best). Between 56.4 and 100% of participants in a specific course gave rank 5; 2 courses reached even an average of 5 (i.e. all participants voted 5); only 31.6% or 6 out of the 19 courses got the ranks < 4.75.

Figure 1 shows the result of the PCA performed for all 4 registered medical faculties in Serbia together. The remaining variables constitute the factors D1 (performance) and D2 (attractiveness) and together explain 71.8% of the data variance. Most relevant in this context are the duration of the courses, the credit points, and the hours *per* credit point gained by lecturers and participants respectively. The fee rates are also relevant but to a mod-erate extend only.

Figure 2 shows how the Belgradian courses with their more detailed data, especially including financial information, being scattered by the two factors identified in the PCA (see annexed Table A2). The first factor (D1 –performance) accounts for 23.3% of the total variance and is derived from seven variables; income related variables loading highest. The second factor (D2 – attractiveness) accounts for 17.4% of the variation and is derived from six variables, describing time and effort. Together the two factors explain 40.7% of the total variance.

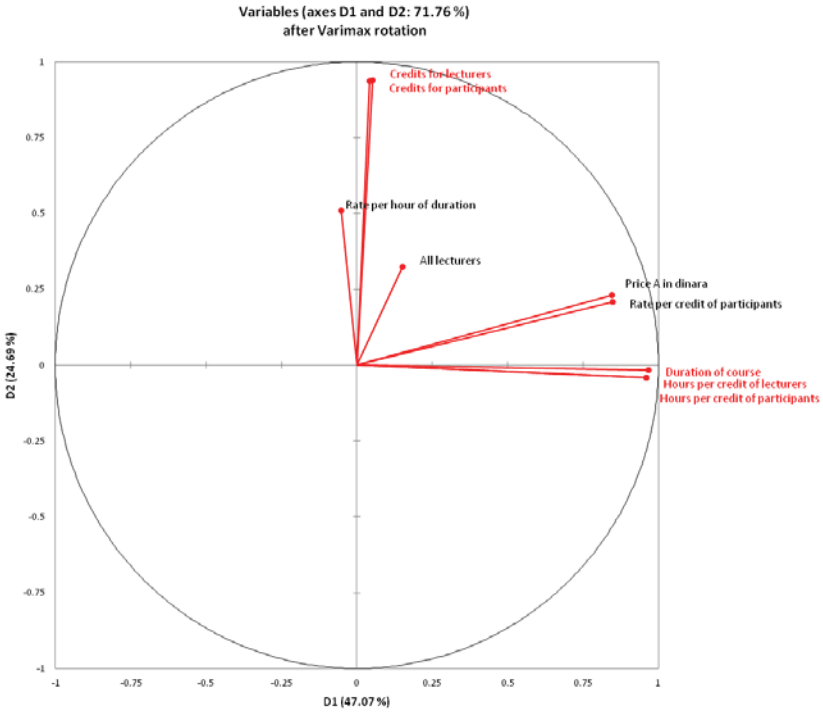

Fig. 1 – The most relevant factors of the principal component analysis (PCA) based on the courses submitted by Serbian medical faculties in 2011 and 2012 (n = 403).

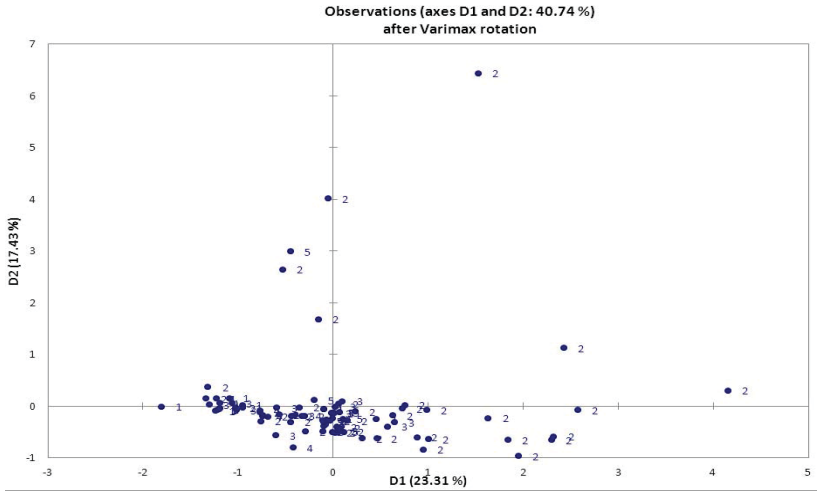

Fig. 2 – Courses by factors D1 – performance and D2 – attractiveness, Faculty of Medicine Belgrade (n = 88).

Course codes: (1) preclinical; (2) clinical; (3) public health; (4) other courses
Threshold: The threshold for exclusion of a variable was set at a loading of < 0.5 [26]

A high proportion of the courses (observations) lies in the third and fourth quadrant (order of quadrants is clockwise, starting from the upper left corner). This means that these courses are rated low in attractiveness and largely also in performance. We can see that clinical courses (#2) are mostly located in the third quadrant, with an outlier in the second quadrant with high attractiveness and relatively high performance. Preclinical courses (#1), Public Health courses (#3), and "Other courses (#4) are located more in the fourth quadrant. They are relatively unattractive and performing below average.

In a second step the variables included in the CCR calculation were selected according to the outcome of the PCA. We calculated four models with varying assumptions but quite consistent results (two of them are shown in the annexed Table A3). Accordingly, the highest positive impact on the number of participants comes from the money spent on amenities like meals etc. (here listed under "all other declared expenses", see also annexed Table A1), and "the number of lecturers *per* course". The highest negative impact comes from the variable "income *per* participant" which includes all donations. In fact, the "*per capita* income" is not an appropriate measure of operating efficiency here, as a decreasing number of participants will increase the ratio. However, together with the variable "official rate" (course fee) it signifies the financial burden to the participants.

Discussion

The conceptual framework for today's continuing medical education largely has been set towards the end of the first decade of this century [27] as discussed in the introduction. The recent call for a competence-based framework [28] requires a national if not European response [29–31], transforming CME in the next years. Medical faculties are best suited to set the standard for CME as far as it is obligatory for medical professionals.

First steps have been made with the National Strategy for Development of Adult Education in Serbia [15] and a subsequent regulation of the FMB [32]. In 2009 the FMB adopted also a by-law on organization and delivery of CME courses [33], aiming to stimulate involvement of teaching staff in management and delivery of CME as well as a better administrative and financial organization, most relevant for the motivation of teaching staff.

Medical faculties in Serbia contribute to CME only with 17.8%, the FMB being the biggest supplier among all the academic institutions.

The reasons for the rather minor role of the medical faculties in general can be better under-stood looking at the data from Belgrade. Already from the descriptive analysis it becomes obvious that far less than half of the 883 lecturers employed at the FMB (as of 15 November 2012) engage in CME, e.g. with 279 "lectorates" in 2012. Although 613 are authorised to coordinate a programme for CME, only 37 or 6.0% did so in 2012, alone or together with colleagues. However, the reasons for the limited interest in CME are also obvious: the financial reward *per* lecturer and *per* hour lectured for most of them is not attractive as half of them earn less than 12,639.00 dinar in total and less than 7,282.00 *per* lecture hour delivered. Also there is an alarming reduction between 2011 and 2012, by about 1/3 of the surplus *per* lecturer and even close to 1/2 *per* hour lectured. The cost of certificates alone amounts to almost 2.5 mio dinar which could increase the remaining total surplus of 6.7 mio dinar for 2011 and 2012 together by up to 36.8%. One can safely assume that the situation is not substantially different with regard to other medical faculties in Serbia as the comparable variables indicate.

Although we could not determine reliably the contribution of donors to the total income (partly by paying fee rates of selected participants, partly by direct contribution to the course budget) we estimate that up to 75% of the total income originates from donors like pharmaceutical industry and government, implying a potential lack of autonomy. There is also an enormous variation in terms of remuneration per hour taught or attended, be it by credit points earned *per* hour or cost *per* credit point. Surprisingly low is the participation in preclinical courses. The best explanation for this observation is a high and possibly stimulated private competition. It is difficult to judge the quality of the courses delivered as we have evaluation sheets by participants only from 19 courses in Belgrade, admittedly with very high rankings. On the other hand the low rate of 1.4% of non-accredited programmes seems to indicate the lack of strict criteria.

The limitations of this analysis lay mainly in the data quality which required careful consid-eration of how to deal with missing or insecure information. A related factor is that full registration of data and even of entire courses is missing. Therefore we could analyse only Belgrade courses, which are accredited and delivered in the same academic year. The PCA shows convincingly that most courses have a low performance and attractiveness, mainly determined by financially related variables. This is confirmed by the CCR which leaves in addition to financial variables only the number of lecturers per course with a potential impact upon the number of participants.

The importance of life long learning has been recognised in recent discussions within the Association of Schools of Public Health in the European Region, based on the results of the ASPHER survey [34, 35] and our analysis of continuing medical education in Serbia.

Conclusion and Recommendations

More comprehensive and sufficiently funded studies in the field are required in order to improve delivery of continuing medical education, based on *a priori* collection of more detailed and comprehensive data and covering also other health professions as especially nurses.

In summarising this first analysis the authors conclude that the faculties of medicine in Serbia and especially the Faculty of Medicine in Belgrade may reconsider the entire structure of their organisation of CME regarding performance and attractiveness:

Administrative Organisation – Improve the data quality of the registration especially to include data on final delivery; Limit the course fee rates *per* hour; Reduce the percentage of obligatory payments to the administration and arrange for a cheap production of certificates in order to save money for remuneration; Request lecturing in CME programmes of the faculties of medicine as obligatory for academic promotion together with an increase of remuneration.

Innovative development – Going online towards blended learning; Adopt best practice from a competitive market; Increase attractiveness for participants from South Eastern Europe (especially from the former Yugoslavia) and from abroad in general (if English speaking); Invest in bilateral agreements with big organisations; Organise a focussed publicity.

Medical faculties of Serbia should develop their national and international standing also by providing CME to a larger professional community irrespective of financial gains.

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Conflict of interest

None

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Addenda

Table A1

Courses for continuing medical education (CME) submitted in Serbia in 2011 and 2012

Parameters of CME	2011/2012			2012		2011	
	Total	Median	Interquatile range (IQR)	Total	Median	Total	Median
I) *All courses submitted for accreditation in Serbia*							
All "lectorates"	17,114	5	5	8,156	5	8,958	5
Duration of courses (hours)		6	3		6		6
Credit points for lecturers		10	7		11		10
Credit points for participants		5	3		5		5
Hours *per* credit of lecturers		0.67	0.35		0.70		0.66
Hours *per* credit of participant		1.33	0.55		1.33		1.33
Rate *per* participant		1,500	4,000		1,500		2,000
Rate *per* hour of duration		214.3	500		214.29		208.33
Rate *per* credit of participants		333.33	833.33		333.33		333.33
II) *All courses submitted for accreditation by medical faculties in Belgrade, Kragujevac, Niš, and Novi Sad*							
All "lectorates"	2,815	5	5	1,285	6	1,530	5
Duration of courses (hours)		7	3.5		7		7
Credit points for lecturers		12	2		12		12
Credit points for participants		6	1		6		6
Hours *per* credit of lecturers		0.67	0.29		0.67		0.64
Hours *per* credit of participant		1.30	0.67		1.33		1.17
Rate *per* participant		4,000	5,000		4,000		4.250
Rate *per* hour of duration		571	500		577.40		500.00
Rate *per* credit of participants		786.7	833.3		666.70		833.00
III) *Courses delivered at the Faculty of Medicine, in Belgrade*							
All "lectorates"	665	6	7	279	6	386	6
Duration of courses (hours)		7.00	4.30		7.50		6.50
Credit points for lecturers		12	2		12		12
Credit points for participants		6	1		6		6
Hours *per* credit of lecturers		0.60	0.30		0.70		0.59
Hours *per* credit of participant		1.20	0.60		1.30		1.17
Rate *per* participant		5,000	7,000		8,000		5,000
Rate *per* hour of duration		714	555		769		667
Rate *per* credit of participants		416	583		667		417
Total number of participants and median participation *per* course	5,600	45	77	2,129	39	3,471	51
Participants *per* lecturer		6	8		6		7
Total income and income *per* course	16,126,495	169,822	258,377	4,663,373	127,743	11,463,122	271,250
All income *per* participant		4,184	8,219		4,284		4,086
10% CME Belgrade	1,447,214	15,881	25,269	466,348	12,775	980,866	23,750
13% Faculty of Medicine, Belgrade: charge	1,880,414	20,646	32,849	605,938	16,607	1,274,476	30,550
All other declared expenses	6,053,226	72,055	109,905	1,572,000	35,998	4,481,226	96,438
Out of them cost of certificates	2,485,600	32,700	49,800	836,400	21,000	1,649,200	47,400
Remaining total surplus	6,745,641	67,317	145,559	2,019,087	48,838	4,726,554	97,026
Remuneration *per* lecturer out of surplus		12,639	16,943		10,238		15,090
Remuneration *per* hour lectured out of surplus		7,282	15,325		5,492		10,101

Table A2

Factor patterns (D1/performance and D2/attractiveness) derived from principal component analysis (PCA), Faculty of Medicine, Belgrade

Factor pattern after Varimax rotation:

Data parameters	D1	D2
Hours No.	0.078	**0.866**
Official rate	-0.019	**0.698**
Credits lecturers	0.221	0.079
Credits participants	0.200	0.046
Domestic lecturers	0.515	0.201
Foreign lecturers	0.175	-0.104
No. participants	0.456	-0.321
No. certificates	0.415	-0.177
Total income	**0.925**	0.239
10% CME	**0.901**	-0.153
13% FAC	**0.901**	-0.153
All other declared expenses	**0.640**	0.289
Out of them festive hall	0.277	-0.044
Out of them certificates	0.617	-0.327
Out of them extra hours	0.247	-0.040
Out of them coffee etc.	0.471	-0.108
Surplus	0.784	0.259
All lecturers	**0.515**	0.201
Hours/credit lecturer	0.074	**0.866**
Hours/credit par-ticipant	0.074	0.866
Rate/hour course duration	-0.041	0.323
Rate/credit participants	-0.023	**0.699**
Surplus/lecturer	0.494	0.261
Surplus/hour lectured	**0.683**	-0.184
Participants/ lecturers	0.160	-0.274
Income/particpant	0.181	**0.643**

Table A3

Standardised coefficients of the correlated component regresion (CCR) for Faculty of Medicine, Belgrade (corresponding arrangement, bolded variables load highest)

Variables in model I	Coefficient	Variables in model II	Coefficient
All other expenditures	**0.403**	**All other expenditures**	**0.368**
All lecturers	**0.378**	**All lecturers**	**0.339**
Total income	**0.303**		
Surplus/hour lectured	0.120	Surplus/hour lectured	0.211
Surplus	0.049		
Hours/credit participants	-0.050		
Hours/credit lecturers	-0.051		
Hours No.	-0.051		
10% CME	-0.190		
13% Faculty	-0.198	13% Faculty	-0.165
Official rate	-0.226	Official rate	-0.198
Income/participant	**-0.355**	**Income/participant**	**-0.369**

CME – continuing medical education

GENERAL REVIEW

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Assessment of implant stability by resonant frequency analysis

Procena stabilnosti implantata analizom rezonantne frekvencije

Vitomir S. Konstantinović*, Filip Ivanjac*, Vojkan Lazić†, Igor Djordjević†

***Clinic for Maxillofacial Surgery, †Clinic for Prosthodontics, Faculty of Dentistry, University of Belgrade, Belgrade, Serbia**

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Ključne reči:
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Implant stability

Implant stability is a principal precondition for the success of implant therapy. Implant stability can be primary or secondary and depends on different factors [1–4].

Primary implant stability.

It is a frictional force between the bone and the implant. Stability is achieved during implant insertion in the bone site which is the result of biomechanical bone-implant relation [3–7]. Primary stability depends on: bone quality, bone amount, surgical technique, implant design and surface [8–10].

Bone quality

The hardness of compact bone is about 10 times higher than cancellous (trabecular) bone, thanks to both its density and mineralization. The higher bone density gives the higher primary implants stability values [11–13]. Considering that cancellous bone has lower biomechanical values, some authors like to name it 'lower quality bone', which is not quite exact and correct term. It is better to name it – 'low density bone'. The most important parameter is the quality of bone that can be classified by its density based on panoramic radiography [14].

Bone is then classified as: type 1 – compact bone; type 2 – thick layer of compact bone which overlays trabecular bone; type 3 – thin layer of cortical bone which overlays dense trabecular bone; type 4 – thin layer of cortical bone which overlays low density trabecular bone (Figure 1).

Regardless bone density, particular concern should be carried out with patients at risk, like patients after radiotherapy [15, 16].

Implant stability can also be differentiated by the location in the jaw bone region. Higher values of primary stability are achieved in the regions with higher bone density (measured by computed tomography – CT), such are intercanine and molar regions. In case of higher bone density, a high value of primary stability will be achieved [17, 18].

Fig.1 – Bone type scheme, drawn by Dr. Filip Ivanjac, inspired by Lekholm and Zarb [14].

