## Dynamics of Metabolic and Inflammatory Parameters in Overweight Patients Undergoing Knee or hip Arthroplasty

# MARIANA CORNELIA TILINCA<sup>1</sup>, TUDOR SORIN POP<sup>1</sup>\*, ORSOLYA ZSUZSA SZASZ<sup>2</sup>, STEFAN BARBU<sup>3</sup>, KINGA NYULAS<sup>4</sup>, ENIKO NEMES NAGY<sup>5</sup>

<sup>1</sup> University of Medicine and Pharmacy Targu Mures, Faculty of Medicine, 38 Gh. Marinescu Str., 540139, Targu Mures, Romania <sup>2</sup> Clinical County Hospital Mures, Targu Mures, 1 Gh. Marinescu Str., 540103, Targu Mures, Romania

<sup>3</sup> University of Medicine and Pharmacy Targu Mures, Center for Advanced Medical and Pharmaceutical Research, 38 Gh. Marinescu, 540139, Targu Mures, Romania

<sup>4</sup> Gedeon-Richter Romania, Targu Mures, 99-105 Cuza Voda Str., 540306, Targu Mures, Romania

<sup>5</sup> University of Medicine and Pharmacy Targu Mures, Faculty of Pharmacy, 38 Gh. Marinescu Str., 540139, Targu Mures, Romania

Osteoarthritis is a common problem in overweight and obese individuals and may lead to severe forms located especially at the knee and hip joints. Arthroplasty in these cases represents the appropriate treatment to solve the pain and to improve joint mobility. This intervention influences the laboratory parameters in different ways. The aim of the study was to compare pre- and postoperative values of metabolic and inflammatory parameters related to joint replacement surgery in patients suffering from advanced stages of knee and hip osteoarthritis, and to assess the relationship between different laboratory findings, taking into consideration the main cardio-metabolic comorbidities. The study was conducted at the Clinic of Orthopaedics and Traumatology of the Clinical County Hospital Mures between 2016-2017 on 57 overweight patients having severe knee or hip osteoarthritis undergoing total knee or hip arthroplasty. Plasma metabolic tests (uricemia, glycemia, triglycerides, cholesterol) and inflammatory markers (fibrinogen, high sensitive C-reactive protein - hsCRP) were followed in the studied overweight patients in the morning just before arthroplasty and 24 h after surgery. Dynamics of the measured laboratory tests and the relationship between them were assessed. Body mass index, waist circumference and cardio-metabolic associated diseases have also been evaluated. Significant decrease of uricemia, cholesterolemia, plasma triglyceride concentration and significant increase of hsCRP could be observed after joint replacement surgery compared to the previous values measured before the intervention. Glycemia was slightly higher after the arthroplasty, but the difference is not quite significant. Negative correlation could be found between preoperative HDLcholesterol and plasma triglyceride level, while triglyceride concentration showed positive correlation with LDL-cholesterol and uricemia. BMI showed positive correlation with postoperative fibrinogen values. Hypertension was the most frequent cardio-metabolic comorbidity in the studied group. Significant difference occured in the level of a sensitive inflammatory marker and several biochemical laboratory tests suffered notable changes before and after arthroplasty in the studied group. Metabolic status was deeply affected by such an intervention during the first day after surgery. Laboratory components of the metabolic syndrome were present in close relationship in several patients. Further studies need to be performed for the dynamic assessment of more complex metabolic and inflammatory parameters in patients with similar pathology in order to evaluate the postoperative evolution and to provide appropriate support for these patients in the recovery process.

Keywords: arthroplasty, overweight, inflammation, metabolism

Overweight and impaired carbohydrate metabolic balance, dyslipidemia and hyperuricemia and can be considered worldwide epidemics, causing serious public health problems [1]. Osteoarthritis affecting the big joints, especially knee and hip, represents one of the common complications related to weight excess. There is strong evidence that hip, knee and hand osteoarthritis is more frequent in patients having increased BMI, especially the incidence of knee osteoarthritis is the highest in overweight and obese patients [2-4].

Patients suffering from osteoarthritis experience painful joints, cartilage degeneration and limitation of joint mobility, having negative impact on the patients' quality of life. In severe forms of osteoarthritis, total hip/knee arthroplasty represents the gold standard in the treatment of this degenerative disease, which is present in 20% of the adult population, and in 50% of elderly people over 65 years of age [5].

