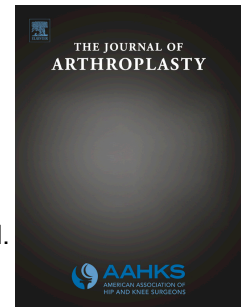


Journal Pre-proof

Questioning the “Nickel Free” Total Knee Arthroplasty

Charles M. Lawrie, MD, MSc, Kimberly A. Bartosiak, MD, Toby Barrack, MD, Ryan M. Nunley, MD, Rick W. Wright, MD, Robert L. Barrack, MD



PII: S0883-5403(22)00343-6

DOI: <https://doi.org/10.1016/j.arth.2022.03.058>

Reference: YARTH 59361

To appear in: *The Journal of Arthroplasty*

Received Date: 3 December 2021

Revised Date: 14 March 2022

Accepted Date: 15 March 2022

Please cite this article as: Lawrie CM, Bartosiak KA, Barrack T, Nunley RM, Wright RW, Barrack RL, Questioning the “Nickel Free” Total Knee Arthroplasty, *The Journal of Arthroplasty* (2022), doi: <https://doi.org/10.1016/j.arth.2022.03.058>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Elsevier Inc. All rights reserved.

TITLE:

Questioning the “Nickel Free” Total Knee Arthroplasty

AUTHORS:

Charles M. Lawrie, MD, MSc¹, Kimberly A. Bartosiak, MD², Toby Barrack, MD², Ryan M. Nunley, MD², Rick W. Wright, MD³, Robert L. Barrack, MD²

INSTITUTION:

¹ Miami Orthopedics and Sports Medicine Institute, Baptist Health South Florida, Miami, FL

² Department of Orthopedic Surgery, Washington University School of Medicine, St. Louis, MO

³ Department of Orthopaedics and Rehabilitation, Vanderbilt University Medical Center, Nashville, TN

AUTHOR CONTRIBUTIONS

Charles M. Lawrie	-	Study design, data collection, data analysis, manuscript preparation
Kimberly A. Bartosiak	-	Data collection, manuscript preparation
Toby Barrack	-	Data collection, data analysis
Ryan M. Nunley	-	Data collection, manuscript preparation
Rick W. Wright	-	Data collection, manuscript preparation
Robert L. Barrack	-	Study design, data collection, data analysis, manuscript preparation

CORRESPONDING AUTHOR:

Charles M. Lawrie, MD, MSc
 Miami Orthopedics and Sports Medicine Institute
 Baptist Health South Florida
 1150 Campo Sano Ave, 2nd Floor
 Miami, FL, 33133
 Office: 786-596-8020
 Fax: 786-533-9301
 Email: charles.lawrie@baptisthealth.net

ACKNOWLEDGEMENTS:

Jackie King, Elizabeth Carnaghi and Alyssa Bjerk, nurse practitioners, for their work in assisting with drain fluid specimen collection.

Venessa Riegler and Rondek Saleh, senior research coordinators for their work enrolling, consenting, collecting and organizing the data for analysis.

Robin Pourzal for his assistance with profilometry.

FUNDING:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

WORD COUNT ABSTRACT: 238/250

WORD COUNT MAIN TEXT: 2516/3000

- 1 **TITLE:**
- 2 Questioning the “Nickel Free” Total Knee Arthroplasty
- 3
- 4

Journal Pre-proof

ABSTRACT

Background: A study was performed to measure metal ions present in the knee joint after performing a total knee arthroplasty (TKA) with standard cobalt chromium (CoCr) components as well as with “nickel free” oxidized zirconium femoral and titanium tibial (OxZr/Ti) components.

Methods: Knee joint fluid was collected prior to arthrotomy and on postoperative day one to determine the amount of metal debris generated when performing a TKA with standard instrumentation from consecutive cases with CoCr components (n=24) and OxZr/Ti components (n=16).