There are similar results for the relationship bone density/implant stability, as well as for the resistance during implant insertion in other publications suggesting that bone density measured by CT can predict implant stability [19–22].

Bone amount

Bone amount is an important factor in implant therapy. The lack of alveolar bone is a limiting factor for implantation. When there is no sufficient bone quantity at least of 10 mm in length, the implantologist have to choose to use more suitable implants, generally smaller and shorter ones, which could jeopardize implant stability [12].

Surgical technique

Surgical technique plays an important role in implant stability as well as in outcome of implant therapy. Surgical trauma is a risk factor which damages bone tissue [19–25]. Pri-

Correspondence to: Vitomir S. Konstatntinović, Clinic for Maxillofacial Surgery, University of Belgrade, Belgrade, Serbia.
E-mail. v.konstantiovic@stomf.bg.ac.rs

mary stability also depends on drill diameter: smaller- diameter drills often give higher values of primary stability.

Implant design

Implant macro and micro design can have influence on implant stability. In other words, it depends on the available implant surface. Increase in implant surface could be achieved by plasma coating, sanding, laser treating and applying crystals of calcium phosphate. These procedures can enlarge the surface up to 10 times. A larger implant surface provides both higher primary stability values and consequently better osseointegration. Implants longer than 10 mm have better primary stability. Root shaped implants have a better force distribution on periimplant tissue, and cylindrical implants show the highest primary stability values, so they are more often used [26, 27].

Secondary implant stability

After implantation, surrounding tissue responds to trauma by bone remodelling which could last from 12 to 18 months. However, the term 'secondary stability' usually refers to the period of 3–6 months after implantation. Implants placed into the cancellous bone as well as in the compact bone modify their stability during the time. Changes occur in cancellous bone which adopts compact bone characteristics in the areas close to the implant surface, which further makes an implant more stable [12, 13, 26, 27].

In compact bone, implant stability is decreased during the time because of a mild bone resorption, so implant stability values both in compact bone and cancellous bone after a time period are closer, nearly equal [28–30].

Sometimes, secondary stability values are lower than primary stability values. Decrease in stability is the result of mild resorption in marginal bone. Some authors deny this fact by achieving high values in resonance frequency quotient after one-year period follow-up. On the other hand, increase of primary stability values is due to bone remodelling, which is influenced by external and internal factors like general health, tobacco and drugs use, or radiotherapy [14, 31].

Secondary stability depends on bone remodellation process on the implant-bone interface which is influenced by both implant surface and healing time [28, 30].

Osseointegration

Per Ingvar Branemark [32], Swedish doctor, was the first researcher to scientifically prove (in 1969) that a direct structural and functional contact between the live bone and a functionally loaded implant is possible. This process is defined by the term 'osseointegration'. Subsequently, it has been known that osseointegration depends on healing abilities, reparation and remodellation of bone tissue. A relation between the bone and an implant is defined as a functionally ankylotic link [21, 28, 31–34, 44].

Osseointegration is a histological term meaning direct bone apposition on the surface of the implant without insertion of soft tissue. It is achieved by bone remodelling during the initial healing period when implant is not loaded in order to ensure smooth bone formation on the implant surface. The process of osseointegration increases bone density, prevents micromovement and the formation of fibrous scar tissue around the implant. Osseointegration is most intense in the first two weeks after implantation. Good osseointegration clinically means a stable marginal bone around the implant with no mobility [28, 31–38].

Implant stability is a combination of the mechanical and biological stability: mechanical stability is the result of compression of bone tissue during implantation; biological stability is the result of newly formed bone cells, which are created on the implant surface during the osseointegration process.

Mechanical stability which is usually high occurs immediately after placing an implant into the bone. However, it decreases with time.

Biological stability does not appear immediately after implantation. It becomes noticeable after the formation of new bone cells on the implant surface. This stability increases over time –secondary stability. As a result of osseointegration, the initial mechanical stability is partly replaced by biological stability. The final implant stability is a combination of these two stabilities [5–9, 31].

Assessment of implant stability

Various methods are used for implant stability testing. Surgeon's subjective assessment of implant stability is based on the resistance during bone preparation and insertion of the implant. However, this method of perception cannot be objectively expressed [20, 39–44].

Insertion torque resistance. Insertion torque is a measure of the resistance that occurs during implantation. It depends on bone strength and density, as well as on implant properties. The disadvantage of this method is its depending on the implant sharpness and the presence of fluid during preparation which may differ in results. The greater the sharpness of the implant or the more fluid in the implant site during preparation, the less resistance. Another disadvantage is that the force of implant placement does not count [20, 44].

Percussion test. It includes percussion of the cervical part of the implant by the handle of the instrument. A conclusion on implant stability is made by the presence of resonant sound. Also, there are electrical devices that are based on the same principle like "perio test" such is - dental mobility checker [43, 44].

Implant loosening test. This is a reverse torque test. Opposite torque test is most often used to measure the secondary implant stability. Implants which show mobility during this test should be considered to be removed. This method is not in use, because testing can lead to gaps caused by microcracks in the implant and bone interface, which can result in implant failure [38].

Measurement of the lateral mobility. Micromovement of an implant in vestibulo-oral or mesiodistal direction (Figure 2) is more reliable than measuring rotational mobility of the implant. Rotationally mobile implants can be laterally stable, which is a good prognostic sign for successful osseointegration [30, 42].

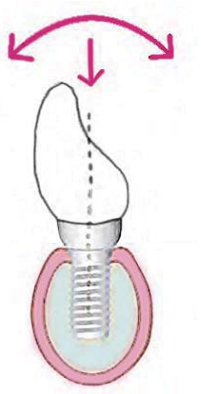

Fig. 2 – Graphic scheme of implant micromovement directions, drawn by Dr Filip Ivanjac inspired by Sennerby et al [4].

Besides, there are techniques such is ultrasonic implant stability testing, as well as the analysis of the resonant frequency (RFA). The bottom line is to measure implant stability in a non-invasive manner without damage to the implant-bone interface. As the success of implant therapy is often associated with biomechanical factors, implant stability assessment provides valuable information that can guide further clinical procedures [39–42].

History of resonance frequency analysis

Resonant frequency analysis (RFA) reflects the implant stability. RFA has been used in clinical research for over 10 years. Coefficient (ratio) of implant stability (implant stability quotient – ISQ) is the result of resonant frequency analysis. RFA is an implant stability analysis method where a very low value of lateral bending force is applied mimicing clinical conditions of implant loading, only in a much smaller proportion. It measures micromovement of an implant in its seat, based on the reflected frequency [1–9].

The first studies about RFA were conducted by Meredith et al. [1] in 1996. They launched a device for measuring implant stability (Ostell®).

Parallely, in Taipei (Taiwan) a similar system – Implomates® Bio Tech One system, was introduced. In the initial studies, Meredith et al. [1, 3] used kilo Hertz (kHz) to measure implant stability in the range of 3500–8500 kHz. Shortly afterwards, ISQ with the values of 1–100, which correlates with the frequency in kHz, was established (1 is the lowest and 100 is the highest stability value).

A newer generation is a device invented by Ostell Mentor®. It functions as an electronic resonant fork, which translates kHz into ISQ. This is a portable device that emits a signal of 5–10 Ncm through a transducer and calculates ISQ value, which is based on the reflected signal. The first resonant frequency of the transduser (fixed to the implant or abutment) is analyzed. The disadvantage of this method were _values depending on the direction of setting up the transduser. With the new generation of Ostell Mentor® devices the transduser is multidirectional. The signal that the device transmits is 5–15 kHz frequency with a power amplitude of 1 V. The reflected resonant signal is red by the analyzer (detector) of frequency and compared with the original signal frequency. The acceptable range of values for the implant stability is 55–85 ISQ units, with the average value of 70 ISQ units [1–9].

RFA frequency depends on three main factors: transduser design (transmitter), implant tightness and its relationship with the surrounding bone and the effective length above the marginal bone level. The effective length is the sum of the length of the transducer and the abutment, which can vary. In the first and second generation, Ostell Mentor® devices were relatively large and connected by cables to the computer. Data was recorded on the hard disk. The results were not comparable to each other, because each transducer had its own frequency, so different transducers had to be calibrated before measuring. The new (third) generation of Ostell Mentor® is a small, portable, wireless device that operates on batteries. The transducer is calibrated by the manufacturer. The result obtained by measuring is a ISQ. It uses a cylindrical metal bar – 'smart peg'. On one end it has a screw which is attached with the implant and a miniature magnet on its top, which is excited by magnetic signals from the transducer of the device. 'Smart peg' vibrates in two directions positioning on 90 degrees one to another, in the direction of the highest value of resonant frequency, and the direction of the lowest value, thus making a single coefficient – ISQ. A better support and stability in the bone, gives the greater value of resonant frequency. There are transmitters for different implant systems and abutments. In this way, all the measurements are comparable regardless of the type of implant or abutment. Each result is stored in a memory card in the tabular form. Data can be transferred to a computer using a cable or wireless infrared connection [4, 8, 9, 19, 45, 46].

Transducer orientation affects measurement of resonant frequency. There may be variations up to 10 ISQ units if the probe is set in parallel rather than perpendicular direction to the alveolar ridge. The new generation device measures the highest and the lowest frequency, whenever there is a difference of 3 ISQ units. Up to 10 units higher values of coefficient are obtained by a new generation of wireless technology device which measures the vibrations in the mesiodistal direction. Lower values are obtaied using the old technique, the buco-oral direction. This value is lower because of the thinner bone, which provides less support. The results are lower also because of different orientation of the transduser in the older generation devices. Resonance frequency analysis can provide a significant information about the relation implant/bone at any stage of treatment [4–9].

The importance of RFA method is in the fact that it helps the implantologist choosing when to load an implant. Also, it can indicate situations when it is necessary to relieve the overloaded implant.

High values of primary stability (ISQ 70 and higher), have no tendency to significantly increase over time. High primary (mechanical) stability decreases with time due to osteoclastic activity. It is replaced by biological stability, which increases because of the osseointegration process. However, slightly lower and low values of primary stability are increased by the process of bone remodelling and osseointegration [4, 9, 18, 26, 45].

Primary stability of ISQ values of 55 and below, could be considered as a warning sign in order to increase the stability of the implant (wider implant diameter) and time for osseointegration [25, 27].

Resonant frequency analysis is the most objective and reliable method of measuring the lateral micromobility of an implant during any stage of implant therapy [4, 19, 26, 45]. It is clinically proven that implant stability plays an important role in the future treatment and provides an insight into the outcome of implant therapy [3–7]. The ability to determine the level of implant stability in different stages of treatment is not only necessary, but an important source of information for further proceedings in therapy [19, 26].

Implant stability determines the loading protocol: immediate implant loading with low primary stability would jeopardize the result of implant therapy. In such a case, a conventional (late) loading protocol is recommended. On the other hand, when primary stability is high, immediate loading protocol could be performed.

Implant stability could also give information on possible implant unloading. Sennerby and Meredith [4] suggest that implant stability determines adequate time to replace immediately loaded temporary prosthesis with permanent. Low values of secondary stability can suggest that the implant has been overloaded with possible failure. In that situation unloading of the implant could help in stability regaining (Figures 3 and 4) [19, 26, 42, 46].

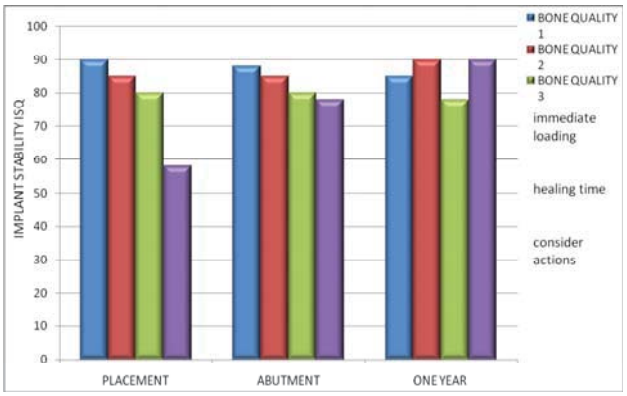

Fig. 3 – Assessment of actions regarding implant stability during the time, drawn by Dr. Filip Ivanjac, inspired by Sennerby et al. [26] .

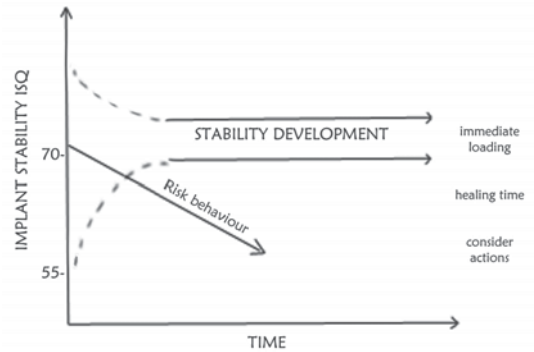

Fig. 4 – Risk behaviour regarding of implant stability and time, drawn by Dr. Filip Ivanjac, inspired by Sennerby et al. [26] .

A period of 2 to 4 weeks after implant placement is referred as "critical". In that period implant stability reduces. It is a transient period between the primary and secondary stability [26, 47] (Figure 5). Osteoclastic activity leads both to bone resorption and primary stability reducing. Decrease in implant stability is created by the weakened bone which is partially absorbed. The bone integrity was compromised by implant placement after which remodelling occurs [47].

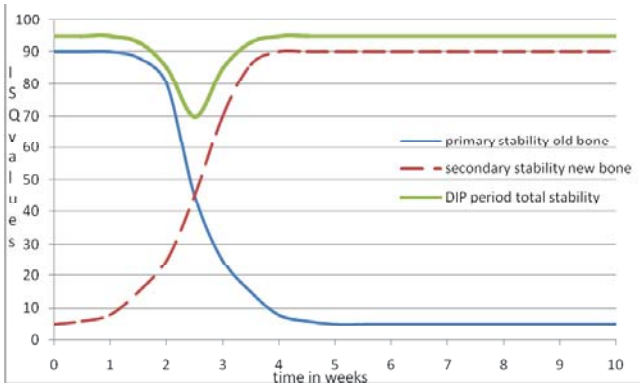

Fig. 5 – Implant dip period, drawn by Dr. Filip Ivanjac, inspired by Sennerby et al. [26].

Bone remodelling occurs on the third day after implantation. Adequate stabilization and mineralization of newly formed bone takes place about 160 days after beginning of bone remodelling. Time for complete bone mineralization is up to 12 months [33, 47].

Clinical success of endosteal implants depends on optimal relation of implant-bone interface. A direct connection of the entire surface of the implant and surrounding bone tissue cannot be obtained. Root-shaped implants obtain the best results, where direct bone-implant connection is achieved in 56–85% of implant surface [48]. Furthermore, root-shaped implants have better force distribution on peri-implant tissue, and cylindrical implants show the highest primary stability values [27]. Cylindrical shape implants show the average 72 ISQ, while tapered implants show slightly lower values on the average of 68 ISQ, depending on the system [26, 27].

Conclusion

Resonant frequency analysis is probably the most objective and reliable method of measuring implant micromobility in various stages of implant therapy. Implant stability is clinically proven to play an important role in the efficiency of treatment, providing the insight into implant therapy outcome.

Implant therapy success depends on biomechanical stability factors data. Good implant stability reduces the risk of failure. Recent researches have shown that high values of resonant frequency analysis indicate therapy success with a minimal probability of failure.

On the other hand, low values of resonant frequency analysis point to possible complications, such as loosening of

the implant, peri-implantitis and poor distribution of force in the surrounding tissue. Since implants failure is often associated with biomechanical factors, assessment of implant stability gives a valuable information. High values of resonant frequency analysis, as well as adequate surgical implantation technique and implant system chosen, could guarantee predictability of implant supported restoration. Generally, the values of implant stability quotient below 55 or 45 (regarding different implant systems) can be taken as a warning for primary stability. In order to increase stability, for example, using of wider and/or longer implant or particular bone condensing techniques could be helpful. A low resonant frequency analysis value in osseointegrated and loaded implants, indicates both disintegration and consecutive resorption of bone tissue around the implant.

Implant stability measuring using resonant frequency analysis is a modern, non-invasive and a relatively precise technique, which provides both information on implant stability in the bone and a reliable guidance to further course of implant therapy.

