Spectrometral and histopathological evaluation of metal ion levels in soft tissue around uncemented implants collected during revision hip replacement.

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Research article

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Abstract

Background The aim of the study was to measure metal ion concentration (Ti, Co, Cr, Mo, Ni, Al) around loosened uncemented hip implants and to compare their levels around the cups and stems. **Methods** Soft tissue samples were collected for analysis in 25 patients (25 hips) during revision hip arthroplasty for aseptic loosening in the years 2007-2009. All tissues collected during the revision arthroplasty were submitted for analysis under a light microscope and ICP – MS analysis. All tissues displayed “foreign body” type chronic inflammatory infiltration with PE and/or metal deposits and metallic inclusions. **Results** The Inductively Coupled Plasma Mass Spectrometry study of cementless hip implants revealed that the metal ions pass from loose elements of the implants to the surrounding tissues in significant concentrations ranging from a few hundred to several thousand $\mu\text{g} / \text{kg}$. Moreover, the tissues surrounding the loosened cups contained significantly higher concentrations of Ti and Ni metal ions than the tissue surrounding the stems. **Conclusions** Of all the metal ions used for construction of hip implants, the highest tissue concentration was noted in the case of Ti ions. In any case, regardless of the type of endoprosthesis, the concentrations of Ti and Ni metal ions were higher in tissues surrounding the cup rather than around the stem.

Background

During revision hip arthroplasty, numerous signs of wear can be seen, not only on the surfaces of the removed implants but also in adjacent tissues. The tissues surrounding certain elements of the hip implants have been seen to contain numerous signs of prosthesis debris, including fragments of metal, polyethylene and/or metallosis: encrustation of tissues with metal. Therefore, to gain a deeper insight into the phenomenon of aseptic loosening and erosion of hip implants in the human body, this study was performed to examine the debris and determine its source.

A detailed analysis of metal ion levels in tissues surrounding uncemented hip implants may clarify the mechanism of loosening and any related factors. As complications experienced during hip resurfacing have recently raised interest in loosening(1), a spectrometric and histopathological evaluation was performed of the tissues surrounding uncemented hip implants which had been removed during revision hip arthroplasty. The tissues were evaluated with regard to their metal ion concentration and the presence of wear products.

The aim of the study was to measure the concentration of metal ions (titanium - Ti, cobalt - Co, chrome - Cr, molybdenum - Mo, nickel - Ni, aluminium - Al) around loosened uncemented hip endoprosthesis and compare their levels around the cups and stems.

Methods

A total of 172 revision hip arthroplasties were performed in our institution between the years 2007 and 2009. 25 of these patients; 15 females and 10 males which is 14.5% of whole group, had undergone

unilateral hip revision for aseptic loosening. The mean age of patients was 61.8 (ranging from 27 to 78). All patients had primary uncemented THR.

The type of primary implant is presented in Table 1. The Bicontact stems and cups were covered with hydroxyapatite and the Mittelmeier stems were coated with granular metal. Neither the Mittelmeier cups nor the entire Parhofer's – Mönch implant were covered or coated with any substances. The mean follow-up from primary hip replacement to revision was 11.2 years (from 2 to 17 years).

The diagnosis of implant loosening was obtained on the basis of clinical examination and radiographic evaluation, and was finally confirmed during revision hip arthroplasty. Standard blood tests, including CRP level measurement to exclude periprosthetic joint infection, were performed before the operation. In all cases, the acetabular component as well as femoral component was replaced. In one patient, a mechanical implant defect, fatigue stem fracture, was identified.

All revisions were performed through an anterolateral approach to the hip with the patient in the supine position. The soft tissue samples were taken during the revision operation, just before implant removing, at the junction between bone and implant at either the stem or the cup. These samples were examined by Inductively Coupled Plasma Mass Spectrometry (ICP – MS) for the presence of metal ions originating from the hip endoprosthesis material (Ti, Co, Cr, Mo, Ni and Al). The spectrometer was calibrated using the ICP multi – element standard solution VI (Merc). Before analysis, the probes were subjected to microwave digestion in a MLS 1200 system (Milestone) and spectrally clear nitric acid (HNO₃). The quality of obtained results was verified by control samples.