Results: CoCr implant patients had statistically higher levels of nickel (Ni) (29.7%, p=.033), cobalt (Co), (1100.7%, p<.0001) and chromium (118.9%, p<.0001) postoperatively. The cutting blocks and sawblades do not contain cobalt, which therefore must have come from the components. The metal ions generated from the sawblades and cutting blocks, therefore, could be discerned from the OxZr/Ti which components don't contain Co, Cr, or Ni. The OxZr patients had significantly higher Cr (9.5x, p<.001) and Ni (5.1x, p<.001) post-TKA vs pre-TKA; Co levels were not significantly different as expected with the absence of cobalt in the components (p=0.60). The nickel levels generated in performing an Oxinium TKA was 3.3 times higher than when performing a CoCr TKA (1.37 vs.41 ppb, p<.001).

Conclusions: The substantial degree of nickel generation resulting from performing a hypoallergenic “nickel-free” TKA calls into questions the rationale of utilizing more expensive lower nickel components on the basis of known or suspected nickel or chromium allergy.

INTRODUCTION

The contribution of metal allergy or hypersensitivity reaction to residual symptoms and early failure in total knee arthroplasty (TKA) remains controversial. Several studies implicate a link between metal ion allergy, especially nickel, and persistent pain, recurrent effusions and aseptic failure after total knee arthroplasty.[1] Evidence to the contrary, refuting metal allergy or hypersensitivity as a mechanism of persistent symptoms or failure of total knee arthroplasty, is equally compelling.[2] Similarly, the use of “hypoallergenic” or “metal sensitive” implants has been reported with mixed success in improving outcomes in patients with known or suspected metal allergy or hypersensitivity.[3-6]

In spite of the conflicting evidence on the topic, the development and use of “hypoallergenic” or “metal sensitive” implants has continued to grow, with most major implant manufacturers offering such a model of their TKA at an increased cost.[7-10] However, little recent attention has been paid to the fact that the instruments used to perform total knee arthroplasty, including saw blades and traditional cutting blocks, may generate a large amount of intraarticular metal ions when performing TKA.[11] This metal debris from sawblade and cutting block damage and wear may lead to high postoperative levels of metal ions in the knee joint even if a “hypoallergenic” or “metal sensitive” implant is used, calling into question the value of these more expensive specialized implants.

Previous studies with in vitro and animal models have demonstrated metal ions are generated using saw blades through captured cutting blocks in TKA.[12, 13] To our knowledge, the intraarticular levels of metal ions after total knee arthroplasty has not been reported on. The purpose of this study is to determine postoperative intraarticular levels of nickel, cobalt and chromium generated during the primary total knee arthroplasty performed with standard instrumentation with “metal sensitive”/“hypoallergenic” implants and standard cobalt chromium implants.

METHODS

A prospective two cohort study was performed. Institutional review board approval was obtained prior to initiation of the study. All patients undergoing primary unilateral cemented total knee arthroplasty for a diagnosis of primary knee osteoarthritis with one of four surgeons (RLB, CML, RMN, RWW) at a single institution during the study period were considered for the study. Patients were excluded if they were unwilling to participate in the study or had a diagnosis of stage III or IV chronic kidney disease. Informed consent was signed by all participants enrolled in the study.

All patients underwent standard perioperative procedures per institutional protocol. Patients with self-reported or known nickel allergies had TKA performed with a nickel-sensitive implant: Legion Primary Knee System with a cruciate retaining Oxinium femoral component, titanium tibial baseplate and cruciate retaining polyethylene tibial bearing (Smith and Nephew, Memphis, TN). Patients without a known or reported nickel allergy had TKA performed with a standard, non-hypoallergenic implant: Evolution Primary Knee System with cobalt chromium femoral and tibial components and a cruciate sacrificing medial pivot tibial polyethylene bearing (MicroPort, Memphis, TN, USA).