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CURRENT TOPIC

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Beta-lactam antibiotics use in intensive care units – The pathophysiological, pharmacokinetic, pharmacodynamic and pharmacoeconomic approach

Upotreba beta-laktamskih antibiotika u jedinicama intenzivne terapije – patofiziološki, farmakokinetički, farmakodinamički i farmakoekonomski pristup

Aneta Perić*†, Maja Šurbatović†‡, Sandra Vezmar Kovačević§, Mirjana Antunović*†, Milić Veljović†‡, Ivana Krstić-Lečić‡, Dragan Djordjević†‡, Vesna Kilibarda†‖, Snježana Zeba†‡, Silva Dobrić†¶

***Sector for Pharmacy, ‡Clinic of Anesthesiology and Intensive Therapy, ‖National Poison Control Center, ¶Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; §Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia**

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Ključne reči:
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Introduction

Sepsis, as a systematic inflammatory response to infection, compromises a number of very complex pathophysiological processes: diffuse endothelial and epithelial injury, increased capillary permeability, impaired hemodynamics, microvascular thrombosis, tissue ischemia, apoptosis and can result in multiple organ dysfunction [1–4]. It is one of the most frequent reasons for intensive care hospitalization. It is estimated that the mortality in severe sepsis patients ranges from 40% to 70%. Moreover, it is the second leading cause of death among patients in non-coronary intensive care units (ICUs) and the tenth leading cause of death overall in the United States [5, 6]. Several recent studies suggest that the mortality rate from severe sepsis is not changed remarkably over the last 30 years. During that time, the incidence of sepsis has been increasing [6]. The mean hospital cost *per* patient was estimated at $22,100 [7]. Vincent et al. [8] studied patients admitted to ICUs all over Europe and found that ICU mortality was almost doubled among patients with sepsis compared to those without sepsis, 27% *vs* 14%, respectively. ICU mortality rate from severe sepsis and septic shock was even higher, 32.2% and 54.1%, respectively. These results are from SOAP study in which our ICU (Clinic of Anesthesiology and Intensive Therapy of the Military Medical Academy, Belgrade, Serbia) participated. The results from the most populous country, China, showed that the overall hospital mortality from severe sepsis was 48.7%. The mean hospital cost was $11,390 *per* patient and $502 *per* patient *per* day [9]. Even if patients survive sepsis, their quality of life is expected to be substantially reduced [5, 6].

The cornerstones for the therapy of sepsis are aggresive fluid resuscitation, source control, and antimicrobial treatment. Antimicrobial agents are one of the frequently utilized drug classes in an ICU [5, 10]. The results of previous investigations showed that antibiotic treatment decreases the concentrations of inflammatory mediators in body fluids [11, 12]. However, in patients with sepsis the rapid clinical deterioration is often seen after the first dose of cidal antibiotics. This phenomenon could be explained with Jarish-Herxheimer reaction (JHR), which is a syndrome with worsening of symptoms immediately after antimicrobial treatment of infection. It is caused by the production of higher inflammatory mediators [2]. Selecting an appropriate antimicrobial in terms of spectrum of activity is the mainstay of antimicrobial therapy. Still, the consistent choice of correct dosage regimen (in terms of both dose and frequency of administration) has been shown to be at least as important for successful clinical cure and microbiological eradication as the choice of drug [13, 14]. Empirical treatment of bacterial infections in an ICU is based

Correspondence to: Aneta Perić, Sector for Pharmacy, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. Phone: +381 11 3609 225. E-mail: aneta.peric@gmail.com

predominantly on the identification and susceptibility of bacteria commonly isolated in that unit [10, 15]. It has been demonstrated that inappropriate use of antibiotics causes an enhancement of antimicrobial resistance. This contributes significantly towards elevated health care costs and patient morbidity and mortality [16–18]. Optimized exposure to antimicrobials has been shown to result in improved clinical outcomes [13].

Besides, pathophysiological changes due to systematic inflammatory response may markedly alter pharmacokinetic (PK) and pharmacodynamic (PD) properties of drugs [19]. Due to this dosage of antibacterial drugs in critically ill patients is not straightforward. However, newer data suggest that antibiotic stewardship programs lead to the reduction in duration of hospital stay and saving in medical expenses [17, 20].

Among numerous antibacterial agents, carbapenems, a group of β-lactam antibiotics with a broad spectrum of activity, are considered to be the first-line empirical antibiotic therapy in critically ill patients. They exibit *in vitro* bactericidal activity against numerous pathogens, including Gram-positive and Gram-negative aerobes and anaerobes, but lack activity against *Enteroccocus faecium*, methicillin-resistant *Staphylococcus aureus* and *Stenotrophomonas maltophilia*. Currently, most often used carbapenems in clinical practice are: imipenem, meropenem, ertrapenem and doripenem. Doripenem and meropenem possess a slightly more potent anti-pseudomonal activity compared to imipenem, while ertrapenem lacks activity against *Pseudomonas aeruginosa* and *Enterococcus* spp. Imipenem, meropenem and doripenem have half-lives of approximately 1 hour, while ertrapenem displays a high protein binding and has the half-live of approximately 4 hours, making it suitable for once-daily administration. Imipenem is susceptible to degradation by enzyme dehydropeptidase-1, and requires co-administration of cilastatin. Ertrapenem is more suitable for the treatment of community-acquired infections and outpatient intravenous antimicrobial therapy. Imipenem and meropenem are used in treatment of moderate to severe nosocomial and polymicrobial infections [21–26].

Considering all of the above, the aim of this study was to review studies with PK and PD concepts in order to get data about the appropriate dosing regimen of carbapenems in critically ill patients with sepsis, having into account specific pathophysiological changes in these patients.

Antibiotic pharmacokinetic/pharmacodynamic considerations in critically ill patients

Critically ill patients receive multiple medications from a variety of pharmacological classes due to the life threatening illness. They are a unique population with diverse disease processes, existing or impending multiple organ dysfunction and altered PK and PD characteristics to which pharmacotherapy is added [27]. PK changes can be the result of organ dysfunction, most notably the liver and kidneys, but can also be a consequence of the acute phase response, drug interactions and therapeutic interventions [28].

Pathophysiology of sepsis in critically ill patients

The pathophysiology of sepsis is complex. Activation of inflammatory cytokine and coagulation cascades are important features of its pathogenesis and strongly influence pharmacokinetic properties of administered medication. Cytokines have the central role in positive and negative regulation of immune responses and in integrating these reactions with other physiological systems, such as the complement and hematopoietic systems. The effect of cytokines *in vivo* varies depending on time and location. They can be classified into proinflammatory [(T helper, Th1; i.e. tumor necrosis factor-(TNF)-α, interleukin-(IL)-1; anti-inflammatory Th2 cytokines; i.e. IL-10, and Th17, different from both Th1 and Th2)]. Some possess both activities, i.e. IL-6. Circulating levels of both proinflammatory and anti-inflammatory cytokines can be either eleveted or decreased in sepsis [29, 30]. They act by binding to specific receptors at the target cell membrane, setting off a cascade that leads to introduction, enhancement, or inhibition of a number of cytokine-regulated genes in nucleus, thereby modulating cytokine-regulated activity of cells. There is a great variability seen in the clinical profile and outcome in patients who encounter similar insults like trauma and/or infection. Now research is focused on genetic determinants of the immunoinflamatory response [31].

Pharmacokinetic changes in critically ill patients

Increase in the volume of distribution (Vd) is common primarily due to the expansion of the extracellular fluid volume (edema). Elimination half-life can also be prolonged due to the increased Vd. Conversely, clearance may be unchanged [32], decreased [33, 34] or most frequently elevated [21, 35–37] as a result of augmented renal clearance, resulting in subtherapeutic concentrations of renally cleared antibiotics. Edematous state, commonly seen in critically ill patients, may alter the distribution of hydrophillic antibiotics (including β-lactams and aminoglycosides) and cause clinical failure of antimicrobial therapy in sepsis and/or trauma [15, 27, 38]. As a general rule, in critically ill patients Vd is 2.5-fold greater than normal, resulting in lower plasma concentrations of antibiotics. Lack of routine drug monitoring for most antibiotics makes it difficult for clinicians to distinguish between insufficient antibiotic concentrations and lack of *in vivo* microorganism susceptibility [39]. Hydrophillic antibiotics are mainly excreted unchanged by the kidney. This elimination will be limited in renal failure, which is common in the critically ill. Renal failure may occur because of trauma, multiple organ dysfunction, extensive burns, cardiogenic or hypovolaemic shock or it may be induced by use of nephrotoxic drugs [15, 27]. Those patients should receive normal antibiotic doses given less frequently, to avoid overexposure and toxic side effects [27, 39].

Hypoalbuminemia is a frequent condition in critically ill patients. It can be caused by increased albumin capillary escape rate through leaky endothelium, fluid overload or malnutrition. Hypoalbuminemia may contribute to fluid extravasation and antimicrobial dilution. On the other hand, the increase of free fraction of drug may increase Vd and clear-

ance [27]. Fortunately, for the majority of antibiotics hepatic metabolism is limited and protein binding is low enough to make no difference to their effectiveness and there is no need to alter doses [39].

Interstitial fluid (ISF) of tissues is the site of most infections and previous results showed that antibiotic concentrations in ISF are 2- to 10-fold lower than plasma concentrations, suggesting that higher plasma concentrations may be required to ensure target concentrations in ISF [40, 41]. However, the antibiotic concentrations appear to vary between different tissues, so the different plasma concentrations may be required for the same bacteria depending on tissue that is infected [38].

Antibacterial PD describes the relationship between the drug concentration and the antibacterial effect – minimum inhibitory concentration (MIC). For time-dependent antibiotics, such as β-lactams, the optimal bacterial kill is achieved by the maximum amount of time (T) over the MIC. Carbapenems require 20% and 40% of T > MIC for bacteriostatic and bactericidal activity [42]. The maximum effect is achieved when the free drug concentration above the MIC is achieved for 90–100% of the dosing interval [15]. It seems that maximum killing effects are reached at the concentration of 4 × MIC [22] to even 6 × MIC, which may represent the target concentration to suppress resistance emergence against *P. aeruginosa* [37]. Based on data obtained from the studies, imipenem is able to maintain serum concentrations higher than or equal to the MIC of 4 mg/L for almost 8 hours after a single intravenous administration. Conversely, meropenem maintains T > MIC for the whole 8-hour interval between doses only for pathogens with the MIC equal or lower than 2 mg/L. However, to obtain adequate concentrations for pathogens with higher MICs (i.e. ≥ 8 for imipenem or ≥ 4 for meropenem), it would be appropriate to increase daily doses, to use more frequent dosing or to change the administration method, from intermittent (a 30-minute infusion) bolus infusion to either a prolonged (a 3-hour/or 4-hour infusion) or continuous (a 24-hour infusion) infusion. Septic patients also may benefit from higher doses, particularly in the first 24–48 hours of the therapy [22, 37, 43]. However, even with an increased dose, the teatment failure is of particular concern for pathogens with a high MIC [37]. Our experience (unpublished data) in a study comparing the standard 30-minute bolus infusion of 1 g of meropenem with a 3-hour infusion in a 7 critically ill patients with sepsis, suggests that at a 30-minute infusion time, the 1 g dose resulted in a %T > MIC of 62.5% at a MIC of 4 mg/L, whereas a 3-hour infusion time of 1 g of meropenem resulted in a %T > MIC of 43.7% at a MIC of 4 mg/L. Against isolates with a MIC of 16 mg/L, a 30-minute infusion of 1 g of meropenem resulted in a %T > MIC of 9.5%, whereas a 3-hour infusion resulted in a %T > MIC of 12.5%. After the second dose of meropenem, about 50% of patients were underdosed with both fixed-dose antibiotic regimens.

Pharmacokinetic/pharmacodynamic concept

Although β-lactams have traditionally been administered by intermittent infusion, continuous or prolonged infusion of those antibiotics is gaining attention because of time-dependent PD and potential economic savings. Continuous infusion and intermittent infusion of β-lactams have similar clinical and microbiological outcomes [44, 45], prolonged infusion dosing strategy has resulted in favorable outcomes. Meropenem 2 g administered over 3 hours every 8 hours maintained serum concentrations and prolonged exposure at the site of infection. The prolonged infusion regimen for piperacillin-tazobactam was adopted into clinical practice in one hospital in the United States. This prolonged infusion regimen means that patients receive 3.375 g of piperacillin-tazobactam every 8 hours as a 4-hour infusion. Data suggest that the prolonged infusion regimen achieves the targeted T > MIC at a total daily dose that is less than total daily dose in standard, intermittent bolus infusion regimen (3.375 g of piperacillin-tazobactam every 6 hours). As a result, the annual reduction in drug acquisition costs was $135,750 [46]. Non-acquisition costs of antibiotic administration (time expended by medical and nursing staff, costs of disposable materials and overhead cost) should be taken into account. According to the literature, the cost-effective strategy for administering antibiotics are infusion with syringe pumps and volumetric pumps, used for prolonged or continuous infusion [47]. The dosage of antibacterial drugs in critically ill patients is not straightforward.

Data derived from two studies comparing intermittent *versus* continuos infusion of meropenem, showed that the administration of the total daily dose of meropenem (3 g) as a continuous infusion appears to increase the likelihood of achieving PD targets (40% of T > MIC) and may improve clinical outcome [48]. Administration of imipenem by continuous infusion requires additional work to reconstitute imipenem in the infusion solution due to its low solubility compared to other β-lactams. Additionally, imipenem and meropenem are the least stable β-lactams. According to the prescribing information, imipenem solutions are sufficiently stable for 4 hours at 25°C, therefore it should be reconstituted every 3 hours for treatment by continuous infusion. Although this requires additional work, it is believed that it is potentially life-saving treatment for critically ill patients [49]. The regimen for meropenem is similar. Meropenem, reconstituted in normal saline solution is stable at room temperature for approximately 6 hours [50] and drug concentration can decrease for 4% [51]. It should be administered in a cold pouch [50]. The main limitation of continuous infusion is that it ties up a line of intravascular access for the entire day, which is not practical. Critically ill patients require multiple infusions and this will require placement of other lines. Extra lines are associated with a higher probability of a central vascular catheter derived infection, which is associated with higher morbidity and cost. Prolonged infusion allows 4 hours between each 8 hours dosing interval, when other agents could be administered through the same intravenous line. The duration of infusion (3–4 hours) approximates the duration of coverage of the dosing interval with free drug in excess of the MIC that provides the maximal microbiological effect [52–54]. According to the literature, the prolonged infusion of piperacillin-tazobactam resulted in cost savings by reducing the dosing frequency from every 6 hours to every 8

hours. Based on the average wholesale price, for a the treatment period of 7 to 10 day for 50 patients in ICU in the United States, $8,765 to $12,522 were saved. The approximate 4-day decrease in ICU length of stay (LOS) resulted in cost savings of $14,000 *per* patient. In the same study, the decrease in the total days of use of meropenem in ICU was seen, because the meropenem dosing regimen did not change, just the infusion time [55]. In order to compare data, we presented our cost in US dollars. The exchange rate of 1$ was considered to be 85 dinars, year value 2012. Based on average wholesale price of piperacillin-tazobactam, for a treatment period of 7 days for the dosing frequency of every 6 hours, the direct cost would be $253 per patient. The direct cost for the treatment period of 7 days for the dosing frequency of every 8 hours would be $190 *per* patient. It seems that $63 *per* patient would be saved by reducing the dosing frequency of piperacillin-tazobactam for the treatment period of 7 days.

In a retrospective cohort study of critically ill patients with infections caused by *P. aeruginosa*, in patients with APACHE II score ≥ 17, the prolonged infusion of piperacillin-tazobactam significantly reduced 14-day mortality compared with the intermittent infusion regimen, as well as ICU LOS [52]. Meropenem administered as prolonged 3 hours infusion in dose of 1 g resulted in greater T > MICs than the dose seen after bolus infusion of the same dose of the drug. It means that the required meropenem dosage may be reduced by one half in patients infected with pathogens for which the MIC < 1μg/mL [51–53]. Another option is to decrease daily meropenem usage by one third, giving 500 mg of meropenem every 6 hours. This strategy provides similar response rates and clinical outcome and cost saving (saving of $38 *per* day for medicational acquisition and supply costs) [56]. Based on average wholesale price in our country, the use of 1000 mg of meropenem every 8 hours costs $43. The use of 500 mg of meropenem every 6 hours costs $31. If we use the same strategy and decrease daily meropenem usage by one third, the cost saving would be $12 per day.

Based on the current knowledge on the PK and PD of β-lactams, continuous or prolonged infusion regimens are recommended for treatment of less-susceptible *P.aeruginosa* and *Acinetobacter species*, due to superior achievement of target exposures in critically ill patients [27]. The delay of onset of antibacterial activity compared with intermittent administration can be circumvented by administration of an initial loading dose before continuous or prolonged infusion [54, 57].

Therapeutic drug monitoring of β-lactams in critically ill patients

Therapeutic drug monitoring (TDM) of antibiotics has traditionally been used to prevent toxicity. TDM is the standard of care for aminoglycosides and glycopeptides. This strategy has not been widely applied for β-lactams because these antibiotics have a wide therapeutic index (a ratio between the toxic dose and the therapeutic dose of drug, used as a measure of relative safety of a drug), but persistent mortality and increasing antibiotic resistance may mean that TDM of β-lactams might be one of the tools for securing favorable therapeutic outcome in critically ill patients. Measurement of drug concentrations requires the use of high-performance liquid chromatography (HPLC). According to the literature, new HPLC assay methods specifically targeting the needs of routine TDM application have been developed, thus enabling simultaneous determination of β-lactams [58–61]. However, HPLC is a relatively slow, costly technique that requires extensive sample preparation and clean-up process and thus not suitable for urgent assay needs. On the other hand, immunochemical assays techniques, which are used for TDM of aminoglycosides and vancomycin, use the cheaper and easy-to-use instrumentations. To date, no technique allows simple and rapid determination of unbound β-lactam plasma concentration, which is ideally required for TDM [37].