The collected histological material was preserved in 4% formalin. Specimens were stained with hematoxylin and eosin, and subjected to histopathological examination under the light microscope. Microscopic evaluation was performed at 20, 50 and 100x magnification.

Statistical analysis.

The minimal and maximal values, as well as the mean and median values, were calculated, while standard deviation and the coefficient of variation were used as parameters of statistical dispersion. As the analysed feature was found to have a non-normal distribution, the Kruskal-Wallis non-parametric test was used to compare the mean values between the three prosthesis models.

Results

All the outline ions were found in tissue samples, both around the cup or stem (table 2). The average levels of titanium in soft tissues around the uncemented loosened cups were about one hundred times higher than those seen in the soft tissues around the stems ($p < 0.001$). The concentration of nickel was about six times higher in the tissue around the cups than around the stems ($p < 0.05$). No statistically significant differences were observed between the two tissue types with regard to the concentrations of Co, Cr, Mo or Al ions (table 2). Macroscopic analysis of the soft tissues collected from patients revealed

encrusting by metal particles (metalosis). In all tissues, microscopic evaluation revealed “foreign body” type chronic inflammatory infiltration with metal and PE deposits (Fig. 1 and 2).

Analyzing the concentrations of metal ions depending on the applied articulation in the studied groups; C-C, PE-C and PE-M were found a statistically significant relationship between the diameter of the head and the concentration of Al ions around the acetabulum ($p < 0.001$), the larger the diameter of the head, the higher the concentration of ions. Analysis of ion concentration in tissues around the stem depending on the diameter of the head showed statistically significant, mean power dependence in the case of Cr ions ($r = -0.48$, $p < 0.05$) - the larger the diameter of the head, the lower the concentration of Cr ions. A statistically significant, strong relationship was found in the case of Al ions and head diameter ($r = 0.77$, $p < 0.001$). Higher concentration of Al ions accompanied a larger head diameter (Table 3).

There was a statistically significant difference in the concentration of Ti ions in the tissues around the of the acetabulum on the combination used ($p < 0.01$). A detailed comparison of the Ti ion concentrations showed a statistically significant difference between the C-C and PE-C connections ($p < 0.05$). Significantly higher concentration was in the group with the PE-C connection. Also, significant differences were in the case of the concentration of ions Co in tissues around the acetabulum cup ($p < 0.05$). This time, a significant difference was observed between the concentration in the PE-C and PE-M articulations ($p < 0.05$), the higher average was observed in the case of the combination of PE-M than PE-C. Again, the concentration of Al differed significantly in the articulations sub-groups distinguished due to combinations ($p < 0.001$). The difference between PE-M and C-C ($p < 0.001$), significantly higher Al concentration in the C-C group and significant difference between the PE-M and PE-C groups ($p < 0.01$) were found, and this time higher concentration was observed in the PE-C group than in PE-M. The remaining concentrations of ions did not differ significantly depending on the articulations used ($p > 0.05$) (Table 4).

Comparison of the concentration of ions in the tissues around the stem also showed several statistically significant differences depending on the articulations used. A significant difference relates to the concentration of Cr ($p < 0.01$). In this case, the lowest concentration was at the combination of PE-C, significantly lower than in the case of C-C ($p < 0.05$) and significantly lower than in PE-M ($p < 0.01$). The smallest concentration was observed in the PE-C articulations, it was significantly smaller than in the C-C articulations and then in PE-M ($p < 0.01$). There were also statistically significant differences in Al in tissues around the stem concentrations depending on the articulations ($p < 0.001$). The lowest concentration of these ions was observed in the combination of PE-M (1428,3 $\mu\text{g} / \text{kg}$), significantly lower than in PE-C (4039,1 $\mu\text{g} / \text{kg}$) and then in C-C (7442.2 $\mu\text{g} / \text{kg}$). The concentrations of the remaining ions in different articulations did not significantly differ ($p > 0.05$) (Table 5).