Knee and hip osteoarthritis represents one of the main causes of global disability, especially in elderly people [6]. Overweight in Romania has a prevalence of 34.6% in adult population according to PREDATORR study. Abdominal obesity was found in 73.90% of the studied patients and metabolic syndrome was present in 38.50% of the subjects [7].

Overweight and obesity induce dyslipidemia, hypertension, glucose intolerance, oxidative stress and inflammatory state, which results in progression of atherogenesis, development of diabetes, cardiovascular diseases and osteoarthritis. Dyslipidemia represents an important risk factor involved in cardiovascular pathology occurrence, such as atherosclerosis [8]. Excess of adipose tissue, especially visceral fat having ectopic localization, is rich in big, insulin-resistant adipocytes, considered to be similar to endocrine glands, being directly involved in the inflammatory process. Adipocyte dysfunction leads to the

<sup>\*</sup> email: sorintpop@yahoo.com; Phone 0744527203

release of several inflammatory cytokines, influencing biochemical laboratory tests, atherogenesis and insulin sensitivity. Hyperglycemia, hypertension, central obesity, hypertriglyceridemia and low high-density lipoprotein cholesterol level are major risk factors which contribute to the development of metabolic syndrome, characterized by insulin resistance [9]. Hyperuricemia occurs very often in patients suffering from metabolic syndrome, especially in male subjects [10]. Increased serum uric acid concentration has been recently found to predict the development of diabetes mellitus, mediating dyslipidemia, fatty liver and insulin resistance [11].

Body mass index (BMI) expressed in  $kg/m^2$  is an objective parameter calculated based on weight and height of the patients showing the amount of fat excess that might affect the state of health in overweight and obese individuals. Abdominal circumference in adults is used especially in patients having a BMI value over 25 kg/m<sup>2</sup> to reveal increased cardiovascular risk associated with high amounts of accumulated abdominal fat.

The most common inflammatory markers are Creactive protein and fibrinogen. The first one belongs to the family of acute-phase proteins, being increased in the patients' serum in case of cell injury or infection. The more sensitive hs-CRP can be used to detect low CRP concentrations to reveal the presence of low grade inflammation, contributing to the prediction of cardiovascular risk [12]. Different forms of arthritis, probably due to chronic, persistent inflammatory state, increase the risk of atherosclerosis. Recent studies found association between the progression of the cardiovascular disease and the duration of joint inflammation [13].

The functional postoperative recovery after joint replacement is highly dependent on the body weight of the patients, especially in case of knee arthroplasty. Higher the body weight, poorer the knee function on short and long term after the intervention [14]. Complications and pain occur more frequently in obese and overweight patients after hip or knee implant surgery in patients with osteoarthritis. Musculoskeletal pain, including joint aching due to this kind of pathology, is the most frequent cause of physical disability worldwide. High BMI is often due to sedentary lifestyle. Physical activity and weight loss before the intervention leads to a better evolution after surgery [15].Especially in overweight patients, waist circumference offers valuable additional information about the level of cardiovascular risk.

Inflammation, mainly at the level of adipose tissue and dyslipidemia are known risk factors for development of osteoarthritis. Patients with metabolic syndrome (characterized by insulin resistance/hyperglycemia, visceral obesity, atherogenic dyslipidemia and hypertension as key features, frequently associated with tendency for excessive blood clotting and inflammation) have increased risk for occurrence and progression of osteoarthritis [16]. According to a recent study, women seem to be more vulnerable, a strong association being revealed between the presence of metabolic syndrome and knee osteoarthritis, but only in the female group. The proposed mechanism includes mechanical overload of the joints in patients with high BMI, pro-inflammatory state promoting destruction of the cartilage, and high risk for embolism in case of surgical interventions due to weight excess, including arthroplasty [17].

The aim of this research was the assessment of inflammatory markers (hs-CRP, fibrinogen) and biochemical laboratory tests (plasma glucose, total cholesterolemia, HDL-cholesterolemia, triglyceridemia, uricemia) in patients diagnosed with severe hip or knee osteoarthritis undergoing arthroplasty, focusing on the perioperative dynamics of these parameters and their interrelationship, related to cardio-metabolic comorbidities.