TDM of β-lactams in an ICU may be appropriate because underdosing is associated with worse clinical outcome; PK changes are frequently large and unpredictible, even when creatinin clearance is used to guide dosage adjustment; suboptimal drug exposures may be important in the development of antimicrobial resistance.

Conclusion

Determining the optimum dosing strategy for β-lactams in critically ill patients is very important. Data from various pharmacokinetic/pharmacodynamic analysis suggest that a clinical difference between continuous/prolonged and intermittent infusion of those antibiotics still exists. Based on literature data, it seems reasonable to use the continuous or prolonged infusion regimen of β-lactams, because improved outcome can be achieved by prolonging the T > MIC. However, until the clinical benefits are clearly confirmed by well-designed large randomized controlled trials, β-lactams are not recommended for routine use as prolonged or continuous infusion. Pharmacoeconomic analysis of these regimens should also be included in future trials.

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CASE REPORTS

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Surgical treatment of disloced fracture of the scapula column and glenoid: A 22-year follow-up

Hirurška fiksacija frakture sa dislokacijom vrata i glenoida lopatice: 22 godine praćenja

Desimir Mladenović, Marko Mladenović , Predrag Stojiljković, Ivan Micić, Saša Karalejić

Clinic of Orthopaedics and Traumatology, Clinical Center Niš, Niš, Serbia

Abstract

Introduction. Most scapular fractures are caused by high-impact blunt injuries, often as the result of motor vehicle accidents, fall from height, etc. In 80% to 90% of cases, scapula fractures are associated with multiple injuries (clavicle fracture, rib fractures, humeral fracture, pulmonary injury, brachial plexus injury). **Case report.** We presented scapular fracture in a 27-years-old male who had sustained a work-related injury when a ground soil brick machine pressed him. Fracture line was identified on radiotherapy and computed tomography scan from the distal scapular angle enclosing scapular neck. The whole lateral part of the scapula was dislocated laterally from the scapular body. Scapular fracture was treated operatively. The posterior approach was used for reposition, while for fixation after reposition we used two Blunt clamps. We presented functional outcome 22 years after the injury and the surgical treatment. The patient can perform all physical activities, still works, and there is no need to remove the ostheosynthetic material as it causes no discomfort nor problems. The strength of the shoulder muscles is estimated as physician as the grade 5. **Conclusion.** Displaced intra-articular fractures of the scapula should be treated operatively, with open reduction and internal fixation.

Key words:
scapula; thoracic injuries; wounds and injuries; orthopedic procedures; recovery of function.

Apstrakt

Uvod. Većina preloma skapule posledica su dejstva sile jakog intenziteta i najčešće se sreću kod povređenih u saobraćajnim nesrećama ili pri padu sa visine. Oko 80–90% preloma skapule udruženo je sa drugim povredama (prelomi ključne kosti, povrede grudnog koša, brahijalnog pleksusa i dr). **Prikaz bolesnika.** Prikazali smo bolesnika, starog 27 godina, sa prelomom skapule i povredom grudnog koša. Povredu je zadobio pritiskom mašine za presovanje zemlje u procesu proizvodnje cigle. Nakon radiološke dijagnostike, (radiografija, kompjuterizovana tomografija) potvrđen je prelom skapule sa velikom dislokacijom lateralnog dela. Prelom je lečen operativno zadnjim pristupom. Urađena je repozicija preloma i osteosinteza sa 2 Blauntove kopče. Prikazali smo funkcionalni rezultat 22 godine nakon povrede. Bolesnik je u radnom odnosu, izvodi sve pokrete u zglobu ramena bez bola uz izuzetnu mišićnu snagu ramenog pojasa (ocena 5 od strane lekara). Osteosintetski materijal nije izvađen jer ne smeta bolesniku u izvođenju punih pokreta. **Zaključak.** Prelome skapule sa dislokacijom treba rešavati operativno, otvorenom repozicijom i osteosintezom.

Ključne reči:
skapula; toraks, povrede; povrede; ortopedske procedure; funkcija, povratak.

Introduction

The scapula is flat and triangular bone located at the posterior-upper chest and is well protected by the chest wall and muscle mass [1]. Scapula fractures are rare, accounting for less than 1% of all fractures and 3–5% of fractures involving the shoulder [2–4]. Most scapular fractures are caused by high-impact blunt injuries, and often are the results of motor vehicle accidents, falls from height etc. In 80% to 90% of cases, scapula fractures are associated with multiple injuries (clavicle fracture, rib fractures, humeral fracture, pulmonary injury, brachial plexus injury) [1, 2, 5–10].

Scapula fractures are usually treated nonoperatively, while displaced intra-articular fractures of scapula should be treated operatively, with open reduction and internal fixation [2, 4, 11].

Case report

A 27-year-old male sustained a work-related injury when a ground soil brick machine pressed him. Clinical and

Correspondence to: Desimir Mladenović, Clinic of Orthopaedics and Traumatology, Clinical Center Niš, Bulevar Zorana Djindjića 48, 18 000 Niš, Serbia. Phone: +381 64 1785182. E-mail: mladenovicdmarko@gmail.com

radiological examinations (radiography, computed tomograpy) showed the fracture of the body of the right scapula and glenoid, and of the third and fourth ribs; on the right side hemopneumothorax appeared, which was accompanied by traumatic shock. Neurological examination revealed paresthesia of the brachial plexus resulting from compression. Radiography of the right shoulder showed a fracture line starting from the lower third of the glenoid over the column of the scapula, along the external edge of the shaft to the lower angle. According to the classification of glenoid fractures by Ideberg et al. [12], it was type V fracture, i.e. its special variation as the fracture line goes to the lower scapula angle. The lower third of the glenoid was 4 cm from the upper part, the dislocation decreased towards the top of scapula and the fracture line without dislocation was visible on the edge (Figure 1).

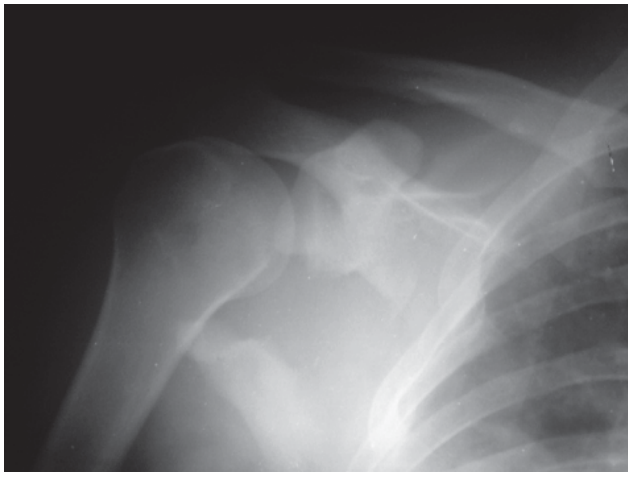

Fig. 1 – Radiography of the right shoulder.

The fractured part of the glenoid and the column of scapula were moved forward and downward, leaning against the surgical neck of humerus. This was the reason of the resistance when trying to perform adduction of the arms – this is why the hand was positioned in 30˚ abduction and external rotation of 10˚. This position was the result of the humeral neck leaning against the detached part of the glenoid which represents the obstacle for performing arm adduction.

Before admission, we undertook the reanimation measures and management of traumatic shock and hemopneumothorax. The attempted orthopedic reposition – arm traction and loosening the contact between the humeral neck and detached part of the glenoid failed. Forced abduction was maintained, as well as paresis of the brachial plexus.

Six days after sustaining the injury the open reduction and fixation of the right scapula column was performed by applying the Judet posterior approach. After sedation and intubation, the patient was placed in the lateral position and the inverted L-incision was performed – vertical cut along the external scapula edge and horizontal edge along the column of the scapula (Figure 2).

After cutting the deltoideus muscle attachment we reached the infraspinatus muscle which was further partly

Fig. 2 – Surgical approach: L-incision along the external right scapula edge.

detached from the attachment in the *fossa infraspinatus*. We further reached *m. teres minor*, then *caput longum m. triceps brachii* which was located under the shaft of *teres m. teres minor*; *m. infraspinatus* was attached to the scapula column. The attachment of *m. teres minor* was also cut to enable a better approach to the column of the scapula. A particular attention was paid to the nerves and the vascular elements, i.e. *a.* and *n. subscapularis* taking care of *a. circumflexa humeri*, *a. circumflexa scapularis,* as well as *n. axillaris* which passed under the *m. teres minor*.

After reaching the fractured area, 90˚ arm abduction was performed as well as the traction which loosened the head and neck of the humerus and prevented their exerting the pressure on the detached part of the glenoid. Thus, a space was provided for the reposition of the glenoid and the column of scapula, taking care not to cause fracture of the scapular body. After the reposition of the glenoid we placed two Blaunt clamps in the massive column of the scapula, close to the glenoid (Figure 3).

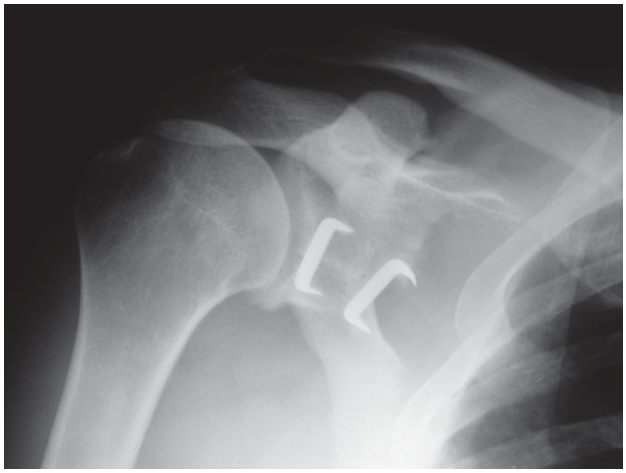

Fig. 3 – Radiography of the right shoulder after the surgery.

Suturing of the lower part of the posterior articular capsule was also, done. A drain was inserted into the operative wound and Desault's bandage was used for the right shoulder – the patient was advised to wear it for three weeks. Three days after the operation, arm paresthesia disappeared. Three weeks later, physical therapy began, lasted two months, and soon after the patient began to work.

Twenty-two years after the operation, clinical examination was performed as well as radiography of the right shoulder which showed the two Blaunt clamps in the column of the scapula, immediately along the edge of the glenoid. There were no radiological signs indicating arthrosis of the shoulder joints and periscapular ossification, and the fracture healed. Disabilities of the arm, sholder and hand score (DASH) [13] was 7.5, while Constant and Marley Score was 91. In both left and right shoulder joints there was a full scope of movements, without pain (Figure 4). The patient could perform all physical activities, still worked, with no need to remove the ostheosynthetic material as it caused no discomfort nor problems. The strength of the shoulder muscles was estimated by the physician as the grade 5.

Fig. 4 – Functional outcome 22 years after the injury.

Discussion

Owing to being protected by the chest wall and muscles of the shoulder belt, scapula fractures are rare, accounting for less than 1% of all bone fractures [1–3]. Fractures are usually caused by high-impact blunt traumas and usually occur concomitantly [14–16]. These fractures are commonly associated with the fractures of clavicula, resulting in the phenomenon of the "floating shoulder". The degree of dislocation and the scope of ligament lesions strongly influence the decision whether to perform the osteosynthesis of the clavicula or not, and thus indirectly shorten the column of the scapula and attain the shoulder stability [6, 17]. Scapula fractures are usually associated with hemopneumothorax, which was diagnosed in the presented patient, as well, while damage of the pulmonary parenchyma caused by the fragments of a fractured scapula is not so common [5–7, 18]. Disrupture of the brachial plexus is also possible [19], as reported here.

Intra-articular glenoid fracture is very rare and results from high-intensity trauma.

There are different types of scapular fractures: fractures of the scapular shaft, neck of the scapula, glenoid rim, glenoid fossa, apophyseal fractures (coracoid, acromion, spina scapulae) and combinations of these types of fractures. Traditionally, scapular fractures are treated conservatively. Indications for surgical treatment are: intra-articular displacement greater than 5 mm, fractures of the glenoid rim associated with dislocation or subluxation of the humeral head, unstable fractures of the scapular neck, severity of displaced apophyseal fractures and floating shoulder [1–6].

Types IV and V glenoid fractures lead to the dislocation of fragments, and the fracture line, over the scapula column, affects the scapula shaft, as well [5, 11, 12]. These types of fractures require open reduction and internal fixation, aiming to achieve an ideal reposition of the articular surface, i.e. the scapular glenoid. With the reposition of the glenoid and the scapular column, the reposition of scapular shaft fragments is also achieved.

The surgical procedure included humerus traction. We managed to move the humeral head from the fracture cavity, thus providing the ground for proper reposition of the glenoid and scapular column and placing the Blaunt clamps on the column of the scapula, just along the edge of the glenoid. We attained normal anatomic and biomechanics' ratio in the glenohumeral and scapulothoracal joints, while the ration in the acromioclavicular and sternoclavicular joints did not change in the initial injury incident, which provided for quicker recovery and regaining of the full function of the injured shoulder joint.

The literature rarely describes cases of the scapular spine nonunion [20], as well as the heterotopic ossification along the lateral edge of the scapula [21]. In this case, radiography shows healing of the scapular body, spine and glenoid, but also the absence of the heterotopic ossification.

Conclusion

Displaced intra-articular fractures of the scapula should be treated operatively, with open reduction and internal fixation.

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CASE REPORT

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Bilateral triple renal pelvis: A case report

Obostrani trostruki pijelon

Tomislav Pejčić*, Miodrag Aćimović*†, Zoran Džamić*†, Helena Maksimović‡, Biljana Marković†‡, Jovan Hadži-Djokić§

***Urological Clinic, ‡Center for Radiology and Magnetic Resonance Imaging, Clinical Center of Serbia, Belgrade, Serbia; †Faculty of Medicine, University of Belgrade, Belgrade, Serbia; §Serbian Academy of Sciences and Arts, Belgrade, Serbia**

Abstract

Introduction. Triple renal pelvis is an extremely rare variation of the renal collecting system. To the authors' knowledge, bilateral triple renal pelvis has not yet been described in the literature. **Case report.** A 55-year-old man was hospitalized due to papillary bladder cancer, detected on ultrasonography. As incidental finding, intravenous urography revealed bilateral triple renal pelvis. Six weeks after transurethral resection of the bladder tumor (TURB) the patient was admitted again, for the second TURB. Computed tomography-urography confirmed the presence of bilateral triple renal pelvis. **Conclusion.** The unique case of bilateral triple renal pelvis was presented as an extremely rare variation of the renal collecting system.

Key words:
urinary tract; congenital abnormalities; diagnosis.

Apstrakt

Uvod. Trostruki pijelon predstavlja izuzetno retku promenu sabirnog sistema bubrega. Koliko je autorima poznato, obostrani trostruki pijelon do sada nije opisan u literaturi. **Prikaz bolesnika.** Muškarac, star 55 godina, primljen je na bolničko lečenje zbog papilarnog tumora bešike viđenog tokom ultrazvučnog pregleda. Kao uzgredan nalaz, na intravenskoj urografiji viđen je i obostrani trostruki pijelon. Šest sedmica posle transuretralne resekcije tumora bešike (TURB) bolesnik je ponovo primljen radi planiranog drugog TURB. Kompjuterizovana tomografija-urografija potvrdila je postojanje obostranog trostrukog pijelona. **Zaključak.** Prikazan je jedinstveni slučaj obostranog trostrukog pijelona, kao izuzetno retka promena sabirnog sistema bubrega.

Ključne reči:
urinarni trakt; anomalije; dijagnoza.

Introduction

The prevalence of congenital anomalies of the kidney and urinary tract (CAKUT) in children is relatively high, 0.3–0.96% [1, 2]. In the prenatal period, CAKUT comprise about 20–30% of all identified anomalies [3]. The most frequent CAKUT in children are vesicoureteral reflux (VUR) and ureteropelvic junction (UPJ) obstruction.

All CAKUT can be anomalies of the kidney (anomalies of the number, ascent, rotation, form and fusion, anomalies of renal vasculature), anomalies of the renal collecting system (RCS) and anomalies of the ureter and the lower urinary tract.

The most common anomalies of the RCS are: absent, rudimentary, double or multiple pyelon, intrarenal and extrarenal pyelon, congenital hydronephrosis and diverticulum of the pyelon, which can occur unilaterally, or bilaterally [4]. The prevalence of unilateral duplex kidney is 1.8%, while the prevalence for bilateral condition is 0.3% [5]. Some of the anomalies of RCS are associated with the organ dysfunction, while other can be considered as anatomical variations [6].

The variations of the collecting system development can be explained by various embryological events; at the 4th week of gestation, ureteric buds grow from the distal portion of the nephric or Wolffian duct and come in contact with the metanephric mesenchyme. This contact induces the so-called mesenchymal-epithelial interaction in which the metanephric mesenchyme induces the ureteric bud to branch and divide. In the same time, the ureteric bud induces the metanephric mesenchyme to induce the formation of nephrons. From the 20th to the 22nd week, ureteric bud branching is completed. After that, peripheral branch segments extend to form the collecting ducts. From the 22nd to the 24th week, the central segments of the collecting system continue to grow and dilate, forming the renal pelvis and calyces.