Discussion

It is commonly known that under *in vivo* conditions, metal implants release ions into the surrounding tissues from where they can penetrate other organs via the bloodstream (1, 2). High levels of metal ions

cause numerous adverse physiological effects, including cytotoxicity, genotoxicity, carcinogenicity and hypersensitivity to metals(3-8). Previous studies have shown that tissues surrounding hip implants contain elevated levels of cobalt, chromium, nickel, titanium, molybdenum, aluminium and vanadium ions (9-11), and that these metal ions influence the bone metabolism, immune system, development of delayed hypersensitivity and the pathophysiology of aseptic loosening of implants in patients after hip replacement (12). The metal parts of endoprostheses are subject to direct biocorrosion caused by osteoclast activity, which leads to the release of substantial amounts of wear particles and metal ions into the surrounding environment (13-16). The released metal ions, in return, stimulate the immune system and bone metabolism by means of direct and indirect reactions, leading to increased osteolytic activity within the bone around the implant, and thus to its aseptic loosening (17-21). According to Wang (22), metallic particles from titanium alloy spinal implants activated a macrophage cellular response in the spinal tissues similar to that observed in joint prostheses. Inducted an inflammatory, foreign-body reaction in the soft tissue structures adjacent to pain. Cook (23) reported that late operative site pain is most likely caused by local soft tissue reaction to the implants, and late operative site pain of no apparent cause after posterior instrumentation of scoliosis is a distinct clinical entity and is relieved by implant removal in most patients.

In our study no signs suggesting an allergic reaction or infection were found on histological examination. Evaluating the concentrations of metal ions released into the synovial membrane and synovial fluid from stainless steel, cobalt-chromium alloy and titanium alloy endoprostheses fixed to the bone by PMMA, Brien notes that in all the groups of stable hip implants, the concentrations of metal ions in synovial fluid were similar. Tissues from stable and aseptically loose implants were examined. However, the phenomenon of aseptic loosening of the hip implant coexisted with an elevated concentration of metal ions in the synovial fluid and membrane, and this increase was disproportionally high in case of implants made of titanium alloys compared to implants made from steel and Co-Cr alloy(24). Similarly, Huo reports that in a group of patients suffering from aseptic loosening of a cemented hip implant, the concentrations of Co and Cr were four times higher, and the concentration of Ti was on average forty-two times higher, in the direct vicinity of a loose implant than in the joint capsule (25).

Our own evaluation revealed that metal ions, the construction materials of the studied uncemented hip implants, were released into the surrounding environment in significant amounts ranging from several hundred to several hundred thousand $\mu\text{g} / \text{kg}$.

- In the tissues around the cup, the highest average concentrations, reaching several hundred thousand $\mu\text{g} / \text{kg}$, were observed for Ti and Mo ions; lower average concentrations of several thousand $\mu\text{g} / \text{kg}$ were observed for Al and Ni ions, whereas the lowest concentrations, being several hundred $\mu\text{g} / \text{kg}$, were observed for Cr and Co ions.
- In the tissues around the stem, Ti and Al ions were found in the highest concentrations, ranging from several to several hundred thousand $\mu\text{g} / \text{kg}$, while the lowest were found for Mo, Ni, Cr and Co, reaching levels of several hundred $\mu\text{g} / \text{kg}$.

The tissues surrounding the acetabular cups contained significantly higher concentrations of some metal ions than those surrounding the stems. Titanium concentration was typically a hundredfold higher, nickel concentration was six times higher and chromium concentration was four times higher, while the levels of aluminum, cobalt and molybdenum were only slightly higher. To decrease possibility of contamination of tissue with metal debris detached for implants during revisions, the samples were taken before implant removing, however we are aware of such possibility. Unfortunately, no reference or limit values referring to concentration of metal ions in tissues surrounding a hip implant can be found. Available reports which deal with similar cases are dedicated exclusively to cemented hip endoprostheses.

Limitations of this study include moderately limited cases and the lack of a control group. However, it was assumed that metal particles were continuously generated from micromotion or macromotion between the implant junctions for the duration of having endoprosthesis.

Conclusions

In the course of prosthesis use, wear products are produced and transferred to the tissues surrounding the constituent hip endoprosthesis elements. It has been confirmed that the metals used for uncemented hip implant construction release ions to the immediate area of the human body, reaching high levels of concentrations. The present study found the highest concentration to be for titanium Ti ions. In addition, regardless of the endoprosthesis model, the concentrations of Ti and Ni metal ions were found to be higher in tissues surrounding the cup rather than in case of those around the stem.