### **Experimental part**

Material and methods

The overweight individuals enrolled in this prospective study were patients suffering from hip or knee osteoarthritis scheduled for arthroplasty during 2016-2017 at the Clinic of Orthopaedics and Traumatology of the Clinical County Hospital Mures. We included in the study group 57 subjects aged ranging between 50-91 years and having BMI between 25-30 kg/m<sup>2</sup> undergoing total knee or hip arthroplasty. Patients under nonsteroidal and steroidal antiinflammatory drugs were excluded from this study to avoid the influence of these substances on the perioperative status regarding laboratory assessment. Written informed consent was signed by each patient for participation in this study, protection of personal data being provided by our research team.

Demographic and antropometric data were collected, waist circumference was also measured. This study was approved by the ethics committee of the Clinical County Hospital Mures. Fasting EDTA- and citrate-blood samples were collected right before arthroplasty and 24 hours after the intervention to determine the dynamics of inflammatory markers (fibrinogen, hs-CRP) and biochemical parameters (glycemia, cholesterolemia, triglyceridemia and uricemia). HDL- and LDL-cholesterol (calculated) values were determined only before the intervention. After centrifugation (1500g, 20 min), separated plasma samples were stored at -80 °C up to the day of processing, except fibrinogen, determined on the day of sampling. Measurement of biochemical parameters was performed on the Cobas Integra 400 Plus analyzer of the Advanced Research Centre of the University of Medicine and Pharmacy in Targu Mures using Roche Diagnostics kits.

GraphPad InStat program was used for statistical processing of the data, applying paired Student t test and chi square test. Gaussian distribution of the values was evaluated by Kolmogorov-Smirnov test. Significancy of the results was considered at p values under 0.05.

#### **Results and discussions**

The average age of the enrolled overweight patients was 66.18 years  $\pm$  8.70 (SD), 63.16% of them being female subjects, 47.37% from urban area. Their mean BMI was 27.64 kg/m<sup>2</sup>  $\pm$  0.76 (SD), ranging between 26.25 and 30 kg/m<sup>2</sup>. Average waist circumference was 98.98 cm  $\pm$  5.99 (SD), the values being between 84 and 111 cm. Separating the genders, we could observe that 94.44% of the female subjects had waist circumference exceeding 88 cm, and only 38.09% of the male patients had a value over 102 cm.

Gaussian distribution of data was obtained for each followed biochemical parameter. Comparing the values of inflammatory markers obtained before and 24 hours after the surgery, a significant increase of plasma hs-CRP concentration could be observed in the postoperative sample (64.35 mg/L  $\pm$  34.35 (SD)) compared to the preoperative one (4.90 mg/L  $\pm$  6.57 (SD)) (p<0.0001) (fig. 1).

Fibrinogen concentration did not show significant difference between the two samples (p=0.7835), the initial average being 369.09 mg/dL  $\pm$  99.61 (SD), 24.56% of the subjects presenting values exceeding 400 mg/dL before

the surgery. Strong correlation could be found between plasma hs-CRP and fibrinogen values, especially before surgery (p<0.0001) (fig. 2).

Regarding the measured metabolic parameters, significant decrease of mean plasma uric acid, cholesterol and triglyceride concentration (fig. 3) could be observed after the intervention compared to the initial values (p<0.0001).

Plasma glucose level of the patients was slightly higher after the surgery, but the difference was not quite significant (p=0.0793) (table 1).

Preoperative triglyceridemia showed negative correlation with HDL-cholesterol level (fig. 4) and positive correlation with LDL-cholesterol (fig. 5) and uricemia (r=0.2827, p=0.0331). Preoperative plasma uric acid level exceeded 7 mg/dL in 21.05% of the patients.

The interrelationship of BMI values with inflammatory markers and with biochemical tests were also studied.



Fig. 1. Perioperative evolution of plasma hs-CRP level (mg/L) in overweight patients



Positive correlation could be revealed between BMI values and plasma fibrinogen concentration (r=0.2783, p=0.0361), considering the levels obtained after the surgery (fig. 6).

The most frequent cardio-metabolic comorbidities were hypertension, which was present in 77.19% of the studied patients, and type 2 diabetes mellitus, documented in 15.79% of the subjects. Obesity was previously diagnosed in 7.02% of the cases.

Postoperative evolution of patients suffering from osteoarthritis undergoing knee/hip arthroplasty is dependent on the presence of comorbidities, such as weight excess, diabetes mellitus, cardiovascular diseases. Components of the metabolic syndrome have negative influence on the outcome of joint replacement [18]. Evaluation of risk factors and associated diseases is an important aspect in the monitoring of these patients, laboratory tests providing useful information for identification of subjects having bad prognosis. The relationship found between BMI and postoperative fibrinogen concentration in our study group underlines the association between overweight and inflammatory state.