Joint aspiration was performed after skin incision, but prior to arthrotomy to establish baseline synovial fluid metal levels. An oscillating dual-cut sawblade made of Sandovik 7C27Mo2 Strip Steel (Stryker, Malwah, NJ, USA) was used through 17-4 Stainless Steel cutting blocks for all bone preparation. Three liters of normal saline were used for irrigation via low pressure pulse lavage throughout the procedure. A single, medium hemovac drain was placed in the suprapatellar pouch and attached to self-suction after skin closure. All patients underwent standard post-operative procedures per institution protocol. All drains were removed at 6:00 AM on post-operative day one and post-operative synovial fluid was collected at that time. Pre-operative and post-operative synovial fluid levels of cobalt, chromium and nickel were measured using standard laboratory procedures. All metal ion levels are reported in parts

per billion (ppb). Material composition of the knee arthroplasty components, cutting blocks and sawblades are shown in table 1.

A representative sample of 6 saw blades underwent wear analysis using scanning electron microscopy and profilometry. They were cleaned with isopropanol for 5 minutes in an ultrasonic bath and then examined in a scanning electron microscope (SEM, IT500HR, JEOL). Secondary electron images (SE) were acquired at 10kV with magnifications ranging from 500x to 2000x to visualize surface damage and morphology. We used an energy dispersive x-ray spectroscopy (EDS) detector (Ultim-Max detector, Oxford Instruments, UK) at 20kV to verify the local and overall chemical distribution of the alloying elements and potential chemical alterations at the worn surfaces. Material loss was assessed with an optical 3D surface profiler (OrthoLux, RedLux, UK). Saw blades were placed in a custom-made fixture and rotated in front of a white light confocal sensor for data acquisition. The original surface was digitally reconstructed based on unworn areas. Volume loss was then computed using the RedLux studio software. Additionally, heat maps and light intensity maps were generated of each saw blade surface. Data collection, organization and statistical analysis was all performed in Microsoft Excel 365 (Microsoft, USA). Paired Student's t-test was used to compare preoperative to postoperative metal ion values. Unpaired Student's t-test was used to compare continuous variables between CoCr and OxZr/Ti groups. Chi-square test was used to compare categorical demographic values between groups.

RESULTS

40 patients who met inclusion and exclusion criteria were enrolled. 24 patients enrolled underwent TKA with the standard, non-hypoallergenic CoCr implants. 16 patients enrolled underwent TKA with nickel-sensitive OxZr/Ti implants. There was no significant difference in demographic data, time to collection of drain fluid and amount of drain fluid between the CoCr and OxZr/Ti groups (Table 2).

The CoCr implant group had statistically higher levels of cobalt (1100.7%, $p < 0.001$), chromium (118.9%, $p < 0.001$) and nickel (29.7%, $p = 0.033$) postoperatively compared to preoperative levels. The cutting blocks and sawblades do not contain cobalt, which therefore must have come from the femoral and tibial components during or after implantation. The debris generation purely from the sawblades and cutting blocks, therefore, could be discerned from the OxZr/Ti implant group as these components don't contain Co, Cr, or Ni. The OxZr/Ti patients had 9.5x significantly higher chromium (0.502 vs. 0.053, $p < .001$) and 5.1x higher nickel (1.370 vs. 0.267, $p < 0.001$) postoperative versus preoperatively while the cobalt level was not significantly different after TKA, as expected with the absence of cobalt in the components (0.124 vs. 0.071, $p = 0.60$). The nickel levels generated in performing an Oxinium TKA was 3.3 times higher than when performing a Co-Cr TKA (1.37 vs. 41, $p < .001$).

Representative scanning electronic microscopy demonstrated significant sawblade surface fatigue wear, abrasive wear, adhesive wear and plastic deformation (Figure 1). Representative profilometry of the 6 sawblades demonstrated median material loss of 0.26 mm^3 (range: 0.0162 to 1.015 mm^3). The greatest material loss from the sawblades was observed the outside edges of the blades.