List Of Abbreviations

Ti - titanium , Co – cobalt, Cr - chrome , Mo - molybdenum, Ni - nickel, Al – aluminium, THR - total hip replacement, Inductively Coupled Plasma Mass Spectrometry - ICP – MS, PE – polyethylene, CRP- c-reactive protein, PMMA- polymethyl methacrylate PE-M- polyethylene-metal, PE-C polyethylene-ceramic, C-C ceramic-ceramic

Declarations

Ethics approval and consent to participate

Ethics committee; KOMISJA BIOETYKI UNIwersytetu Medycznego w Łodzi approved the study. Committee's references numer RNN/2/12/KE

The consent to participate was collected from the patients. They gave general consent for storage and further use of their data in the manuscript.

Consent for publication

Not Applicable

Availability of data and materials

The dataset supporting the conclusions of this article is available upon readers request – please contact corresponding author (aborowski@xl.wp.pl)

Competing interest

The authors declare that they have no competing interests

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Authors' contributions

KK; study conception and design, interpretation of data, drafting of manuscript

PK; acquisition and interpretation of data, critical revision

MS; acquisition and interpretation of data, critical revision

AB; study conception and design, interpretation of data, drafting of manuscript, critical revision

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Not Applicable

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Tables

Table 1. Types of implants used during primary hip arthroplasty

Type of implant	Number of patients	Articulation
Mittelmeier (Osteo)	9 (9 joints)	Autophor stems, CTS screwcup with vitalium (5) or ceramic (4) heads
Parhofer – Mönch (Aesculap)	8 patients (8 joints)	Isotan F stems, Isotan screwcups with Isodur heads
Bicontact (Aesculap)	8 patients (8 joints)	Plasmapore stems, Plasmapore screwcups with Isodur (4) and Biolox (4) heads

Table 2. Metal ion concentrations in tissues surrounding uncemented cups and stems, together with a statistical comparison.

Metal ions		Parameters of ion concentration in µg/kg						P and Z value
		min	max	x	Me	SD	v (%)	
Titanium	stem	768.5	999999	55308.6	12268.6	197431.8	356.9	z=4.672
	cup	2419	999999	553895	999999	495747	89.5	p<0.001
Aluminium	stem	567.8	7977.2	3779.8	3464.7	2374.0	62.8	z=0.987
	cup	888.0	8873.6	4469.8	4383.5	2466.1	55.2	p>0.05
Nickel	stem	54.4	1353.7	568.3	468.2	438.5	77.2	z=2.194
	cup	110.5	27323	3066.4	1057.6	5677.2	185.1	p<0.05
Chrome	stem	113.4	1345.8	553.7	455.7	347.8	62.8	z=1.216
	cup	2.3	31311.5	2104.8	822.0	6239.9	296.5	p>0.05
Cobalt	stem	11.2	367.3	124.4	44.8	126.3	101.5	z=1.317
	cup	6.7	456.7	176.7	188.9	147.9	83.7	p>0.05
Molybdenum	stem	12.9	999999	40787.9	444.7	199841.3	489.9	z=0.073
	cup	13.1	999999	44967.7	807.5	203495	452.5	p>0.05

Min - minimum, max - maximum, x- mean, Me - median, SD - standard deviation , v (%) - variance, p - statistical significance (P - value), z - z value.

Bold fonts indicate significant differences.

Table 3. The relationship between the diameter of the head and the concentration of ions in the tissues around the acetabulum cup and the stem.

Relationship between head diameter and:	Correlation coefficient r	Coefficient of determination r^2	The value of T test	The significance p
The concatenations of ions around the acetabulum cup:				
Ti	-0,22	0,050	1,072	p>0,05
Ni	0,09	0,008	0,430	p>0,05
Mo	-0,32	0,104	1,601	p>0,05
Cr	-0,35	0,12	1,737	p>0,05
Co	-0,32	0,101	1,560	p>0,05
Al	0,73	0,53	4,954	p<0,001
Stężeniem jonów w okolicy trzpienia:				
Ti	-0,34	0,11	1,708	p>0,05
Ni	-0,34	0,12	1,756	p>0,05
Mo	0,14	0,020	0,684	p>0,05
Cr	-0,48	0,23	2,643	p<0,05
Co	-0,36	0,13	1,862	p>0,05
Al	0,77	0,59	5,761	p<0,001

Table 4. The concentration of ions around the acetabulum cup depending on the articulation.

