Does metal porosity affect metal ion release in blood and urine following total hip arthroplasty? A short term study

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Alessandro Bistolfi[1], Andrea Cimino[2], Gwo-Chin Lee[3], Riccardo Ferracini[1], Giovanni Maina[2], Paola Berchialla[2], Giuseppe Massazza[1,2] and Alessandro Massè[1,2]

[1] AO Città della Salute e della Scienza. Department of Orthopeadics, Traumatology and Rehabilitative Medicine, CTO Hospital, Turin, Italy

[2] University of the Studies of Turin, Turin, Italy

[3] Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, PA, USA

Corresponding author:

Alessandro Bistolfi,

AO Città della Salute e della Scienza. Department of Orthopeadics, Traumatology and Rehabilitative Medicine,

CTO Hospital, Via Zuretti 29,

Turin 10126, Italy.

Email: abistolfi@cittadellasalute.to.it

Abstract

Introduction: The surface area of exposed metal in a trabecular-titanium acetabular component is wider compared to traditional-titanium implants. The purpose of this study is to establish if this increase in surface area can lead to a significant increase in systemic metal levels.

Methods: 19 patients with conventional acetabular component and 19 with trabecular-titanium cup were compared. Aluminum, Vanadium and Titanium in blood and urine were assessed before surgery and at intervals for 2 years. The samples were analyzed using an inductively coupled plasma mass spectrometry.

Results: Patients with trabecular-titanium did not have significantly higher metal ion levels compared to patients with conventional cups up to 2 years. A trend over time was statistically significant in both blood and urine for aluminum and titanium concentrations.

Conclusions: The three-dimensionality and the wide surface of the trabecular-titanium acetabular component did not affect metal ion release compared to traditional implants after 2 years.

Keywords

Total hip arthroplasty, ion release, trabecular titanium

Introduction

Total hip arthroplasty (THA) has been shown durable and reliable at relieving pain and improving function in patients with hip arthritis. Titanium alloys are commonly used for uncemented acetabular and femoral components due to their favorable mechanical properties and corrosion resistance and are generally considered to be bio-inert and biotolerant. [1-4]

However, all metals, when implanted in vivo, can undergo degradation and wear and processes such as galvanic and fretting corrosion can lead to release of metal ions and surface degradation products.[5–7] While the focus on metallosis following THA has centered on the release of cobalt and chromium ions from contact between articular surfaces, trunions, and modular neck junctions[8] the role of the ion released from the bulk of metal implants is still unclear. The pattern of interaction is double: first, the metal ions may enter the cells locally and alter the intracellular processes; second, they may undergo wider systemic dissemination reaching tissues and organs such as spleen, lymph nodes, liver, lungs which may be adversely affected.[6,9,10] Deleterious effects including bone loss, prosthetic loosening, local tissue toxicity, hypersensitivity reactions, and malignant cell transformation have also been associated with titanium ions.[11,12]

When studying the effect of metal ion release from implants, the surface area in contact with the biologic environment (bone, blood, muscles) is an important consideration. Trabecular titanium has been successfully used in total hip arthroplasty with excellent survivorship and low complication rates.[13] Its three dimensional architecture (porosity), high coefficient of friction, and modulus of elasticity similar to cancellous bone promote implant stability and bony integration.[14,15]

However, again for the three dimensional architecture, for a given cup size, the surface area of exposed metal in a trabecular titanium acetabular component can be as high as several times compared to a traditional titanium acetabular component (Figure 1). Based on these considerations, the hypothesis of this study is that this increase in porosity and surface area can lead to a significant increase in systemic titanium levels. Consequently, the purpose of this study is to (1) compare the serum and urine concentrations of titanium, aluminum, and vanadium in patients undergoing primary THA using a trabecular titanium acetabular component compared to a traditional titanium acetabular component and (2) follow these ion concentrations up to 2 years following THA.

Materials and methods

Study design

This is a prospective, case-controlled, randomized, blinded study aimed to compare the concentrations in serum and urine of titanium, aluminum and vanadium in two groups of patients implanted with a conventional full Ti6Al4V (titanium, aluminum, vanadium) cup versus a highly porous titanium cup for primary total hip arthroplasty. The study has been approved by IRB Ethic Committee and all patient gave informed consent. Documentation is available upon request.

Implant type and design Control group: Group-D. The Delta-PF acetabular cup (Lima Corporate, Villanova di San Daniele, Udine, Italy) is a plasma-sprayed coated Ti6Al4V hemispherical press-fit metal-backed component with a tapered internal design that enables the use of all bearing couplings in terms of material (ceramic, metal, cross-linked or conventional polyethylene).