The duplication of the renal pelvis might be the result of early beginning of ureteric bud branching (pyelon fissus);

Correspondence to: Tomislav Pejčić, Urological Clinic, Clinical Center of Serbia, 11 000 Belgrade, Serbia; Phone: +381 11 2121 616, +381 66 8301 085. E-mail: tomislav_pejcic@vektor.net

in some cases, the ureteric bud branches very early, so the two ureteral buds are moving toward the metanephric blastema (ureter fissus) (Figure 1). If the two ureteric buds arise from the nephric duct, the result is complete duplication, or a duplex renal pelvis with two separate ureters (Figure 2). The triplication of renal pelvis is the result of the additional division of the ureteric branches that make the renal pelvis. This variation is known as triple or trifid renal pelvis and it is extremely rare.

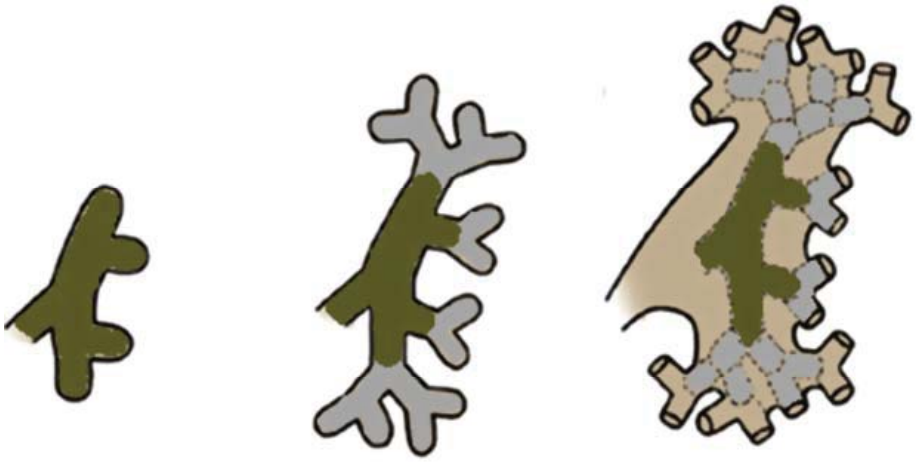

Fig. 1 – Ureteric bud branching (adapted from ref. [7]).

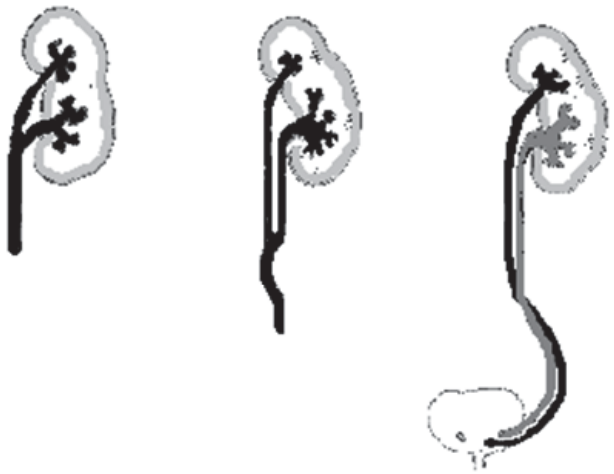

Fig. 2 – Duplex kidneys: bifid renal pelvis, ureter *fissus* and duplicated ureter.

Case report

A 55-year-old man from southern Serbia was hospitalized due to 2 cm large papillary bladder tumor, detected on ultrasonography. As incidental finding, intravenous urography (IVU) revealed a bilateral triple renal pelvis. The patient underwent complete transuretheral resection of bladder (TURB) tumor, located on the bladder base, on the left side. The pathological examination confirmed low grade transition cell cancer (TCC), stage T1. Six weeks after TURB, patient was admitted again, for second TURB. Computed tomography-urography confirmed the presence of bilateral triple renal pelvis (Figure 3).

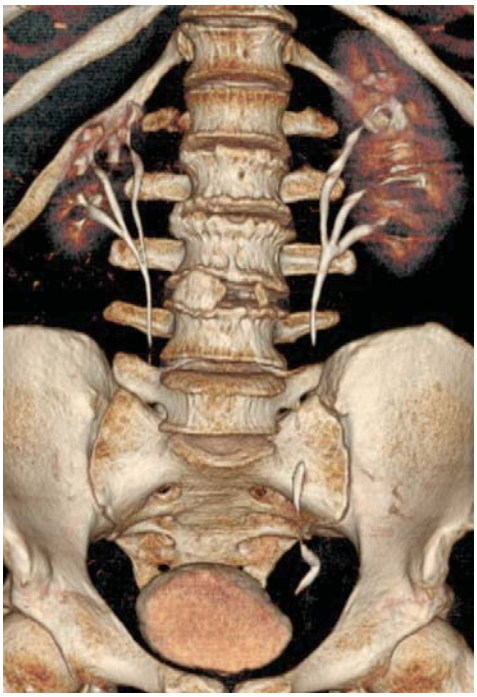

Fig. 3 – Computed tomography-urography presenting bilateral triple renal pelvis. In both kidneys, three separate renal pelves drain separate calyces. The hypoplastic right kidney.

Discussion

Current classification of RCS branching variations makes a difference between terms “duplex kidneys” and “duplex RCS” [8]. Duplex kidney denotes two separate pelvicalyceal systems, while duplex RCS denotes pelvicalyceal systems which can drain into single, bifid or two separate ureters. Two RCSs can join at the level of the pelviureteric junction and drain into the single ureter (bifid pyelon, or pyelon fissus); bifid ureter, or ureter fissus, denotes the two ureters that unite

proximally to the bladder. Double RCS denotes the two pelvicalyceal systems with the two separate ureters that open separately in the bladder (complete duplication).

The duplex kidney has nine times higher risk for developing pelvicalyceal dilation and chronic pyelonephritis, than the non-duplex kidney. This could be explained by the higher prevalence of reflux in patients with duplex kidneys in the childhood. In adults, duplex kidney is seldom associated with pathological conditions. In some cases, urine can move from one branch to another, producing the phenomenon, called "yo-yo" effect or "saddle reflux". It is possible that this phenomenon can sometimes be associated with the flank pain [9].

The etiology of duplex or multiple RCS is still poorly understood, as in all CAKUTs. It is clear that it is associated with the pattern of the ureteral bud branching, in various branching generations. However, exact signalling pathways that determinate the branching morphogenesis of the ureteric bud during the mesenchymal-epithelial interaction are still unclear. It is possible that the most important signalling for ureteral branching is bone morphogenetic protein-activin like kinase 3 (BMP-ALK3) signalling [10]. The pattern of ureteric bud branching depends on ALK3: activation of ALK3 induces bifid ureteric branching, while inactivation of ALK3 promotes trifid branching and increases the number of first and second-generation branches [11, 12]. It is known that a variety of CAKUTs share common genetic etiology; the gene encoding the nuclear steroid hormone receptor ESRRG is a candidate gene for CAKUT [13].

From the clinical point of view, anomalies like duplex or multiple RCS are significant only if they are associated with some pathological conditions; in their absence, they may be considered as anatomical variations. Generally, complete RCS duplicity may be associated with VUR and dilated pyelocalyceal system, while partial RCS duplicity is usually of no clinical significance.

Triple renal pelvis was described for the first time by Feilden [14] in 1929. So far, only few cases have been published, describing triple renal pelvis associated with UPJ, double ureters and solitary kidney [15–17]. In the presented case, the right kidney was hypoplastic, probably due to a common genetic cause that led to RCS triplicity. Also, there is a possibility that the patient had transient VUR and/or pyelonephritis in the early childhood.

Conclusion

Triple renal pelvis is an extremely rare variation of the renal collecting system. Like the other cases of partial renal collecting system duplicity/multiplicity, it is seldom associated with pathological condition in adults. However, if associated with vesicoureteral reflux or pyelonephritis in the early childhood, it can be followed by renal function impairment. The presented case is interesting because to the authors` knowledge, bilateral triple renal pelvis has never been described in the literature before.

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CASE REPORT

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Unilateral galactocele in a male infant

Jednostrana galaktocela kod muškog deteta

Aleksandar Vlahović*†, Slaviša M. Djuričić‡§, Sladjana Todorović‖

***Department of Plastic and Reconstructive Surgery, ‡Department of Clinical Pathology, ‖Department of Endocrinology, Mother and Child Health Care Institute of Serbia „Dr Vukan Čupić", Belgrade, Serbia; †Faculty of Medicine, University of Belgrade, Belgrade, Serbia; §Faculty of Medicine, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina**

Abstract

Introduction. Galactocele, generally occuring in young women during or after lactation, is an extremely rare cause of breast enlargement in infants and children of exclusively male gender. Only 26 cases have been published so far, including two our cases. **Case report.** We described unilateral, cystic, breast enlargement, without any endocrinologic and other abnormalities in a 29-month-old boy. A typical clinical and histopathologic presentation of galactocele was followed with a complete excision. **Conclusion.** This was a 27th well documented case of galactocele in a male infant with typical clinical and histopathologic presentation. There are several hypotheses regarding etiology of the lesion, but it is likely to be multifactorial. Because of its extreme rarity, there are some difficulties in differential diagnosis and treatment options of galactocele in male infants.

Key words:
breast neoplasms; child, preschool; diagnosis; histological techniques; magnetic resonance imaging.

Apstrakt

Uvod. Galaktocela se obično javlja kod mladih žena za vreme ili nakon laktacije i predstavlja veoma redak uzrok uvećanja dojke kod odojčadi i dece, isključivo kod muškog pola. Do sada je objavljeno samo 26 slučajeva, uključujući i naša dva slučaja. **Prikaz bolesnika.** Opisano je jednostrano, cistično uvećanje dojke kod deteta, uzrasta 29 meseci, bez endokrinoloških ili drugih poremećaja. Opisana je tipična klinička i histopatološka slika galaktocele koja je bila praćena njenom kompletnom ekscizijom. **Zaključak.** Ovo je 27. kompletno dokumentovan primer galaktocele kod muškog deteta sa tipičnom kliničkom i histopatološkom prezentacijom. Postoji nekoliko pretpostavki u vezi sa etiologijom promene, ali najverovatnije postoji više uzročnika. Zbog njene izrazite retkosti, postoje određene poteškoće u određivanju diferencijalne dijagnoze i pristupa u lečenju galaktocele kod muške dece.

Ključne reči:
dojka, neoplazme; deca, predškolska; dijagnoza; histološke tehnike; magnetska rezonanca, snimanje.

Introduction

Galactocele has been described as a cystic enlargement of the mammary gland containing milk or milk-like fluid [1]. It generally occurs in young women during or after lactation [2]. Galactocele is a very rare cause of breast enlargement in infants and children [1–3]. Because of its rarity, there are many difficulties in diagnosing, treatment and attempts to explain pathogenesis of galactocele in early childhood. We have recently described two new cases of galactocele in boys with a detailed analysis of cases published in medical journals in English and other languages [4]. Cattani [5] reported the first case of a galactocele in male infants back in 1880 and so far now only 26 cases have been published.

We here presented another case of unilateral galactocele with a typical clinical and histopathologic presentation in a 29-month-old boy, without any endocrinologic and other genetic, clinical, and laboratory abnormalities.

Case report

A 29-month-old male infant was referred with a 16-month history of unilateral left-sided, slowly progressive breast enlargement (Figure 1). The child was born at term by normal vaginal delivery after an uneventful pregnancy. There was no history of nipple discharge, trauma, infection, maternal medication, contact with estrogen products, or familial breast problems. Clinical examination showed a cystic,

Correspondence to: Aleksandar Vlahović, Department of Plastic and Reconstructive Surgery, Institute for Mother and Child Health Care of Serbia „Dr Vukan Čupić", Radoja Dakica Street 6-8, Belgrade, Serbia. Phone +381 11 7 462 462,
E-mail: aleksandarvlahovic@yahoo.com

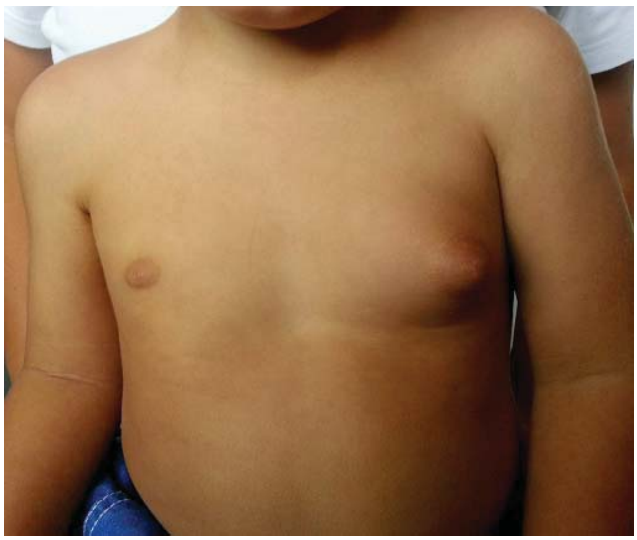

Fig. 1 – Left-sided galactocele in a 29-month-old boy.

painless, freely moveable lump of the left breast, 50 × 40 × 30 mm in size. The right breast was normal. The left-sided nipple and areola were larger with no signs of inflammation. The external genitalia were normal. Both testes were prepubertal, 1–2 mL in size. There were no signs of puberty or endocrinologic abnormalities. Laboratory investigations including complete blood count, blood glucose, serum electrolytes, renal and liver function tests, serum lipid profile, and urinalysis were all within the normal range. Endocrine evaluation revealed levels of luteinizing hormone, follicle-stimulating hormone, estradiol, cortisol, thyroid-stimulating hormone, prolactin and thyroxin within normal range. Chromosomal analysis revealed normal male karyotype 46, XY. Magnetic resonance imaging (MRI) demonstrated an unilateral, unilocular cystic breast mass 43 × 18 mm in size (Figure 2). The right breast had a normal MRI appearance. The cystic mass was then excised completely using semicircular intra-areolar incision (Figure 3). The postoperative course was uneventful.

Microscopic examination of the resected specimen revealed an unilocular, irregularly shaped cyst with smooth, focally rugged inner surface. Thin, fibroelastic wall of the cyst was lined by columnar epithelium. In some of epithelial cells, clear vacuoles were nicely visible as an expression of apocrine secretory process. Cyst wall was poorly defined from the surrounding mammary fibrous tissue containing rare terminal duct lobular unites (Figure 4).

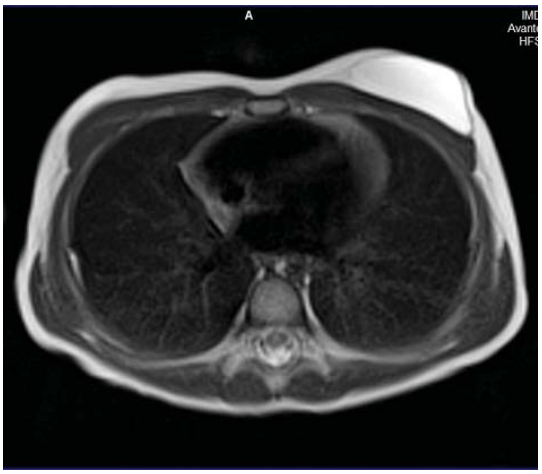

Fig. 2 – Magnetic resonance imaging revealing cystic lesion at the left side of the thorax.

Fig. 3 – Intraoperative view of excised galactocoele.

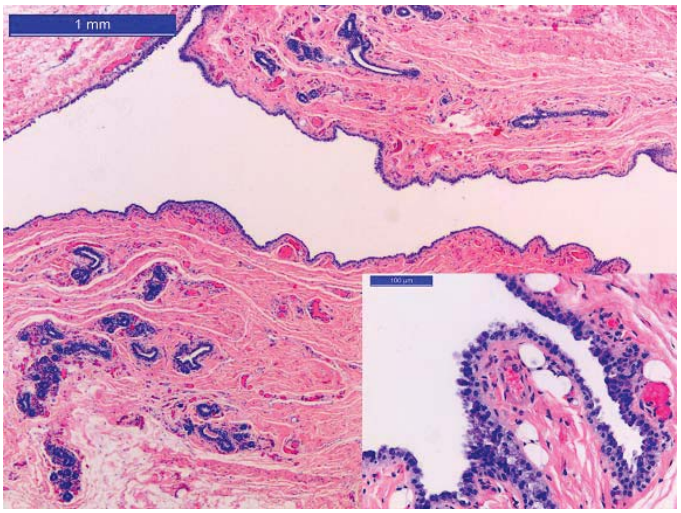

Fig. 4 – Histopathology of galactocele with a poorly defined, thin fibrous wall and the surrounding mammary fibrous tissue containing one terminal duct lobular unit. Galactocele is lined by the columnar epithelium (hematoxylin and eosin, × 25); Some of the epithelial cells show clear intracytoplasmic secretory vacuoles (inset - hematoxylin and eosin, × 250).