Articulation	The concentrations of ions [µg/kg]					
	min	max	x	Me	SD	v (%)
Ti						
C-C	5,786,8	88994,6	24911,1	11677,8	35934,4	144,4
PE-C	16331,5	999999	737207,0	999999	450252	61,1
PE-M	2419,0	999999	673296,1	999999	490166	72,8
comparison	H=9,241; p<0,01					
Ni						
C-C	110,5	1091,8	755,6	876,5	394,3	52,2
PE-C	257,4	27323,6	4848,8	1261,8	8009,1	165,2
PE-M	373,4	5447,1	2261,7	1213,6	2012,3	89,0
comparison	H=1,670; p>0,05					
Mo						
C-C	13,1	9843,7	4751,9	4159,7	4492,6	94,5
PE-C	33,4	18857,6	3529,9	431,9	6631,2	187,9
PE-M	45,8	999999	112991,6	344,2	332658	294,4
comparison	H=0,507; p>0,05					
Cr						
C-C	366,8	1873,4	949,4	844,6	555,9	58,6
PE-C	2,3	1345,6	658,0	678,1	461,8	70,2
PE-M	465,4	31311,5	4411,5	983,2	10096	228,9
comparison	H=4,063; p>0,05					
Co						
C-C	13,1	389,3	242,3	296,7	153,2	63,2
PE-C	6,7	456,7	85,2	22,9	140,9	165,5
PE-M	145,4	370,9	253,3	234,5	74,6	29,4
comparison	H=7,515; p<0,05					
Al						
C-C	7672,1	8873,6	8154,0	7893,7	492,5	6,0

PE-C	2752,3	5998,1	4737,0	4570,3	950,1	20,1
PE-M	888,0	3223,4	1709,6	1567,2	773,4	45,2
comparisons	H=20,311; p<0,001					

Table 5. The concentration of ions around the stem depending on the articulation.

Articulation	The concentrations of ions [µg/kg]					
	min	max	x	Me	SD	v (%)
Ti						
C-C	768,5	21088,4	8898,0	3411,0	8985,4	101,0
PE-C	4576,8	18732,4	12457,4	12268,6	4018,4	32,3
PE-M	1832,2	999999	133465,9	36407,4	325782,4	244,1
comparison	H=1,408; p>0,05					
Ni						
C-C	98,1	1233,3	555,4	167,1	574,8	103,5
PE-C	78,3	897,7	464,2	435,3	265,8	57,3
PE-M	54,4	1353,7	702,6	765,3	536,8	76,4
comparison	H=0,823; p>0,05					
Mo						
C-C	17,0	999999	201754,0	843,8	446243,8	221,2
PE-C	12,9	1678,5	615,6	456,2	528,7	85,9
PE-M	24,3	1254,6	461,9	200,9	508,4	110,1
comparison	H=1,164; p>0,05					
Cr						
C-C	428,0	863,6	670,4	685,2	165,5	24,7
PE-C	113,4	1148,6	341,3	234,9	285,9	83,8
PE-M	388,9	1345,8	748,5	567,2	365,8	48,9
comparison	H=11,901; p<0,01					
Co						
C-C	44,8	367,3	208,9	207,1	125,8	60,2
PE-C	11,2	68,9	25,7	21,2	16,1	62,7
PE-M	22,5	356,9	198,1	237,5	125,1	63,1
comparison	H=14,737; p<0,001					
Al						
C-C	6973,2	7977,2	7442,2	7439,8	369,9	5,0

PE-C	2281,1	5231,1	4039,1	4567,3	1038,4	62,7
PE-M	567,8	3464,7	1428,3	1244,7	891,7	62,4
comparison	H=19,260; p<0,001					

Figures

Figure 1

Microscopic evaluation revealed "foreign body" type chronic inflammatory infiltration with metal deposits and metallic inclusions in all tissues.

Figure 2

Microscopic evaluation revealed "foreign body" type chronic inflammatory infiltration with PE deposits and metallic inclusions in all tissues.