The external circumferential grooves improve primary stability, while the external macro-roughened surface has a porous structure that promotes bone integration. The presence of three holes allows for the improvement of the fixation in the case of difficult primary stability or poor bone stock.

Study group: Group-TT. The DELTA-TT (Lima Corporate, Villanova di San Daniele del Friuli, Italy) is a cementless, hemispherical press-fit acetabular component manufactured in titanium alloy (Ti6Al4V) via Electron Beam Melting (EBM) treatment to provide three-dimensionality and surface texture.15 The geometry and specifications are identical to that of the DELTA-PF acetabular component. The DELTA-TT cup is a single body with an external, porous surface with a solid inner surface devoid of screw holes. The proprietary manufacturing process is not a coating: the absence of an interface between the trabecular structure and the bulk promotes structural rigidity, and fatigue resistance while preventing coating detachment and galvanic effects. The structure of this biomaterial is characterized by an average porosity of 65% and by a mean pore diameter of 640 μm to favor the integration with bone.16,17 Studies showed that the material has osteoconductive properties by stimulating osteoblasts proliferation and differentiation18 and osteoinductive properties by favoring human adipose stem cells adhesion, proliferation and differentiation into osteoblasts.19,20 Figure 1 show the macroscopic aspect of the two different studied cups.

All patients from the two groups received the same model of femoral stem: PLS uncemented Ti-Al femoral stem (Lima Corporate, Villanova di San Daniele del Friuli, Italy). This is a press-fit tapered conventional stem. This choice was driven by the intention to eliminate the differences in ions release given by the stem: if the stem is the same for all patients and for both groups, eventual effects given by the stem itself would be the same in all cases.

Patient selection

38 patients undergoing total hip arthroplasty for arthritis were enrolled and randomized into the two groups: (1) Group-D (control group): 19 subjects (10 females, nine males; 69 ± 12 average age) implanted with a conventional plasma-sprayed coated Ti6Al4V hemispherical press fit metal-back acetabular component (Delta-PF cup, Lima Corporate, Udine, Italy) and (2) Group-TT (study group): 19 subjects (nine females, 10 males; 65 ± 8 average age) implanted with a cementless, hemispherical press-fit, trabecular titanium Delta-TT cup (Lima Corporate, Udine Italy). The Aluminum (Al), Vanadium (V) and Titanium (Ti) in both blood and urine were assessed on each patient before surgery (T0) and after surgery at scheduled times: one week (T1), 6 months (T2), 1 year (T3) and 2 years (T4) after THA. At the same time, patients were clinically evaluated. The two groups were matched for age, sex, pathology, and BMI (Table 1).

Clinical and radiographic evaluation Patients were clinically assessed prior to surgery and at 3 months, 6 months and annually after surgery using the Harris hip score (HHS) which is a disease-specific scoring system that includes the categories of function, pain, range of motion and deformities. Additionally, radiographic evaluations were performed at one week, 6, 12, and 24 months postoperatively with standard pelvic anteroposterior (AP), AP and lateral views of the operated hip. The radiographs were used to evaluate cup position, inclination angle, radiolucencies, osteolysis, and any presence of heterotopic peri-articular ossifications.

Analytical methods

Samples collection. Blood samples were obtained from all patients. In an attempt to ensure standardization of total blood volume within the subjects, height and weight were also measured in order to calculate BMI. All vessels used for the collection of blood specimens were verified to be free of metal contamination. Blood samples were collected using two type of Vacutainer tubes: one containing EDTA

anticoagulant to measure Titanium and Vanadium in whole blood, one without anticoagulant to measure Aluminum in serum. The samples for Aluminum were centrifuged at 3,000 rpm for 10 min. Urine samples have been collected by patients at home, stored at 4°C and taken to the laboratory. The samples were frozen and stored at −20°C until the analysis.

Sample analysis. The samples were analyzed using an inductively coupled plasma mass spectrometry (ICP-MS, AGILENT 7500ce) equipped with collision cell (with He for gas collision). The calibration standards were prepared using standard solutions of single elements (PanreacQuimica) ranging from 0.1 to 20 μg/L. The samples of serum and blood were diluted with Triton X100 0.1% while the urine samples were diluted with bi-distilled water, for inorganic trace analysis.