Seven months after the surgery there were no signs of recurrence or any other pathological abnormalities (Figure 5).

Fig. 5 – Clinical appearance 5 months postoperatively.

Discussion

Galactocele generally occurs in young women during or after lactation because of the continuous production of milk with impeded evacuation which leads to engorgement and cystic dilatation of the mammary ducts. The pathogenesis of the condition is considered so simple that, with the exception of one of the major textbooks of pathology, Sternberg, it is not even mentioned in either Rosai, Silverberg or Anderson [3]. Galactocele paradoxically and extremely rarely may be the cause of breast enlargement in infants and children, exclusively of male gender [1–4].

The three major factors have been suggested to be important for the development of galactocele in young boys: previous or present stimulation by prolactin, the presence of secretory breast epithelium, and ductal obstruction. Some authors suggest that galactocele may develop after a local nipple trauma and inflammation which induce enlargement of small and silent retention cyst already formed in the neonatal period [1, 2]. It was also postulated that it could develop due to unsuccessful hollowing of ducts due to lesser sensitivity of male breast to the maternal hormones responsible for canalization of the buds and their transformation into lactiferous ducts [3]. Some authors believe that etiology and pathogenesis of galactocele in male infants are multifactorial [1, 2].

We have recently described two new cases of galacatocele in young boys with analysis of 26 well documented cases in the world medical journals in English and other languages published until 2012 [4]. The analyzed articles were usually single case reports. There was only one article describing three [6] and two articles describing two cases, respectively [4, 7]. Unilateral involvement predominates and only one third of patients had bilateral galactocele (8/26) [4]. The median age of onset was 7 months, and the median age of clinical presentation 15 months (range from 2 to 72 months). Only one patient had breast enlargement since birth. The onset of the disease in the presented patient at the age of 16 months, and clinical presentation of unilateral galactocele at the age of 29 months, respectively, were in the expected age range.

The presented patient and the most of the previously reported patients were without any developmental and clinical abnormalities, including endocrinological. However, one previously reported 28-month-old boy with unilateral galactocele had persistent hyperprolactinemia [8] and another 18-month-old infant with bilateral breast involvement had elevated insulin-like growth factor-1 because of growth hormone treatment of congenital hypopituitarism [9]. In only 3 reported cases, all with unilateral galactocele, isolated congenital malformation was described: renal dysplasia [1], ventricular septal defect [10], and cleft lip [11].

Differential diagnosis includes lymphatic malformations, at the first place. The dilemma can be resolved by needle aspiration of cyst, which can obtain milk-like fluid suggesting the diagnosis of galactocele. Other diagnostic possibilities include hemangioma, ductal ectasies, hypertrophic mastitis, and also gynecomastia in older boys [4, 6, 7]. Ultrasound examination of galactocele may show well-defined subcutaneous fluid collection or a complex mass [2, 7]. MRI was performed as a diagnostic procedure in 4 cases only, including one of our previously published cases and also this one [2, 4, 7]. There were no specific mammographic findings in children, but plain mammograms can reveal water-fat level, which is characteristic for galactocela in adults [2, 4].

Most authors agree that the best treatment of galactocele is surgical. Simple excision through the intra-areolar incision was curative in all reported cases [2, 4, 8–11], as was in this patient. The needle aspiration of cyst fluid may eliminate the need for the surgery but there are only three such cases reported in the literature [4, 5].

Conclusion

Galactocele is an extremely rare condition in male infants. We presented a 27th case of galactocele in a male infant published in the world literature. The clinical presentation and the age of the patient are typical. There are several hypotheses regarding etiology of the lesion, but it is likely to be multifactorial. Because of its extreme rarity, there are some difficulties in differential diagnosis of galactocele in the pediatric age. Surgical intra-areolar incision is the treatment of choice and was curative in all the reported cases.

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CASE REPORT

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Emotional stress as a cause of syncope and *torsade de pointes* in patients with long QT syndrome

Emocionalni stres kao uzrok sinkope i *torsade de pointes* kod bolesnika sa produženim QT intervalom

Mihailo Vukmirović*, Irena Tomašević Vukmirović†, Lazar Angelkov‡, Filip Vukmirović§

***Center of Cardiology, †Center of Radiology, §Center of Patology, Clinical Center of Montenegro, Podgorica, Montenegro; ‡Institute of Cardiovascular Disease Dedinje, Belgrade Serbia**

Abstract

Introduction. Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by the prolongation of QT interval and high risk propensity of *torsade de pointes* (TdP) that can lead to syncope, cardiac arrest and sudden death. Episodes may be provoked by various stimuli depending on the type of the condition. **Case report.** A 25-year-old famele patient was hospitalized due to syncope that occurred immediately after her solo concert, first time in her life. The patient studied solo singing and after intensive preparations the first solo concert was organized. Electrocardiography (ECG) on admission registered frequent ventricular premature beats (VES), followed by polymorphic ventricular tachycardia – TdP that degenerated into ventricular fibrilation (VF). After immediate cardioversion magnesium and beta-blockers were administered. TdP was registered again several times preceded by VES. The corrected QT interval (QTc) was 516 msec. For secondary prevention of sudden cardiac death, a cardioverter defibrillator was implanted, and beta-blockers continued. After a 1-year follow-up there were no recurrent episodes of TdP, and measured QTc was reduced to 484 msec. **Conclusion**. Patients with syncope following intensive emotional stress should be evaluated for malignant arrhythmias in the context of LQTS.

Key words:
syncope; stress, psychological; torasades de pointes; drug therapy; electrophysiologic techniques, cardiac.

Apstrakt

Uvod. Sindrom produženog QT intervala (LQTS) je poremećaj repolarizacije miokarda koji se karakteriše prolongacijom QT intervala i sklonosti ka ventrikularnim aritmijama koje mogu dovesti do sinkope, srčanog zastoja i iznenadne smrti. Epizode aritmija mogu biti izazvane različitim stimulusima, u zavisnosti od tipa LQTS. **Prikaz bolesnika.** Bolesnica, stara 25 godina, hospitalizovana je zbog krize svesti koja se javila neposredno nakon solističkog koncerta. Na prijemnom elektrokardiogramu (EKG-u) registrovane su učestale komorske ekstrasistole (VES), a potom i polimorfna ventrikularna tahikardija – *torsade de pointes* (TdP), koja se degenerisala u ventrikularnu fibrilaciju (VF). Pristupilo se hitnoj električnoj kardioverziji, nakon čega je ordiniran magnezijum i beta-blokatori. U daljem toku, u par navrata, ponovo je registrovana TdP kojoj su prethodile VES. Urađeno je merenje korigovanog QT intervala (QTc) koji je iznosio 516 msec. Zbog sekundarne prevencije iznenadne srčane smrti bolesnici je implantiran kardioverter defibrilator, a nastavljena je i terapija beta-blokatorima. Nakon jednogodišnjeg praćenja nije bilo epizoda ponovnog javljanja TdP, a izmereni QTc redukovan je na 484 msec. **Zaključak.** Bolesnica sa sinkopom nastalom neposredno nakon intenzivnog emocionalnog stresa, trebalo bi da se ispita zbog mogućeg postojanja maligne aritmije u sklopu LQTS.

Ključne reči:
sinkopa; stres, psihički; torsad de puant; lečenje lekovima; elektrostimulator srca.

Introduction

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by the prolongation of QT interval, as well as the high risk propensity of *torsade de pointes* (TdP) that can lead to syncope, cardiac arrest and sudden death. Congenital LQTS is a genetic disease as more than 700 mutations described in 12 genes (LQT 1-12) which tend

Correspondence to: Mihailo Vukmirović, Center for Cardiology, Clinical Center of Montenegro, Ljubljanska bb, 81 000 Podgorica, Montenegro. Phone: +382 20 412 258. E-mail: mihailovukmirovic@t-com.me

to prolong the duration of the ventricular action potential, thus lengthening the QT interval [1]. The three most common forms of the disease, which together account for up to 65% are LQT1, LQT 2 and LQT3 [2, 3]. Episodes may be provoked by various stimuli depending on the type of the condition[2]. In LQT1 episodes of ventricular arrhythmias predominantly occur during sympathetic stimulation or physical activity, especially during swimming [4, 5]. Triggers for life-threatening arrhythmias in LQT2 are often emotional stress, auditory stimuli and rarely occur during sleeping or physical activity [4]. The greatest risk of ventricular arrhythmias in LQT3 is during sleeping or bradycardia [6].

The aim of our case report was to indicate that syncope immediately after intense emotional stress should be evaluated in the context of LQTS.

Case report

A 25-year-old famele patient was hospitalized due to the syncope that occurred immediately after her solo concert, first time in her life. The patient studied solo singing and after intensive preparation the first solo concert was organized. Electrocardiography (ECG) on admission registered frequent ventricular VES (Figure 1) followed by polymorphic ventricular tachycardia (TdP) that degenerated into VF (Figure 2).

After immediate electrical cardioversion, magnesium and beta-blockers were administered. Repetitive TdP was registered several times, preceded by VES. The corrected QT interval (QTc) measured by Bazett's formula was 516 msec (Figure 3).

Laboratory tests did not show abnormalities of electrolytes (Na^+ 142 mmol/L, K^+ 4.8 mmol/L, Mg^{++} 1.02 mmol/L, total Ca^{++} 2.3 mmol/L), nor of thyroid hormones (TSH 0.70 mlU/L, FT4 12.6 pmol/L, FT3 3.5 pmol/L) and drug induced QT prolongation also was excluded. Ultrasound of the heart showed normal heart size cavities, preserved global systolic function of the left chambers, ejection fraction was estimated at 60%. There was no sudden cardiac death in her family. QTc measurements were performed on her family members, but normal values were obtained. Due to technical limitations genetic mutations analysis was not performed. Cardioverter defibrillator (ICD) was implanted due to high risk of sudden cardiac death. Permanent cardiac pacing with continuously treatment of β-blockers (propranolol 120 mg *per* day) prevented bradycardia and 'short-long-short' cycle length sequence

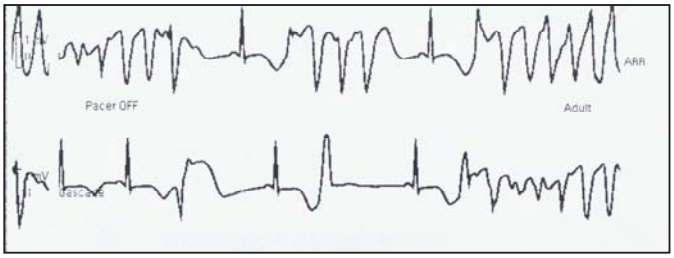

Fig. 1 – Electrocardiography (ECG) on admission registered frequent ventricular extrasystoles (VES) followed by *torsade de pointes*.

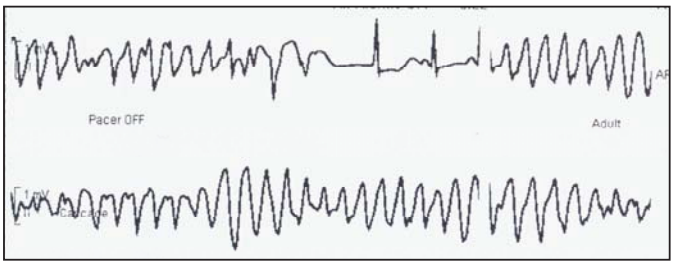

Fig. 2 – *Torase de pointes* degenerated into ventricular fibrilation.

Fig. 3 – Corrected QT interval (QTc) measured by the Bazett's formula was 516 msec.

and reduced QT interval. Recurrent episodes of TdP were not registered during a 1-year follow-up and the measured QTc was reduced to 484 msec (Figure 4). The patient is well now, but stopped singing.

Fig. 4 – Atrial stimulation reduced QTc to 484 msec, but with low-amplitude and the most prominent notched T-waves in precordial leads.

Discussion

LQTS is characterized by the corrected QT interval prolongation leading to TdP and sudden cardiac death. The most frequent LQTS phenotype is LQT2, accounting for 35–40% of the LQTS phenotypes and mutations [2, 3].

The diagnosis of LQTS is not easy, because 2.5% of the healthy population have the prolonged QT interval and 10–15% of LQTS patients have the normal QT interval[7]. A commonly used criterion to diagnose LQTS is the Schwartz et al. [8] LQTS "diagnostic score". The current criteria are based on clinical history, family history and ECG findings.

According to these criteria the presented patient had syncope with stress, QTc more than 480 msec, TdP was registered as well as notched T-wave at least 3 leads which indicates the total score of 8 points and leads to the high probability of LQTS. Namely, in the presented patient the low-amplitude and the most prominent notched T-waves were registered in precordial leads, while 12-lead surface ECG) at rest showed a prolonged corrected QT (QTc) interval with low T-wave amplitude and a double-notched T-wave morphology indicating LQT2 [9]. The prolong QTs interval showed no further extension during exercise testing which also could indicate LQT2 type. These facts also support life-threatening ventricular arrhythmias occuring immediately after emotional stress.

Cardiac activity is influenced *via* autonomic fibers of the sympathetic and parasympathetic nervous system. In patients with congenital long QT syndrome, noradrenaline and adrenaline as predominant mediators of sympathetic action commonly trigger *torsade de pointes* in a so far unknown mechanism. The human ether-a-go-go-related gene (hERG or KCNH2*)* encodes the α subunit of the channel underlying the rapid components of rectifier potassium current (I_{Kr}), which is crucial for the repolarization of cardiac action potentials (AP) [10]. There is increasing evidence that hERG/I_{Kr} channels are modulated by various G protein-coupled receptors including α- and β-ARs, which act through the intracellular signaling modulators cAMP, protein kinase A (PKA), and protein kinase C (PKC) [11]. Malfunction of slow (I_{Ks}) and rapid (I_{Kr}) components of rectifier potassium current (Ik) may play important role in arrhythmias in long QT [12]. Namely, the length of the cardiac action potential is largely determined by both I_{Kr} and I_{Ks} [12]. The rapid component of delayed rectifier potassium current (I_{Kr}) is modulated by β-adrenergic stimulation, so the high dose of catecholamines due to intense emotional stress leads to the prolongation of QT interval particularly in patients with congenital prolonged QT interval with the consequent induction of TdP [13]. Pheochromocytoma as well as another clinical application of high-dose catecholamines like dobutamine–atropine stress echocardiography is often associated with QT prolongation and ventricular arrhythmias like *torsades de pointes* [13, 14].

Beta-blockers, preferably a non-selective beta-blocker such as propranolol or nadolol, are the first line therapy in patients with LQTS for minimizing effects of the adrenergic stimulation [15]. These drugs reduce QT hysteresis and decrease dispersion of repolarizatio and may normalize response of repolarization to adrenergic stimulation [16]. Beta blockers also attenuate the beta receptor mediated enhancement of L-type calcium channels and restore balance of cardiac ion channel forces [16]. These drugs are not completely protective in preventing cardiac events such as syncope, aborted cardiac arrest and sudden cardiac death particularly in patients with symptoms prior to therapy, younger age, longer baseline QTc (> 500 msec), and a genotype other than LQT1 [16].

ICD is the most successful therapy for the prevention of sudden cardiac death. According the to current recommendations, implantation of an ICD along with the use of beta-blockers is recommended for LQTS patients with previous cardiac arrest, so the presented patient was implanted ICD (Class I, Level of Evidence: A) [17].

Conclusion

Prolonged QT interval is a problem in clinical practice with increasing attention that should be the area of intensive research. Patients with symptoms during or immediately af-

ter intense emotional stress should be evaluated for malignant arrhythmias in the context of LQTS. Improving knowledge about genetic mutations gives hope that genetic therapies, as therapy of the future can stabilize repolarization and reduce the possibility of life-threatening arrhythmias and sudden cardiac death.