DISCUSSION

This study describes the levels of intraarticular cobalt, chromium and nickel present after primary total knee arthroplasty performed with standard manual instrumentation. The interference between the sawblades and cut blocks seems to be the major source of nickel and chromium ions. Specifically, the captured cutting blocks seem to be a major source of nickel during performance of total knee arthroplasty. While impaction of the final implants seems to have caused release of cobalt release into the joint, as they are the only possible source of cobalt, the implants do not appear to have been a major source of nickel in the joint on postoperative day one. In fact, performing a hypoallergenic “nickel-free” TKA with the specific knee system we used in this study resulted in substantially greater levels of intraarticular nickel levels than conventional cobalt chromium containing implants, possibly due to the design of the cutting blocks. Our results demonstrate nickel and chromium levels in the joint are elevated by the actual performance of TKA, calling into question the rationale of utilizing more expensive hypoallergenic lower nickel content components on the basis of suspected nickel or chromium allergy.

Despite controversy regarding the role of metal hypersensitivity in persistent symptoms or failure of TKA, hypoallergenic implants are routinely used for total knee arthroplasty in patients with reported allergies to nickel, cobalt or chromium. The self-reported incidence of dermal hypersensitivity to metal is 10-15% in the general population.[3, 14] However, the correlation between dermal hypersensitivity and synovial hypersensitivity resulting in implant failure is unclear.[5] Furthermore, patients with reported allergy to nickel, cobalt or chromium have poorer outcomes as compared to patients without these allergies, regardless of implant choice.[4, 6, 15] Psychosocial and emotional factors have been implicated in the link between metal allergy and poor outcomes after TKA.[16, 17]

Prior studies have demonstrated significant metal debris generation occurs during performance of TKA. Gotterson et al. performed bony resections simulating TKA in a pig model and collected metal debris

from sawblades, cutting blocks and bone surfaces in attempt to characterize this phenomenon. On average, 1.13mg of metal was lost from the sawblades alone. Based on material composition, they determined that cutting blocks were the major source of this debris, followed by the sawblades, with an estimate that millions of metal particles are generated during standard TKA resections.[12] Interestingly, they also found that uncaptured cutting blocks led to increased metal debris generation, which the authors hypothesized was from surgeons pushing harder on the cutting block in attempt to maintain an accurate cut. [12] In another in vitro study, the metal ion generation using an end-only oscillating saw blade (Precision Saw Blade, Stryker, USA) significantly decreased metal ion generation as compared to a conventional saw blade. [13] The same study found that the majority of material loss with performance of TKA was from the cutting blocks, not the saw blades, as a result of the blades having a higher hardness value than the 4-in-1 cutting blocks. [13] Similarly, the profilometry we performed in our study demonstrated little overall material loss from the saw blades, and significant material deposition on the surface of the blades. De Baets et al. performed a similar study in vivo, recovering all pulsed irrigation fluid at the conclusion of TKAs performed in live patients to look at potential sources of wear debris generated during TKA. They found that on average 134.9mg of debris was present in the lavage fluid, including 1.96mg of metal particles.[18]

These findings support our hypothesis that the interference between the sawblade and cutting blocks is a major source of metal wear debris generation intraarticularly while performing TKA. This hypothesis is further supported by our the representative profilometry which demonstrated the wear on the sawblades concentrated at the peripheral edges, presumably from interference with the captured cutting blocks. Despite irrigation of the wound prior to closure that would remove some of the debris as reported by De Baets et al., a significant amount of cobalt, chromium and nickel remained intraarticularly as demonstrated by high levels in the drain fluid collected on postoperative day one. Sunderman et al. found levels of serum and urine nickel after TKA performed with titanium alloy

implants containing <0.2% nickel content remained elevated up to 2 weeks postoperatively; they concluded the source of these ions was from instrumentation used during performance of the TKA.[11] At a minimum of one year postoperatively serum nickel levels are not significantly different than preoperative values, and are not affected by the use of “hypoallergenic”, “nickel-free” or “coated” implants.[19] Of further concern is that the majority of the metal particulate debris generated during total knee arthroplasty has been measured to be in the 1 to 2 micrometers.[12, 13] Particles in this size range are well established to activate inflammatory macrophages, resulting in synovitis and osteolysis.[20]