The accuracy of the method was determined using certified reference materials (SERONORM Trace elements: whole blood reference 2,12,105; serum reference 2,01,405; urine reference 2,10,605). There was 90% accuracy while the coefficients of variation (CV) were 4%, and 8% (blood Titanium and Vanadium), 4% (serum Aluminum), and 2%, 3% and 4% for urine Titanium, Aluminum, and Vanadium, respectively). The limit of detection (LOD), calculated as three standard deviations of the background signal obtained on 10 white samples, was 0.3 μg/L, 0.1 μg/L, 0.2 μg/L for Titanium, Vanadium and Aluminum, respectively.

Urinary creatinine was determined by a HPLC (high performance liquid chromatography) (GILSON Mod 234) equipped with Lichrospher column RP-18 (5 μ) and detector DINAMAX Mod UV-1.)) and detector DINAMAX Mod UV-1.high-performance liquid. In blood, serum the results were reported in μg/L as well as for Titanium concentrations in urine while the concentrations in urine for Aluminum and Vanadium were expressed in relation to the creatinine excretion (μg/g creatinine) to account for urine dilution variations.

Statistical analysis

Continuous variables were expressed as median and interquartile range as measure of variability. Two factor ANOVA (group vs. time) with repeated measures on the factor time was used to test the effect of Delta versus TT. Comparison at baseline was performed using Mann-Whitney test. Statistical significance was assumed at $p \leq 0.05$. Data were analyzed using R version 3.02. A power analysis based on differences in metal concentration at T4 (2 years) was conducted prior to recruitment. This analysis, which applied a Dunn Sidak correction for multiple endpoints, indicated that 18 subjects per group would provide statistical power of 75% to detect an effect size of 0.8 for differences in metal concentration at 2 years between groups.

Conflict of interest. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Results

Clinical and radiographic results

The average follow up for this cohort of patients was 3.1 years (range 2–5.5). No patients were lost to follow up. Clinically, all hips were functioning well and no hips were excluded from the final analysis. There were no significant differences in terms of patient demographics, distribution of acetabular component sizes, Harris Hip scores, and acetabular component orientation and position between the 2 groups (Table 1). There were no fractures, infections, aseptic loosening, and dislocations in either group.

Ion analysis results

Patients undergoing THA using a highly porous acetabular component did not have significantly higher metal ion levels compared to patients receiving conventional acetabular components. The metal ion concentrations of Titanium (Ti), Aluminum (Al), and Vanadium (Va) in blood and urine and reported in Tables 2 and 3, respectively, with median and interquartile range as measure of variability are presented at baseline (T0), at 7 days (T1), 6 months (T2), 1 (T3) and 2 years (T4). At baseline, differences between groups were not statistically significant.

A trend over time was statistically significant in both blood and urine for aluminum ($p < 0.001$ and $p = 0.025$ respectively) and titanium ($p = 0.035$ and $p = 0.026$ respectively) concentrations. However, Group x time interaction was not statistically significant for all metals (Ti, Al, Va) in either blood or urine up to 2 years. Figures 2 and 3 compare the result between the two groups over time.

Discussion

Metallosis and adverse events associated with metal ions following THA, with a dose-dependent correlation and with specificity to the type of metal, have come under increased scrutiny and interest in recent years.[6, 21,22]

While most studies have focused on the release and effects of cobalt and chromium ions and particles,[8,23] others studies have also reported issues concerning serum titanium and aluminum levels. Liao and Wurtz showed that titanium and aluminium ions influence mineral formation and osteoid nodules in animal models,[24] while Thompson and Puleo sustained that they affect the normal differentiation of bone marrow stromal cells to mature osteoblasts in vitro.[25] In addition, although the biocompatibility of titanium has been attributed to its oxide film, some authors raised concerns about the corrosion resistance of the titanium.[26,27] The release of titanium from prosthetic devices has been described in animals[28–30] and humans with both well-functioning and failed hip arthroplasties and other devices.[31,32] Krischak and Gebhard studied the accumulation of metals (Fe, Cr, Mo, Ni, and Ti) in the local tissues retrieved after a 12-months implantation period of stainless steel and pure titanium plates for fractures and showed the increased release of toxic, allergic, and potentially carcinogenic ions adjacent to stainless steel but also high concentrations of Ti ions.[33]

Therefore, although titanium ions are usually considered as non-dangerous, the question should be not underestimated (for instance Ti dioxide was recently classified as type 2B carcinogenic) and some authors even claimed that titanium plates should be removed.[34] Since titanium ions have also been associated with severe adverse effects on bone and soft tissues,[11,12] this study sought to evaluate whether the wider surface due to the three-dimensionality of the bulk of the implant (acetabular component) affected the elution of metal ion levels in serum and urine following primary THA.