Fig. 2. Correlation between inflammatory markers measured in overweight patients before arthroplasty (hs-CRP mg/L, fibrinogen mg/dL)

Biochemical	Average value (mg/dL) ± standard	Average value (mg/dl) ±	p value	]
parameters	deviation before arthroplasty	standard deviation 24 h after		
measured in		arthroplasty		
plasma samples				
Uric acid	6.17 ± 1.64	$5.24 \pm 1.32$	<0.000	1
			1	nv
Cholesterol	207.02 ± 50.38	$141.52 \pm 38.40$	< 0.000	
			1	
Triglycerides	187.61 ± 99.54	$113.95 \pm 57.14$	< 0.000	
			1	
Glucose	105.24 ± 28.03	$110.18 \pm 23.40$	0.0793	1
HDL-cholesterol	43.98 ± 17.75	-		]
LDL-cholesterol	125.52 ± 42.03	-		1

Table 1DYNAMICS OF METABOLICPARAMETERS IN OVERWEIGHTPATIENTS BEFORE AND AFTERJOINT REPLACEMENTSURGERY



Fig. 4. Interrelationship between triglycerides and HDLcholesterol level in overweight patients before and after joint replacement (negative correlation, r=-0.5701, p<0.0001)

Fig. 5. Interrelationship between triglycerides and LDL-cholesterol level in overweight patients before joint replacement (positive correlation, r=0.2902, p=0.0286)



Taking into consideration the high incidence of metabolic syndrome in the population, evaluation of biochemical parameters and prevention of cardiovascular complications should be an important issue of health care services. The quality of life in patients suffering from several disorders, especially elderly individuals, is a very serious problem; this involves complex short and long term follow up [8].

According to recent research data, hyperuricemia might induce insulin resistance by increasing mitochondrial oxidative stress and decreasing insulin-linked stimulation of nitric oxide at the level of endothelial cells. Some clinical studies showed the benefic effect of decreasing uricemia to increase insulin sensitivity, which can be a useful therapeutic tool to prevent impairment of carbohydrate metabolic balance [11].

Cooperation between the patient with osteoarthritis and the medical team is essential because changing the risk factors before surgery can influence the outcome of the intervention and reduce the complications, also the cost of the treatment. The main important modifiable risk factors are weight excess, lack of physical exercise, unhealthy diet and smoking. Good control of diabetes mellitus in patients suffering from this comorbidity is also very important [19].

Steroidal and non-steroidal anti-inflammatory drug administration is commonly used in patients with osteoarthritis to reduce pain and inflammation. Corticosteroids are the most powerful anti-inflammatory drugs. Perioperative corticotherapy is controversial, because steroids can have some adverse effects like delay of bone and wound healing, deep infection and hyperglycemia. Still, some studies showed that glucocorticoids helped the patients in reducing pain after surgery and could shorten the period of hospitalization [20].

Several guidelines recommend topical non-steroidal anti-inflammatory drugs (NSAID) for treatment of osteoarthritis. According to recent studies, diclofenac patches were the best to relief the pain, and piroxicam was most effective to improve the function of the joints. Except salicylate gel, topical NSAIDs proved to be safe, without local or systemic adverse effects on gastrointestinal tract and kidneys [21]. There is limited long term effect of NSAID treatment on improving joint disability especially in elderly subjects [5]. In severe cases, when conservative treatment is not satisfactory, surgical intervention is required.

A study based on a 20 year follow-up showed the interrelationship between the presence of cardio-metabolic risk factors and the increased risk of bilateral osteoarthritis and reduced long-term survival. The researchers concluded that lowering cardio-metabolic risk factors should be an important treatment strategy to increase survival in patients suffering from osteoarthritis, particularly in those undergoing arthroplasty [16].

In our study group, a small percentage of patients achieved the goal of weight loss before the surgery, most of them managed to decrease their BMI value from the range corresponding to class II obesity to overweight.

A similar study was performed on patients undergoing hip or knee surgery, biochemical and inflammatory markers being determined before the intervention and after 48 hours. Significant rise in the serum CRP concentration was reported and significant decrease in serum uric acid concentration [22].