This study is not without limitations. The cutting guides had variable prior use before being used in the study, and were not able to be removed from clinical use for wear analysis. Furthermore, the amount of metal ions released from the cutting blocks and sawblades is likely dependent on the design of the cutting blocks, with some designs with tighter tolerances for the sawblade, central posts or peripheral pins that may increase the contact with the sawblade and therefore increase the amount of metal deposition in the joint. Several other potential sources of metallic ions including surgical instruments, scalpels, fixation pins for cutting jigs, suture needles and drain trochars cannot be ignored; however the use of these other potential metal sources were uniform during the TKAs performed. Lastly, the ion levels on post-operative day one may not be indicative of the ion levels weeks to months post-operatively and thus may not be the most important measure for risk of metal hypersensitivity.

In conclusion, this study shows significant levels of chromium and nickel ions are generated by performance of total knee arthroplasty with standard instrumentation. Cutting blocks, and to a lesser extent saw blades, appear to be the major sources of these metal ions, and therefore use of hypoallergenic implants does not mitigate this generation of metal debris into the knee joint. Furthermore, standard TKA implants contain less than 0.5% nickel, are polished and hardened, and articulate against plastic, and are therefore unlikely to represent a significant source of intraarticular

nickel ions in the long term. Indeed, studies have failed to demonstrate elevated serum nickel levels in well-functioning TKA at greater than one year postoperatively, although data on intraarticular metal ion concentrations beyond the early postoperative period are lacking.[19] Standard cutting blocks contain 8-10x as much nickel as the standard TKA implants and liberate substantial micron and submicron size debris from abrasion by the harder saw blade. Our results indicate that the generation of metal ions, specifically nickel, during performance of TKA may be more significant than the nickel generated by a well-functioning TKA over time. This calls into question the rationale of using hypoallergenic implants when performed with standard manual instrumentation, as the level of intraarticular metal ions on postoperative day one are elevated even with these implants.

TABLES AND FIGURES

	Material	Cobalt	Chromium	Nickel
MicroPort Evolution Femoral and Tibial components	Cobalt Chromium	58%	30%	<0.5%
Smith and Nephew Legion Femoral component	Oxidized Zirconium	<0.002%	<0.02%	<0.0035%
Smith and Nephew Legion Tibial component	Titanium (Ti6Al4V)	0%	0%	0%
Captured cutting guides	17-4 Stainless Steel	0%	17.5%	4%
Saw blade	Strip Steel (7C27Mo2)	0%	13.5%	<0.01%

Table 1. Composition of metallic materials used during TKA procedure.

	Cobalt Chromium Group	Oxidized Zirconium Group	P-value
Sex (#)			
Male	14	6	0.259
Female	11	10	
Age, years (mean $\pm$ SD)	62.6 $\pm$ 10.02	66.75 $\pm$ 7.92	0.170
BMI, kg/mm² (mean $\pm$ SD)	31.97 $\pm$ 4.60	32.4 $\pm$ 6.61	0.808
Drain Collection Time, hours postoperatively (median (range))	17.8 (12-21)	17.3 (13.5-19.5)	0.569
Drain Output, cc (median (range))	215 (45-540)	240 (20-400)	0.849

Table 2. Demographic data of the two patient groups.