This study has several limitations. First, the sample size is relatively small and therefore can be subject to type 1 error. However, an a priori power analysis demonstrated that the current sample size would be sufficiently sensitive to detect small changes in ion concentration, thus lessening the likelihood of bias and allows for identification of general trends. Second, this study only evaluates serum and urine oncentrations of titanium and other trace metals and thus, we cannot comment on the ion release at the local implant, joint, and soft tissue levels. However, Lass and Grübl demonstrated high correlation between the joint fluid aspirate cobalt and chromium concentrations to those found in the serum.35 Third, the relatively small sample size did not allow for subgroup analysis of our results based on acetabular component size. Nevertheless, because the median acetabular component diameter was similar between the 2 groups, the impact of this variable is hopefully minimized. Finally, these results did not account for the contributions of the femoral stems to the titanium and trace metal release following surgery. We attempted to control this variable by using the exact femoral stem in both groups, and therefore we

considered as none the effects of the stem on the ion release. Nevertheless, the size of the implant, degree of surface exposure, and quality of host bone can all introduce variability to the release of metal ions from the femoral side. While a solution to this problem would have been to use cobalt chrome femoral components, the primary goal of this study was to attempt to study whether implant porosity and micro-architecture of the acetabular component could affect the degree of release of metal ions. We considered that the difference of the surface area of the two acetabular implants is huge compared with the stems area differences, which therefore have been considered insignificant.

The results show that the serum and urine concentrations of Ti, Al, Va are not affected by the porosity of the acetabular component up to 2 years following primary THA. While little information is available on the effect of implant porosity and metal ion release on orthopedic implants, these results were a bit surprising and contradictory to prior published reports. Ducheyne and Willems showed that release of titanium ions was greater in porous compared to dense bulk implants in a canine model.[36]

Additionally, some authors have shown that increased implant porosity has been associated with increased risk for crevice corrosion and metal ion release. Fojt and Joska reported that susceptibility to crevice corrosion increased once porosity level of the Ti-39Nb dental implant exceeded 24–33%.37 The porous acetabular component used in this study has a modulus of elasticity and implant porosity exceeding these thresholds. Therefore, a difference in serum and urine concentrations would have been expected.

One possible explanation is that crevice corrosion is a process that develops over a longer period of time. Two years may not be sufficient time period to evaluate this variable. Future, longer term studies are necessary to determine the precise influence of implant micro-architecture on corrosion and metal ion release.

The results of this study also show an increasing level of Ti, Al, Va in both serum and urine over time following primary THA. There were no differences in the degree and rate of ion concentrations between both groups. The persistence of elevated titanium levels following arthroplasty is consistent with previously published reports. Nam and Keeney evaluated the concentrations of various metals following THA in young and active patients and reported that whole blood titanium levels were consistently elevated at all postoperative points versus preoperative levels.[38] Similarly, Yi and Bo reported in a prospective series of 89 ceramic on metal primary THAs that serum Ti levels were significantly elevated compared to normal reference lab values at a mean of 50 months follow up.[39] Finally, Hutt and Lavigne demonstrated that while whole blood Ti levels remained persistently elevated following surgery, there was no appreciable increase between years 2–5 following primary THA.40 The clinical significance of these elevations in titanium ion concentrations or its long term effects are currently unknown.

Although, titanium and its byproducts are generally considered relatively bio-inert, Ti ions have been shown to influence osteogenesis and osteoblasts differentiation.[39,40] Thus, the presence of elevated Ti ion levels following arthroplasty or factors influencing their release should not be neglected.

Conclusion

The three-dimensionality and the wide surface of the trabecular metal acetabular component in contact with bone and blood, did not affect the rate and quantity of Ti, Al, Va ion release in patients undergoing primary THA up to 2 years, when compared to traditional titanium implants. Therefore the hypothesis of the study that metal porosity may affect metal ion release in blood and urine following THA, has not been confirmed. Following the implant of the arthroplasty, there was a similar increase over time in Ti ion serum and urine concentration for both groups (trabecular and conventional cups). Nevertheless, since trabecular implant have reached a great popularity, the results may have a clinical implication: while these findings show certain amount of metal release from the bulk implant, they also show that trabecular

titanium, despite of the wider surface, is as safe as conventional implants at the state-of-the-art in the terms of metal ions release, at least after two years follow-up.

Authors' note

This study has been approved by IRB Ethic Committee on July 15th 2009, dossier CEI 456 and resolution 301/DG/2009/DS.