A large cohort study concluded that the major cause of death during the first three months after the surgery in patients undergoing hip or knee arthroplasty was represented by ischemic heart disease in 30% of the followed patients [23].

A longer follow-up could provide more accurate data on the evolution of cases regarding osteoarthritis and comorbidities. The goal of the treatment is to improve the patients' state of health and quality of life, including their reintegration in daily activities in the family and society, as soon as possible.

#### Conclusions

Dynamics of biochemical parameters showed significant changes due to joint replacement surgery in overweight patients suffering from osteoarthritis. Cholesterolemia, triglyceridemia and uricemia had significant decrease, while glycemia was slightly increased after the surgical intervention. Strong correlation could be found between different components of the lipid profile.

The most important perioperative change occurred in the concentration of hs-CRP, the mean value being increased 13-fold after the intervention compared to the initial average.

Components of the metabolic syndrome were present in the majority of the studied patients, having a negative influence on the predicted evolution of the cases after total knee/hip arthroplasty, thereby increasing the risk of complications.

Further studies need to be performed for assessment of a more complex range of metabolic and inflammatory parameters followed in dynamics in patients having similar pathology.

Acknowledgements: This study was provided by a private research grant with the financial support of SC CATTUS SRL and with involvement of University of Medicine and Pharmacy Targu Mures, contract no. 5068/26.04.2016. Many thanks to the staff of the Clinic of Orthopedics and Traumatology of the Clinical County Hospital Mures and to the staff of the Center for Advanced Medical and Pharmaceutical Research University of Medicine and Pharmacy Targu Mures for their involvement in this research project.

#### **References**

1.BOITOR, G.C., CORMOS, G., STETIU, A., STEF, L., ORMENISAN, A., MARIS, M., COMANEANU, R.M., CERNUSCA MITARIU, M., Associating certain salivary parameters with oral health for a group of patients with type II diabetes mellitus, Rev. Chim. (Bucharest), **67**, no. 11, 2016, p. 2314

2.REYES C., LEYLAND K.M., PEAT G., COOPER C., ARDEN N.K., PRIETO ALHAMBRA D. Association Between Overweight and Obesity and Risk of Clinically Diagnosed Knee, Hip, and Hand Osteoarthritis: A Population Based Cohort Study, ARTHRITIS & RHEUMATOLOGY, **68**(8), 2016, p. 1869-75

3.\*\*\* WORLD HEALTH ORGANIZATION. World Health Organization obesity and overweight fact sheet, 2016

4.PLOTNIKOFF R., KARUNAMUNI N., LYTVYAK E., PENFOLD C., SCHOPFLOCHER D., IMAYAMA I., JOHNSON S.T., RAINE K. Osteoarthritis prevalence and modifiable factors: a population study, BMC PUBLIC HEALTH, **15**(1), 2015, p. 1195-1204

5.STAHL I., GINESIN E., HOUS N., KOTLYARSKY P., NORMAN D., PESKIN B. Non-arthroplasty treatment for knee osteoarthritis, HAREFUAH, **156**(7), 2017, p. 455-9

6.CROSS M., SMITH E., HOY D., NOLTE S., ACKERMAN I., FRANSEN M., BRIDGETT L., WILLIAMS S., GUILLEMIN F., HILL C.L., LASLETT L.L. et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study, ANN RHEUM DIS, 2014, 10.1136/ annrheumdis-2013-204763

7.POPA S., MOTA M., POPA A., MOTA E., SERAFINCEANU C., GUJA C., CATRINOIU D., HANCU N., LICHIARDOPOL R., BALA C., ROMAN G. Prevalence of overweight/obesity, abdominal obesity and metabolic syndrome and atypical cardiometabolic phenotypes in the adult Romanian population: PREDATORR study, J ENDOCRINOL INVEST, **39**(9), 2016, p. 1045-53

8.GROZDAN, A.M., GHIURU, R., BOTEZ, C., GAVRILESCU, C.M., DUMA, O., BUZDUGA, C., GEORGESCU, C., STRAT, L., MUNTEANU, D. Correlations Between Cardiovascular/Cardiometabolic Risk and Standard Biochemical Investigations, Rev. Chim. (Bucharest), **6**, no. 9, 2016, p. 1804

9.ZHANG R., DONG S.Y., WANG F., MA C., ZHAO X.L., ZENG Q., FEI A. Associations between Body Composition Indices and Metabolic Disorders in Chinese Adults: A Cross-Sectional Observational Study, CHIN MED J, **131**(4), 2018, p. 379-388