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CASE REPORT

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Kidney failure as an unusual initial presentation of biclonal gammopathy (IgD multiple myeloma associated with light chain disease) – A case report

Biklonalna gamapatija (IgD mijelom i bolest lakih lanaca) inicijalno ispoljena bubrežnom insuficijencijom

Violeta Rabrenović*†, Zoran Mijušković†‡, Slobodan Marjanović†§, Milorad Rabrenović‖, Dragan Jovanović*†, Svetlana Antić*, Ljiljana Ignjatović*, Milica Petrović*, Dejan Pilčević*†

***Clinic of Nephrology, ‡Institute of Medical Biochemistry, §Clinic of Hematology, ‖Center of Hyperbaric Medicine, Military Medical Academy, Belgrade, Serbia; †Medical Faculty of the Military Medical Academy, University of Defense, Belgrade, Serbia**

Abstract

Introduction. Immunoglobulin D (IgD) myeloma is a rare disease, about 2% of all myelomas, even rarer when accompanied with another multiple myeloma in biclonal gammopathy. We presented a case of biclonal gammopathy – associated manifestation of IgD myeloma and light chain disease in a patient who initially had renal failure. **Case report.** 37-year-old male approximately one month before hospitalization began to feel malaise and fatigue along with decreased urination. Laboratory analysis revealed azotemia. A dialysis catheter was placed and hemodialysis started. The patient was then admitted to our hospital for further tests and during admission, objective examination revealed pronounced paleness with hepatosplenomegaly and hypertension (170/95 mmHg). Laboratory analysis showed erythrocyte sedimentation rate 122 mm/h, expressed anemic syndrome (Hb 71 g/L) and renal failure dialysis rank: creatinine 1,408 μmol/L, urea31.7 mmol/L. There was two M components in serum protein electrophoresis: IgD lambda and free light chain lambda. Proteinuria was nephrotic rank (5.4 g/24 h), whose electrophoresis revealed 2 M components – massive in α 2 fraction of 71%; 7% in the discrete β fraction, beta 2M /serum 110 mg / L, in urine 1.8 mg/L – extremely high; IgL kappa / lambda index 1 : 13 (reference value ratio 2 : 1). The findings pointed to double myeloma disease: IgD myeloma and Bence Jones lambda myeloma. Bone biopsy confirmed IgD myeloma lambda 100% infiltration medulla predominantly plasmablasts. The treatment continued with hemodialysis 3 times *per* week with chemotherapy protocol bortezomib, doxorubicin, dexamethasone. After 4 cycles of chemotherapy, there was a decrease of IgD, λ – light chains, reduction in proteinuria (1.03 g/24 h), so hemodialysis was reduced to once per week. Six months after treatment initiation the patient underwent autologous bone marrow transplantation. In a 2-year follow-up period double myeloma disease showed complete remission. **Conclusion.** The presented rare form of double myeloma disease with initial renal insufficiency underscores the importance of careful observation and teamwork that can alter the course of this serious disease.

Key words:
kidney failure, acute; multiple myeloma; diagnosis, differential; biopsy; histological techniques.

Apstrakt

Uvod. Imunoglobulin D (IgD) mijelom veoma je retko oboljenje jer čini oko 2% multiplih mijeloma, a još ređe se opisuje njegova udružena pojava sa drugim mijelomom u okviru biklonalne gamapatije. Prikazan je bolesnik sa IgD mijelomom i bolešću lakih lanaca koje su se inicijalno manifestovale bubrežnom insuficijencijom. **Prikaz bolesnika.** Kod muškarca, starog 37 godina, mesec dana pre hospitalizacije javili su se malaksalost, zamaranje i smanjeno mokrenje. U laboratorijskim analizama zapažena je azotemija, pa je plasiran dijalizni kateter i započeto je sa hemodijalizama. Nakon toga hospitalizovan je radi daljeg ispitivanja. Pri prijemu u objektivnom pregledu zapaženo je izraženo bledilo uz hepatosplenomegaliju i arterijsku hipertenziju (170/95 mmHg). U laboratorijskim analizama sedimentacija je bila ubrzana – 122 mm/h, bio je izražen anemijski sindrom (Hb 71 g/L), i bubrežna insuficijencija dijaliznog ranga: kreatinin 1 408 μmol/L, ureja 31,7 mmol/L. U elektroforezi proteina u serumu zapažene su dve M komponente – IgD lambda i slobodni laki lanci lambda tipa. Registrovana je proteinurija nefrotskog ranga (5,4 g/24 h), a elektroforezom proteina u urinu zapažene su 2 M komponente – masivna u α 2 frakciji (71%); diskretna (7%) u β frakciji; beta 2M u serumu 110 mg/L, a u urinu 1,8 mg/L –

Correspondence to: Violeta Rabrenović, Clinic of Nephrology, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia.
E-mail: violettarab@gmail.com

izuzetno povišeni; IgL kapa/lambda indeks 1:13 (normalna vrednost odnosa 2:1). Nalaz je ukazivao na dvostruku mijelomsku bolest: IgD mijelom i Bence Jones lambda mijelom. Učinjenom biopsijom kosti dokazan je IgD mijelom lambda – 100% infiltracija medule, pretežno plazmoblastima. Nastavljeno je lečenje hemodijalizama tri puta nedeljno uz hemioterapiju po protokolu: bortezomib, doksorubicin, deksametazon. Nakon četiri ciklusa hemioterapije došlo je do smanjenja koncentracije IgD, lakih lanaca-λ, smanjenja proteinurije (1,03 g/24 h). Broj hemodijaliza je takođe smanjen na jednu nedeljno. Nakon šest meseci od započinjanja lečenja učinjena je autologna transplantacija matičnih ćelija koštane srži. U periodu praćenja od dve godine kod prikazanog bolesnika osnovna bolest bila je u remisiji. **Zaključak.** Prikazana retka dvostruka mijelomska bolest koja se ispoljila inicijalno bubrežnom insuficijencijom, ističe značaj pažljivog ispitivanja i timskog rada kojim se može izmeniti tok ovog ozbiljnog oboljenja.

Ključne reči:
bubreg, akutna insuficijencija; multipli mijelom; dijagnoza, diferencijalna; biopsija; histološke tehnike.

Introduction

Multiple myeloma is a plasma-proliferative disease characterized by uncontrolled proliferation of a pathologic plasma cell clone, and its incidence is about 10% of all malignancies [1]. Tissue damage in multiple myeloma are complex, but essentially is the immunobiological activity of monoclonal immunoglobulin (Ig). Every abnormal clone of plasma cells normally secretes one monoclonal immunoglobulin, which indicates the type of myeloma (IgG, IgA, IgM, IgD, IgE-kappa and lambda). Joint appearance of two malignant clones, named biclonal gammopathy, is as rare as about 1% [2]. One of the rarest multiple myelomas is IgD myeloma (2%), so its appearance in biclonal gammopathy is also extremely rare. IgD myeloma is often accompanied by complications such as the occurrence of renal failure, thus the treatment and survival of these patients is very uncertain [3]. We reported a patient with IgD myeloma associated with light chain disease with the initial manifestation as renal failure.

Case report

Approximately one month before hospitalization, a 37-year-old male began to feel malaise and fatigue along with decreased urination. Laboratory analysis revealed azotemia, so a dialysis catheter was placed and hemodialysis started. The patient was then hospitalized for further tests and during admission objective examination, pronounced paleness with hepatosplenomegaly, and hypertension (170/95 mmHg) were noted. Laboratory analysis showed erythrocyte sedimentation rate 122 mm/h, expressed anemic syndrome (Hb 71g/L) and renal failure dialysis rank: creatinine 1,408 μmol /L, urea 31.7 mmol /L were presented. There was two M components in serum protein electrophoresis: IgD lambda and free light chain lambda. Proteinuria was nephrotic rank (5.4 g/24 h), whose electrophoresis revealed 2M components – massive in α 2 fraction of 71%, and 7% in the discrete β fraction, serum beta 2M 110 mg/L, in urine 1.8 mg/L – extremely high; IgL kappa / lambda index 1:13 (reference value ratio 2 : 1). The findings pointed to double myeloma disease: IgD myeloma and Bence Jones lambda myeloma (Figures 1a and b).

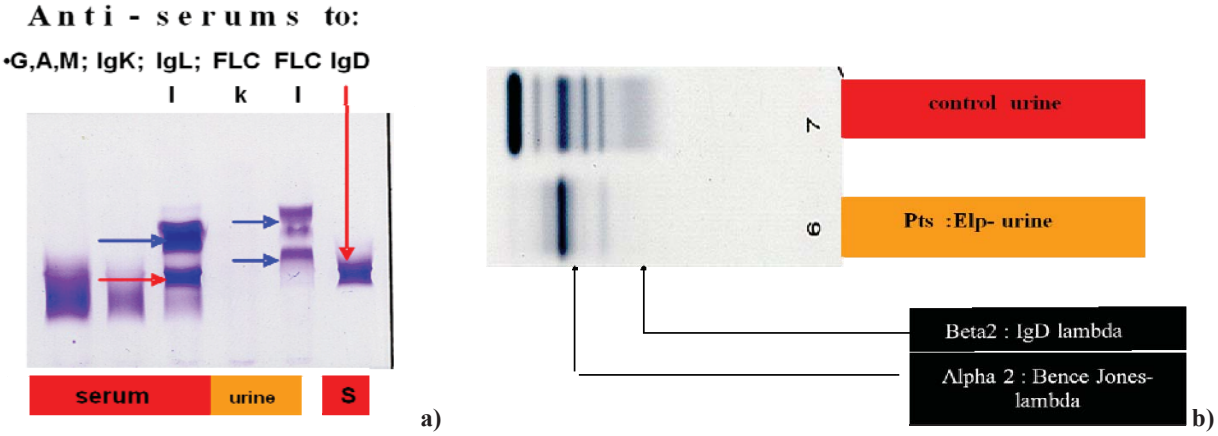

Fig. 1 – Immunofixation (IF) of the serum and urine.
a) IF in the serum shows homogenious fraction to immunoglobulin (IgD) and IgL lambda antibodies (red arrows). IF of the urine confirmed a fraction which belongs to IgD and a fraction of free light chain (FLC) lambda – possible dimmers or tetramers molecules (blue arrows); b) Urine protein electrophoresis confirmed the existence of 2 homogeneous fractions: IgD and FLC lambda.
G,A,M – antibody to class Ig.; IgK – antibody on light chain Ig kappa type; IgL – antibody on light chain Ig lambda type; FLC-k – Free kapa; FLC-l – free lambda; S – serum.

Bone biopsy proved myeloma IgD–lambda, 100% infiltration of the medulla mainly with plasmablasts, CD20-/CD3-/Kappa-/IgG-/IgA-/IgM-/CD138+ (Figure 2).

X-ray indicated osteolytic changes in craniograph and the pelvis (Figure 3).

The treatment continued with hemodialysis 3 times *per* week with the chemotherapy protocol: bortezomib, doxorubicin, dexamethasone. After 4 cycles of chemotherapy, a re-

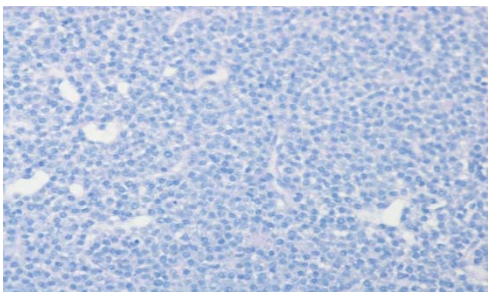

Fig. 2 – Bone biopsy proved myeloma IgD-lambda: 100% infiltration of the medulla mainly with plasmablasts, CD20-/CD3-/Kappa-/IgG-/IgA-/IgM-/CD138+ [periodic acid schift (PAS), × 20].

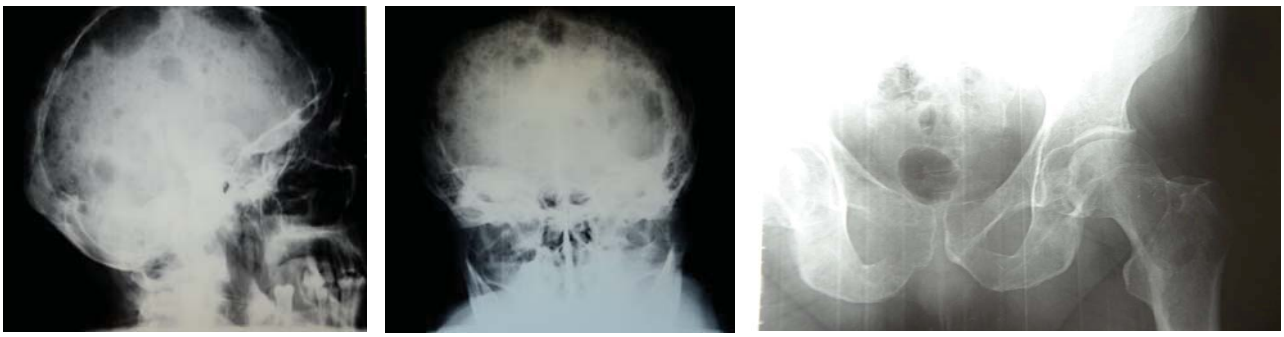

Fig. 3 – X-ray indicated osteolytic changes in craniography and the pelvis.

duction was noted in IgD from 52,888 mg/L, to 3,201 mg /L (ref. value 3–140 mg/L) free light chains from 23,900 mg/L to 4,740 mg/L (ref. value 5,7–26,3 mg/L) and reduction of proteinuria (1.03 g/24 h). Hemodialysis was reduced to once *per* week.

Repeated bone biopsy 5 months after the treatment, showed infiltration of mature plasma cell immunophenotype lambda light chains 40%. Immunophenotype plasma cells: CD138 + / CD20- /CD3- / kappa- / lambda + / cyclin D1 + (Figure 4).

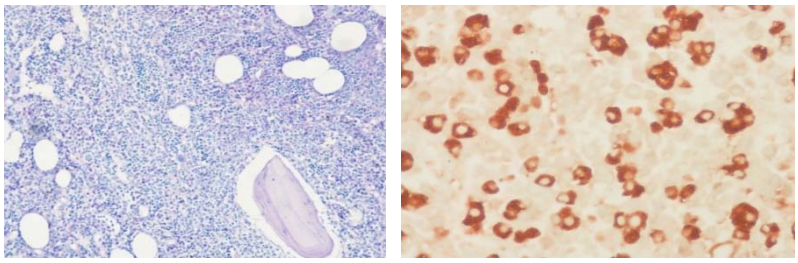

Fig. 4 – Repeated bone biopsy 5 months after the treatment showed infiltration of mature plasma cell immunophenotype lambda light chains 40%. Immunophenotype plasma cells : CD138 +/ CD20-/CD3-/ Kappa-/ Lambda +/ Cyclin D1 + [periodic acid schift (PAS), × 40].

Six months after initiation of the treatment the patient underwent autologous bone marrow transplantation. In a 2-year follow-up period double myeloma disease showed complete remission.

Discussion

Biclonal gammopathy in which the occurrence of IgD myeloma is associated with other myeloma such as in this case of light chain disease is very rare, occurring in about 4% of biclonal gammopathies [3]. However, the very appearance of IgD myeloma is rare which is confirmed by many authors [1–3]. Among them is an interesting study by Kyle et al. [4] who examined 1,027 patients with multiple myeloma and found IgD myeloma with the incidence of 1% [4]. IgD myeloma has an extremely unfavorable course and serious complications, with median survival of about 12 months [3, 5, 6].

In the presented patient there was a combined occurrence of IgD myeloma and Light Chain disease, where the initial manifestation was oliguria with a consequent azotemia of dialysis rank and anemic syndrome. Describing a group of 16 patients with IgD myeloma, Lin et al. [5] observed that renal failure occurs in about 75% of cases. Among other complications, the most common are related to the gastrointestinal tract (38%), bone pain (56%), and loss of body weight (25%).

Renal failure in multiple myeloma can be acute or chronic which is much more frequent. Changes in tubules are dominant while glomeruli and intersticium are affected to a

lesser extent [7]. Renal impairment in multiple myeloma occurs due to different mechanisms – tubule damage caused by immunobiological activity of malignant clones and deposition of immunoglobulin light chains with obstruction of tubules and the consequent development of tubulointerstitial nephritis. The development of renal lesion is effected by hyperviscosity, infection, hypercalcemia, hyperuricemia, medication and many other factors.

Therefore, patients with multiple myeloma and renal failure have many reasons for unfavorable course of treatment and shorter survival [8, 9]. The cases such as the one described by Tharp et al. [10] of a patient with IgD myeloma survival longer than 9 years are rare. They concluded that the survival of IgD kappa myeloma is somewhat better compared to the lambda type.

In patients with acute renal failure (which is more often the case with Light Chain disease as in the presented patient) the favorable results are achieved by removing the light chains either by therapeutic plasma exchange or hemodiafiltration along with chemotherapy application protocol [11].

According to Hutchison et al. [12] the high cut-off hemodialysis is the method of reducing the influence of the concentration of light chains and contributes to recovery of renal function. In recent years, modern protocols and new drugs (thalidomide, bortezomib) significantly improve survival, both through use in treatment as well as induction agents in bone marrow stem cell transplantation [13, 14].

The presented patient received modern treatment protocol (bortezomib, doxorubicin, dexamethasone) and after 4 cycles of chemotherapy, bone biopsy demonstrated a significant reduction of malignant cells. Infiltration of bone marrow in the presented patient initially was 100% mainly plasmablasts, while after 4 cycles of chemotherapy infiltration was 40% plasmacytes. Along with chemotherapy, the patient underwent hemodialysis 3 times a week, with gradual reduction to once *per* week after the establishment of diuresis.

By analyzing 75 patients with IgD myeloma Kim et al. [15] concluded that in the group that was transplanted after induction therapy, the average survival was 30 months while for patients treated with conventional therapy, the average survival was 16,4 months. The presented patient, 6 months after initiation of the treatment underwent autologous bone marrow transplantation and after a 2-year follow-up period double myeloma disease showed complete remission.

Conclusion

The presented rare form of double myeloma disease with initial manifestation of renal insufficiency underscores the importance of careful observation and team work which can alter the course of this serious disease.

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PERSONAL OPINION

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Quo vadis homine? Or where the marriage goes?