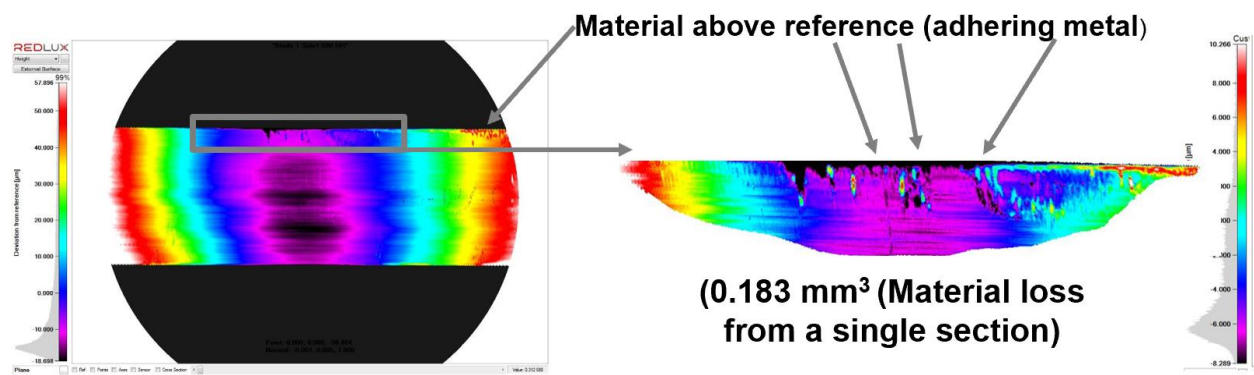
Metal Ion	Pre-Op	Post-Op	P-value
Chromium Median (range)	.127 ± .126 (.028-.554)	.278 ± .191 (.067-.807)	< .001
Cobalt Median (range)	.115 ± .079 (.010-.363)	1.382 ± 1.802 (.007-8.209)	.002
Nickel Median (range)	.316 ± .196 (.058-.866)	.410 ± .158 (.116-.700)	.033

Table 3. Preoperative and postoperative Chromium, Cobalt and Nickel converted to part per billion for TKAs performed with CoCr implants (N=24).

Metal Ion	Pre-Op	Post-Op	P-value
Chromium Median (range)	.054 ± .021 (.020-.090)	.502 ± .209 (.170-.840)	< .001
Cobalt Median (range)	.071 ± .034 (.120-.030)	.124 ± .421 (.010-1.750)	.601
Nickel Median (range)	.267 ± .167 (.140-.810)	1.37 ± .707 (.550-2.99)	<.001

Table 4. Preoperative and postoperative Chromium, Cobalt and Nickel converted to part per billion for TKAs performed with OxZr/Ti implants (N=17).

A)



B)

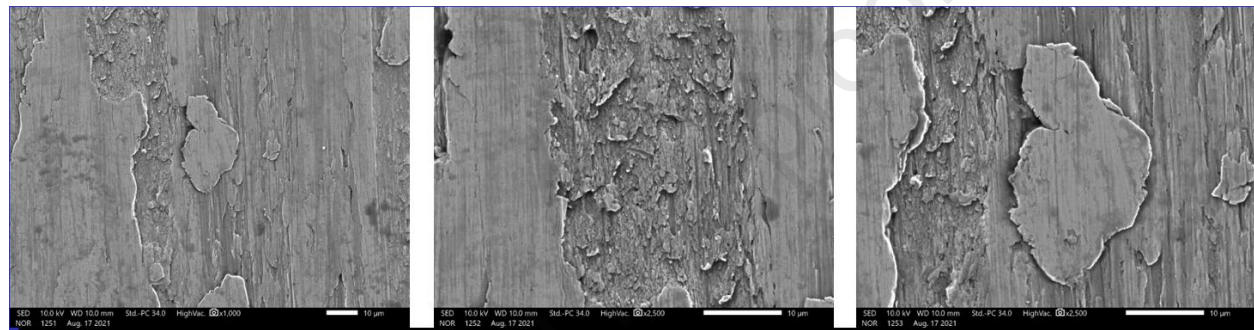


Figure 1. Profilometry (A) and scanning electron micrography (B) of a representative portion of a sawblade used for TKA bone cuts through captured femoral and tibial cutting blocks.