10.WOYESA SB, HIRIGO AT, WUBE TB. Hyperuricemia and metabolic syndrome in type 2 diabetes mellitus patients at Hawassa university comprehensive specialized hospital, South West Ethiopia, BMC ENDOCR DISORD, **17**(1), 2017, p. 76-83

11.KING C., LANASPA M.A., JENSEN T., TOLAN D.R., SANCHEZ-LOZADA L.G., JOHNSON R.J. Uric Acid as a Cause of the Metabolic Syndrome. In URIC ACID IN CHRONIC KIDNEY DISEASE, Trevino-Becerra A., Iseki K. (eds.), Vol. **192**, Karger Publishers, 2018, p. 88-102

12.GAVRIL, R.S., MITU, F., LEON, M.M., MIHALACHE, L., ARHIRE, L.I., GROSU, C., GHERASIM, A., NITA, O., UNGUREANU, I.O., OPRESCU, A.C., GRAUR, M. Biomarkers of Inflammation in Patients with Type 2 Diabets Mellitus and Hepatic Steatosis, Rev. Chim. (Bucharest), **67**, no. 9, 2016, p. 1828

13.PARVU M., COMAN S., VOIDAZAN S. Rheumatoid arthritis and atherosclerosis: Why is important to evaluate this?, ATHEROSCLEROSIS, **252**, 2016, p. e17

14.MANIAR R.N., MANIAR PR., SINGHI T., GANGARAJU B.K. WHO Class of Obesity Influences Functional Recovery Post-TKA, CLIN ORTHOP SURG, **10**(1), p. 26-32

15.POZZOBON D., FERREIRA P.H., BLYTH F.M., MACHADO G.C., FERREIRA M.L. Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? A meta-analysis of cohort studies, BMJ OPEN, **8**(2), 2018, e017689

16.BUCHELE G., GUNTHER K.P., BRENNER H., PUHL W., STURMER T., ROTHENBACHER D., BRENNER R.E. Osteoarthritis-patterns, cardiometabolic risk factors and risk of all-cause mortality: 20 years followup in patients after hip or knee replacement, SCI REP, **8**(1), 2018, p. 5253 17.MADDAH S., MAHDIZADEH J. Association of metabolic syndrome and its components with knee osteoarthritis, ACTA MED IRAN, **53**(12), 2015, p. 743-8

18.FOURNIER M.N., HALLOCK J., MIHALKO W.M. Preoperative optimization of total joint arthroplasty surgical risk: obesity, J ARTHROPLASTY, **31**(8), 2016, p. 1620-4

19.DEFRODA S.F., RUBIN L.E., JENKINS D.R. Modifiable Risk Factors in Total Joint Arthroplasty: A Pilot, RIMJ, **99**(5), 2016, p. 28-31

20.ZHONG J., SI H.B., ZENG Y., YANG J. ZHOU Z.K., PEI F.X., SHEN B. Comparison of cortisol and inflammatory response between aged and middle-aged patients undergoing total hip arthroplasty: a prospective observational study, BMC MUSCULOSKELET DISORD, **18**(1), 2017, p. 541-550

21.ZENG C., WEI J., PERSSON M.S., SARMANOVA A., DOHERTY M., XIE D., WANG Y., LI X., LI J., LONG H., LEI G., ZHANG W. Relative efficacy and safety of topical non-steroidal anti-inflammatory drugs for

osteoarthritis: a systematic review and network meta-analysis of randomised controlled trials and observational studies, BR J SPORTS MED, 2018, 10.1136/bjsports-2017-098043

22.WALDRON J.L., ASHBY H.L., RAZAVI C., THOMAS O.L., CHUGH S., DESHPANDE S., FORD C., GAMA R. The effect of the systemic inflammatory response, as provoked by elective orthopaedic surgery, on serum uric acid in patients without gout: a prospective study, RHEUMATOLOGY, **52**(4), 2013, p.676-678

23.HUNT L.P., BEN-SHLOMO Y, WHITEHOUSE M.R., PORTER M.L., BLOM A.W. The main cause of death following primary total hip and knee replacement for osteoarthritis: a cohort study of 26,766 deaths following 332,734 hip replacements and 29,802 deaths following 384,291 knee replacements, JBJS, **99**(7), 2017, p. 565-75

Manuscript received: 11.11.2017