Quo vadis homine? Ili: Kuda ide brak?

Rajko Igić

Department of Anesthesiology and Pain Management John Stroger Hospital of Cook County, Chicago, USA, and Department of Clinical Pharmacology, Medical Faculty, University of Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Individuals are consanguineous if they are descended from a common ancestor no more remote than a great, great grandparent. The progeny of consanguineous parents are regarded as inbred. Within a particular society, the population structure and social customs determine the frequency of consanguineous mating; certain marriage requirements as set forth by the church and/or state, are designed to prevent very close mating.

Inbreeding of domestic animals can preserve and fix desirable properties and eliminate unfavorable characteristics from livestock. Closely related animals may be mated to produce pure breeds of animals and select offspring of specific desirable types. However, because homozygote is less fit than heterozygote, inbreeding over a long period risks the loss of vigor in the offspring. Similarly, plants are inbred for improved characteristics, either by self-pollination or crossing with closely related plants.

The situation in humans is far more complex. Genetic effects of inbreeding can be detected in the inbreed individual, in the form of gene doubling. Affected genes appear as a single line in each of the common ancestors but double in the progeny. In other words, modern genetic technology allows us to show how consanguinity reveals recessive inheritance and recessive traits.

One means of reducing the accumulation of undesirable or potentially dangerous genetic material in human population is to prevent conception. Same sex marriage, legalized in some countries, does not produce children and is thus exempt from consanguinity restrictions. If same sex marriage became universally legal, mating among close cousins, or even brothers or sisters, uncle and nephew, and aunt and nice. A same sex marriage without the possibility of conception is the most efficient way to control reproduction, but this idea is not universally accepted. In the first place, only a small percentage of the population would likely be affected, since the heterosexual population is much larger than a homosexual one. Secondly, and more importantly, many people consider a homosexual relationship to be an unnatural, even evil. It thus becomes increasingly difficult to predict in which direction marriage will go.

Marriage at Square One

Each nation or state has its own requirements for what constitutes a valid marriage. These marriage laws form a contract that allows two persons to live together as husband and wife. Most marriage laws apply some restrictions, including a statement that cousins or closer relatives may not marry among themselves.

Every society considers incest as a taboo. An accumulation of recessive traits, including morality, in the progeny of consanguineous mate undermines and weakens society and can impose long lasting social and medical problems. In almost all societies mating between parent and offspring, brother and sister, and among first cousins is considered to be incestuous, and steps were often taken to prevent it. For example, The Dušan's Code (1349) required priests to determine if bride and groom were closely related, and marriages between persons more closely related than fourth cousins were prohibited (Figure 1). According to the Byzantine customs of the time, a widowed daughter-in-law was considered by her father-in-law to be his own blood kin. Families of three or four generations of South Slavs ("zadruga") lived together under similar marriage and sexual restrictions, and punishment for breaking the rules was severe [1].

Nowadays, unions between parent and child or brother and sister, where 50% of the genome is shared, frequently result in abnormal offspring. As a result, these incestuous unions are considered illegal in most societies. An exception is that marriages between uncle and niece or aunt and nephew may be permitted in Southern India [2] and some isolated locations. The closeness of this particular relationship is determined by Napoleonic Code (NC) III to have an Inbreeding

Correspondence to: Rajko Igić, Department of Anesthesiology and Pain Management John Stroger Hospital of Cook County, Chicago, USA. E-mail: igicrajko@gmail.com

Fig. 1 – Mating at the level of the third cousins. According The Dušan's Code, consanguinous matings were considered between uncle and nice, aunt and nephew, first cousins, second cousins, and third cousins, including «full» and «half» siblings in the chain of descent. Full siblings have both parents in common; half siblings have one parent in common. □= male, ○ = female, ◆ = an individual of either sex.

Coefficient F (IC) 1/8. The inbreeding coefficient F presents the probability that an individual receives two identical genes at the same locus.

Marriages between cousins are the most common types of consanguineous mating. They are covered as follow: First cousin marriage (NC IV, IC 1/16), second cousin marriage (NC VI, IC 1/64); and third cousin marriage (NC VIII, IC 1/256). In some societies marriage between cousins was acceptable, as in the Nineteenth Century England when Charles Darwin married his first cousin, Emma Wedgwood [3]. Among first cousin unions, where 1 : 8 genes are shared, the risk of abnormal offspring is 3–5%, as compared to a risk of about 2% for a non-consanguineous union [4]. For marriages between less closely related cousins, the risks seem little if any increased over those for the non-consanguineous population. There is little reason to discourage marriages between less closely related couples, unless they belong to highly inbreed groups where heterozygosis for deleterious genes is often greatly increased. Restrictions of third and fourth cousin marriage appear to be based mainly on social and moral grounds.

Full siblings have both parents in common, and half siblings share only one parent. Marriages of first cousin and first half cousins belong to NC VI and IC 1/32, and those between second cousin and second half cousin belong to NC VII and IC 1/128. In the Middle East today first cousin marriage occurs at a frequency of around 11 to 68%. Due to specific social, traditional and religious factors, consanguinity in Saudi Arabia is very high, with first cousin marriages at approximately 30 percent [5]. Overall consanguinity in a human population is expressed by an inbreeding coefficient α ($\alpha = \sum p_i F_i$; p_i is the relative frequency of inbred individuals with inbreeding coefficient Fi) [6]. The highest inbreeding coefficient is 0.032 in the Andra-Pradesh (India), due to preferential uncle-niece mating. High values of inbreeding coefficients also occur in some other isolated populations, but not in Polar Eskimos, where a careful avoidance of inbreeding keeps this value low (< 0.003). For uncle-niece, aunt-nephew, first cousins, second cousins marriages in human populations round the globe (from Argentina and the USA to France, Italy, and India and Japan) the average inbreeding coefficient is generally about 0.001 or 1 per 1000 [6]. Marriage in the USA and in many other countries, is prohibited "between an ancestor and or descendant; or between a brother and a sister; between an uncle and a niece; or between an aunt and a nephew, whether the relationship is through half or whole blood or adoption" [7].

Marriage at Square Two

In most civilized countries, consanguinity is the main, but not the only reason for the restrictions against marriage between close relatives. Social, moral, and religious factors influence an acceptable degree of consanguinity in many parts of the world.

In contrast to the heterosexual marriage of man and a woman, same sex marriage does not produce children, thus eliminating the dangers of inbreeding. Same sex marriage could become legal among close cousins, brothers, sisters, uncle-nephew, and aunt-nice provided that the social, moral, and religious restraints would permit. If Marcus Tallius Cicero were alive, he would certainly shout: *O tempora! O mores!*

Commentary

Despite current technologies for birth control, the total population of the Earth continues to increase. From time to time, man and nature reduce population growth through wars and various disasters, but such measures are insufficient. Wars, famine, and infective or parasitic diseases that spread among poor and uneducated people are disastrous means of controlling the population explosion.

Perhaps marriage without the possibility of conception, e.g., same sex marriage, could be an additional way to control reproduction. Indeed, some global strategists might push for the existing Marriage Laws to be changed accordingly. The question remains as to how well such a solution would be accepted. As of today, many individuals still consider homosexual unions as unnatural. It is thus unclear where this trend in marriage may go.

Rather than seek such a limited solution to our burgeoning population problem, we should better make efforts towards global peace, spread education to every human being, reduce inequality, and provide social and economic justice. Let us again read Dante Alighieri [8], the greatest poet of the Middle Ages, who suggests in Il Convivio (The Banquet) that the greatest danger to mankind comes from avarice. Wealth is not equally distributed, and the craving for it is the greatest danger to humanity. He believed he had the solution to avoiding war, but his idea unfortunately did not influence the rulers who prefer to solve problems militarily. We do hope that before long strong and creative persons will come up with a modern formula to find the best way for solution of rapidly increasing population problem—the sooner the better.

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LETTER TO THE EDITOR

A comment on the article: *Stošić S, Karanović N.* Health care economics in Serbia: current problems and changes. Vojnosanit Pregl 2014; 71(11): 1055–1061.

Komentar članka: *Stošić S, Karanović N*. Ekonomija zdravstvenog sistema Srbije: tekući problemi i promene. Vojnosanit Pregl 2014; 71(11): 1055–1061.

To the Editor:

In the latest November 2014, issue of the *Vojnosanitetski Pregled* I was pleased to read a remarkable article by Stosic S. and Karanovic N. entitled: „Health care economics in Serbia: Current problems and changes“ [1]. This current topic paper analysed a variety of issues relevant to the health care funding and provision in the Republic of Serbia during the past few decades. It gave a thorough insight into the patterns of funding common to European national health systems as well as their common strengths and weaknesses. The case of Serbia as the largest Western Balkan market was dealt with particular attention. Some of the key weaknesses of current national management and financing practice were properly addressed. Authors provided an excellent insight into the current revenue collection strategies deployed by the National Health Insurance Fund. Key changes such as the introduction of capitation payment for physician salaries and diagnosis-related groups (DRG)-based hospital payment were presented. Particularly interesting was media coverage provided in the article and an explanation of accumulated health care attributable public debt due to delayed payments of drug wholesalers to the manufacturers. Although highly valuable for regional professional audience, according to my opinion this piece of contribution omitted several core developments in the national health economics. Clarification of missing issues is crucial for this current topic paper to be fully comprehensive and up-to-date.

One of such issues is the remnant of top-to-the-bottom thinking so characteristic of former centrally planned socialist economies. With regards to provision of medical services this means that Serbian system tended to be poorly responsive to the real population needs [2]. Demand-based planning of resources to health care although attractive to policy makers couldn't become reality simply due to lack of local evidence. Some of the pioneering cost-of-illness assessments have been conducted and published in high impact journals over the course of the past decade. Prosperity illnesses encompassed by these efforts were risky pregnancies [3], alcoholic dependency [4] and detoxification procedures [5], opioid addiction [6], diabetes mellitus [7], community acquired pneumonia [8], malignant disorders [9], COPD [10], hepatitis C [11] and few others. Many more remain untouched. Reliable field studies on the resource use patterns and costs of care attributable to major illnesses in a peculiar Balkan hospital setting have become a necessity. This fact is emphasized by the substantially different microeconomic setting of high income markets where most health economic assessments are published. It has been proven that such cost-effectiveness conclusive remarks are not simply transferable to the Eastern European health systems. A large part of these Serbian national efforts were orchestrated by the Academia in trials non-sponsored by industry but conducted by one of the two major 5-year fundamental research projects funded by the Ministry of Education Science and Technological Development of the Republic of Serbia (2006–2015). Smaller scale research is being conducted by a variety of state- and private-owned universities and institutes throughout the country funded by internal resources of these facilities.

In a health system showing concerning signs of financial unsustainability as authors properly emphasized, some cutting edge technologies with substantial budget impact might have higher relevance compared to mature economies. Although quite an issue even in markets most abundant with resources such as Switzerland or Japan, these novel technologies in middle income countries of Western Balkans might affect access to other affordable but essential medical services. Back in the 1990s economic assessment of exact burden of these medical technologies in Serbia were virtually unknown and only approximately evaluated based on Western sources. Today academic research cores around the country have made their contributions on radiation oncology [12], monoclonal antibodies [13], implant technologies used in orthopedics and interventional radiology, imaging diagnostics [14] and several other high cost branches of clinical medicine. Such data open opportunities of the first evidence-based resource allocation in Serbian health care [15]. One step further it was proven in a sound methodological design that it is possible to contain costs of care in domestic university hospitals without bargaining for quality by using cutting-edge good clinical practice guidelines [16]. Another successful strategy to cut drug acquisition costs to the system already proven in largest global pharmaceutical markets is generic replacement of brand name medicines [17]. As authors have noticed DRGs based hospital payment and capitation based physician salaries introduction, regardless of few setbacks, will most likely present the bold moves forward for the system, beyond current limitations.

Education initiatives will certainly remain one more key pillar promising long term successes. This is particularly crucial while bearing in mind lagged capacity building efforts in health economics and other interdisciplinary health sciences around most of the Central and Eastern Europe (CEE) [18]. Some of the early shy efforts in this direction were made by establishing first obligatory graduate curricula in Pharmacoeconomics among state owned universities in Kragujevac 2009 to be followed by others. Health economics is slowly becoming an integral part of doctoral programs and there is a growing number of defended doctoral dissertations around the country. Frequency of accredited continuous medical education courses in these interdisciplinary health sciences targeted to the professional audience increased in a parallel manner. An essentially different mindset of traditional academic expert cores around CEE region made these developments more challenging compared to the mature free market economies. One of major moves forward was publishing of the first complete university level textbook on health economics and pharmacoeconomics in Serbian language – pioneering effort for most Western Balkan languages [19]. Frankly speaking, in a cradle of health economics among the US core universities similar things were happening as early as in the 1960s.

Although authors have pointed out the lack of official Health Technology Assessment (HTA) in the country, it is relevant to notice substantial, so far unsuccessful efforts invested into HTA establishment in Serbia. In between 2005 and 2008 there have been two consecutive cycles of the World Bank's investment projects on capacity building and the systemic implementation of the Health Technology Assessment (HTA) in Serbia. Governments of the time responded with "Feasibility Study on HTA Agency in Serbia" and the "Basic Benefit Package on the Way towards Evidence-Based Health Care in Serbia" in the framework of the "Serbia Health Project". Unfortunately, even after a decade of joint efforts there is no mature political will for institutional and systematic assessment of medical technologies in terms of costs and benefits. Unlike Serbia, some „light" or „heavy" model of official HTA agency is already in place in many new eastern EU members with Hungary [20], Poland and Latvia on the lead [21].

With regards to health expenditure dynamics and long term trends in Eastern Europe authors cited the source which although comprehensive at the time of publishing in 2008, seven years later is seriously outdated [22]. Some key economic shifts took place in the meantime while the Russian Federation and most of post-2004 EU members became high-income economies, thus capable of spending more for health care [23]. Another key consequence of global changes ultimately affecting Balkans is the rise of leading emerging Brazil, Russia, India, China (BRICs) countries and their long lasting impact on reshaping global health care market [24]. Relying on WHO estimates on total health expenditure per capita in Serbia in terms of purchasing power parity (PPP$) although falling during key years of global recession we notice serious signs of recovery and increase (PPP$ 1195 in 2008; PPP$ 1163 in 2009 and PPP$ 1250 in 2012) [25]. These promising developments oppose to the pessimistic forecasts in the source article (Projections for the future do not predict increase of public funding for health care) which at the time when original article was written were fully grounded in reality [26].

Many of the bold new advances described in the initial article as well as this comment indicate that the time for changes has inevitable come. Serbian preexisting national difficulties in health care provision only became worsened with accelerated pace of globalization, population aging and worldwide economic crisis. Whether one European health system hosting two centuries of public health tradition shall timely respond to these challenges is yet about to be seen.

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Mihajlo B. Jakovljević
Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia (E-mail: sidartagothama@gmail.com)

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Authors' reply:

After receiving comments of Prof. Jakovljević on our article, we wish to thank him for the explanation in more details of some issues that our article just mentioned, considering that they were not in the main focus, so we had no space to further explore them in the published paper.

Professor Jakovljević pointed out that the Serbian system tended to be poorly responsive to the real population needs. Indeed, the responsiveness, i.e. responding to people's legitimate expectations, as well as improvement of the health of the population they serve and fair financing, are the main goals of health systems according the WHO. The health system is as efficient as it is able to meet these goals, given the resources available to the system.

As Prof. Jakovljević mentioned in the comment, reliable data on the resource use and costs of care in Serbia are lacking, and we would like to add to that transparency of financing, adequate planning and public control are also lacking in many ways. In the comment, based on his outstanding work, Prof. Jakovljević highlights that the assessment of cost/effectiveness of selected groups of interventions may improve the health system performance and we agree that such data are basic for adequate resource allocation. Of course, education of managers in healthcare and their proper decisions are essential for the functioning of health service provision at local and national levels.

However, in our article we address financial sustainability of Serbian health system in general, from revenue collection to payment to the providers of service. Though it might be not emphasized in the article, we believe that increased financing and providers motivation are crucial for improving the efficacy of the Serbian health system. However, based on negative indicators of Serbian economy, we predicted that the funds for health could not be increased. Unfortunately, according to the state budget for 2015, funds for healthcare are even less than in the previous year. Thus, we could expect more "out of pocket" spending for health service and delay of crucial reforms in healthcare in the next few years. Anyway, as we both agree, even within very limited funds, there are many aspects of the health system performance in Serbia that may be improved.

Sanja Stošić
Health Care Management, Graduate School of Business Studies, Megatrend University, Belgrade, Serbia
(E-mail: stosicsanja@gmail.com)

VOJNOSANITETSKI PREGLED
VOJNOMEDICINSKA AKADEMIJA
Crnotravska 17, 11040 **Beograd, Srbija**
Tel/faks: +381 11 2669689
vsp@vma.mod.gov.rs
vmavsp@hotmail.com

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Primeri referenci:

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Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se kao dopunske datoteke u sistemu **aseestant**. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Slike treba da budu jasne i obeležene brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti metod bojenja i podatak o uvećanju.

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