REFERENCES

1. Mitchelson AJ, Wilson CJ, Mihalko WM, Grupp TM, Manning BT, Dennis DA, Goodman SB, Tzeng TH, Vasdev S, Saleh KJ. Biomaterial hypersensitivity: is it real? Supportive evidence and approach considerations for metal allergic patients following total knee arthroplasty. *Biomed Res Int* 2015; 137287, 2015
2. Middleton S, Toms A. Allergy in total knee arthroplasty: a review of the facts. *Bone Joint J* 98-B(4): 437, 2016
3. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 83(3): 428, 2001
4. Graves CM, Otero JE, Gao Y, Goetz DD, Willenborg MD, Callaghan JJ. Patient reported allergies are a risk factor for poor outcomes in total hip and knee arthroplasty. *J Arthroplasty* 29(9 Suppl): 147, 2014
5. Bravo D, Wagner ER, Larson DR, Davis MP, Pagnano MW, Sierra RJ. No Increased Risk of Knee Arthroplasty Failure in Patients With Positive Skin Patch Testing for Metal Hypersensitivity: A Matched Cohort Study. *J Arthroplasty* 31(8): 1717, 2016
6. Nam D, Li K, Riegler V, Barrack RL. Patient-Reported Metal Allergy: A Risk Factor for Poor Outcomes After Total Joint Arthroplasty? *J Arthroplasty* 31(9): 1910, 2016
7. Biomet Z. Persona The Personalized Knee Ti-Nidium Knee. In. 2021
8. Orthopedics M. Evolution Nitrx Knee System. In. 2021
9. Systems AI. Vega System Knee Implant. In. 2020
10. Nephew Sa. Oxinium Oxidized Zirconium for hip and knee replacement. In. 2021
11. Sunderman FW, Jr., Hopfer SM, Swift T, Rezuze WN, Ziebka L, Highman P, Edwards B, Folcik M, Gossling HR. Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. *J Orthop Res* 7(3): 307, 1989
12. Gotterson PR, Nussem I, Pearcy MJ, Crawford RW. Metal debris from bony resection in knee arthroplasty--is it an issue? *Acta Orthop* 76(4): 475, 2005
13. Sydney SE, Pickering SA, Bell CG, Crawford R. Reducing metal debris generation during total knee arthroplasty. *Orthopedics* 30(12): 999, 2007
14. Bloemke AD, Clarke HD. Prevalence of self-reported metal allergy in patients undergoing primary total knee arthroplasty. *J Knee Surg* 28(3): 243, 2015
15. McLawhorn AS, Bjerke-Kroll BT, Blevins JL, Sculco PK, Lee YY, Jerabek SA. Patient-Reported Allergies Are Associated With Poorer Patient Satisfaction and Outcomes After Lower Extremity Arthroplasty: A Retrospective Cohort Study. *J Arthroplasty* 30(7): 1132, 2015
16. Ferrer T, Hinarejos P, Goicoechea N, Leal-Blanquet J, Sanchez-Soler J, Torres-Claramunt R, Monllau JC. Anxiety is the cause of the worse outcomes of allergic patients after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc* 28(10): 3135, 2020
17. Pena P, Ortega MA, Bujan J, De la Torre B. Decrease of Quality of Life, Functional Assessment and Associated Psychological Distress in Patients with Hypoallergenic Total Knee Arthroplasty. *J Clin Med* 9(10), 2020
18. De Baets T, Waelput W, Bellemans J. Analysis of third body particles generated during total knee arthroplasty: is metal debris an issue? *Knee* 15(2): 95, 2008
19. Postler A, Beyer F, Lutzner C, Tille E, Lutzner J. Similar outcome during short-term follow-up after coated and uncoated total knee arthroplasty: a randomized controlled study. *Knee Surg Sports Traumatol Arthrosc* 26(11): 3459, 2018
20. Schwarz EM, Lu AP, Goater JJ, Benz EB, Kollias G, Rosier RN, Puzas JE, O'Keefe RJ. Tumor necrosis factor-alpha/nuclear transcription factor-kappaB signaling in periprosthetic osteolysis. *J Orthop Res* 18(3): 472, 2000