Declaration of conflicting interests

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Figure and Tables

Figure 1. Macroscopic aspect of the two cups similar to those used for the study to show the difference in roughness and 3D surface area between the two materials. 1 (above), Delta-PF acetabular cup (Lima Corporate, Villanova di San Daniele, Udine, Italy). (1a) macroscopic aspect of the cup (50 mm diameter) (1b) detailed image of the surface (the scale reported by the rule is millimeter). 2 (below), Delta-TT (Lima Corporate, Villanova di San Daniele del Friuli, Italy). (2a) macroscopic aspect of the cup (50 mm diameter) (2b) detailed image of the surface (the scale reported by the rule is millimetre).

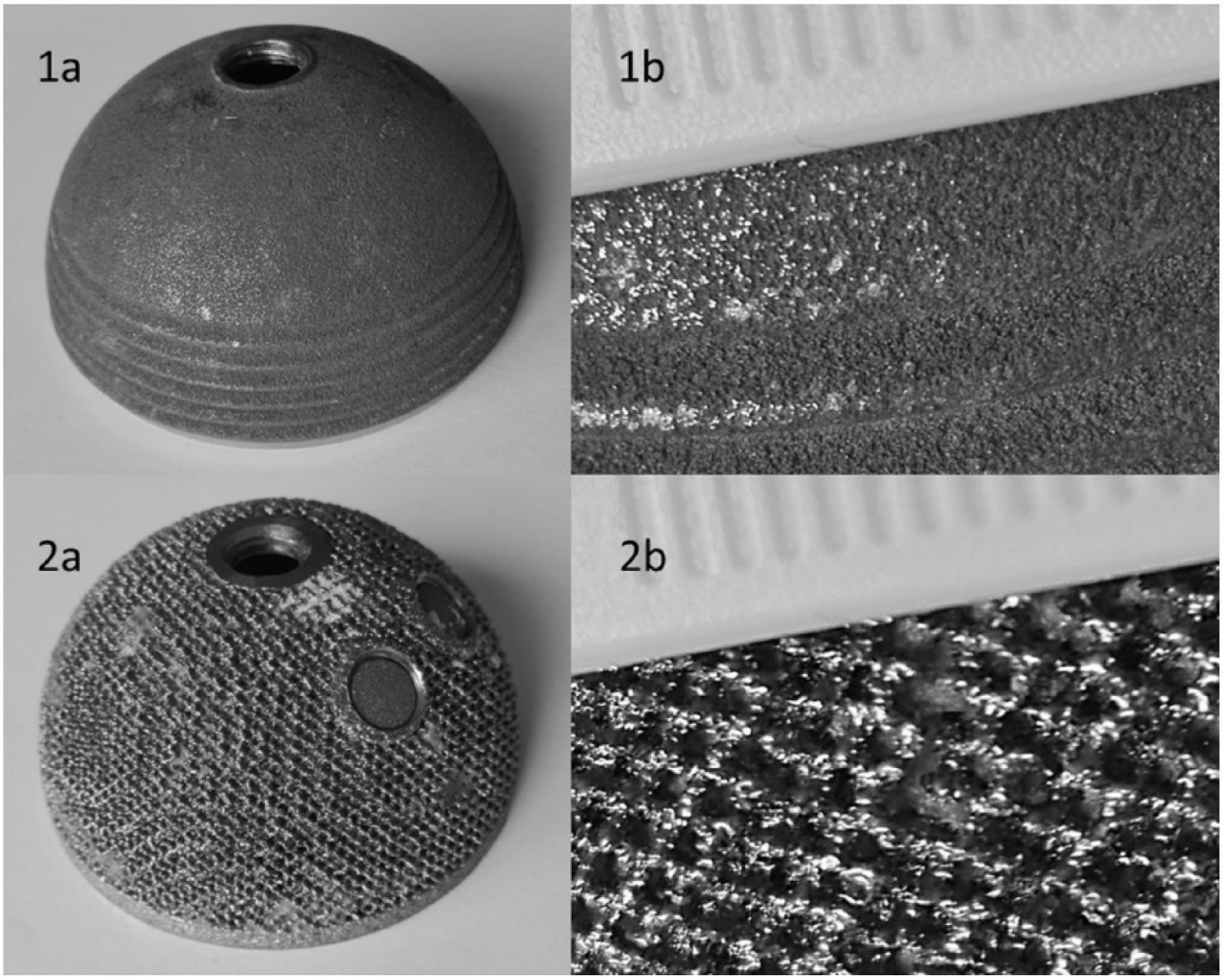

Figure 2. Metal concentration in blood by group over time. The results are reported in µg/L. D = Group-D (control group), Delta PF cup (conventional cup); TT = Group-TT (study group), Delta TT cup (trabecular cup).

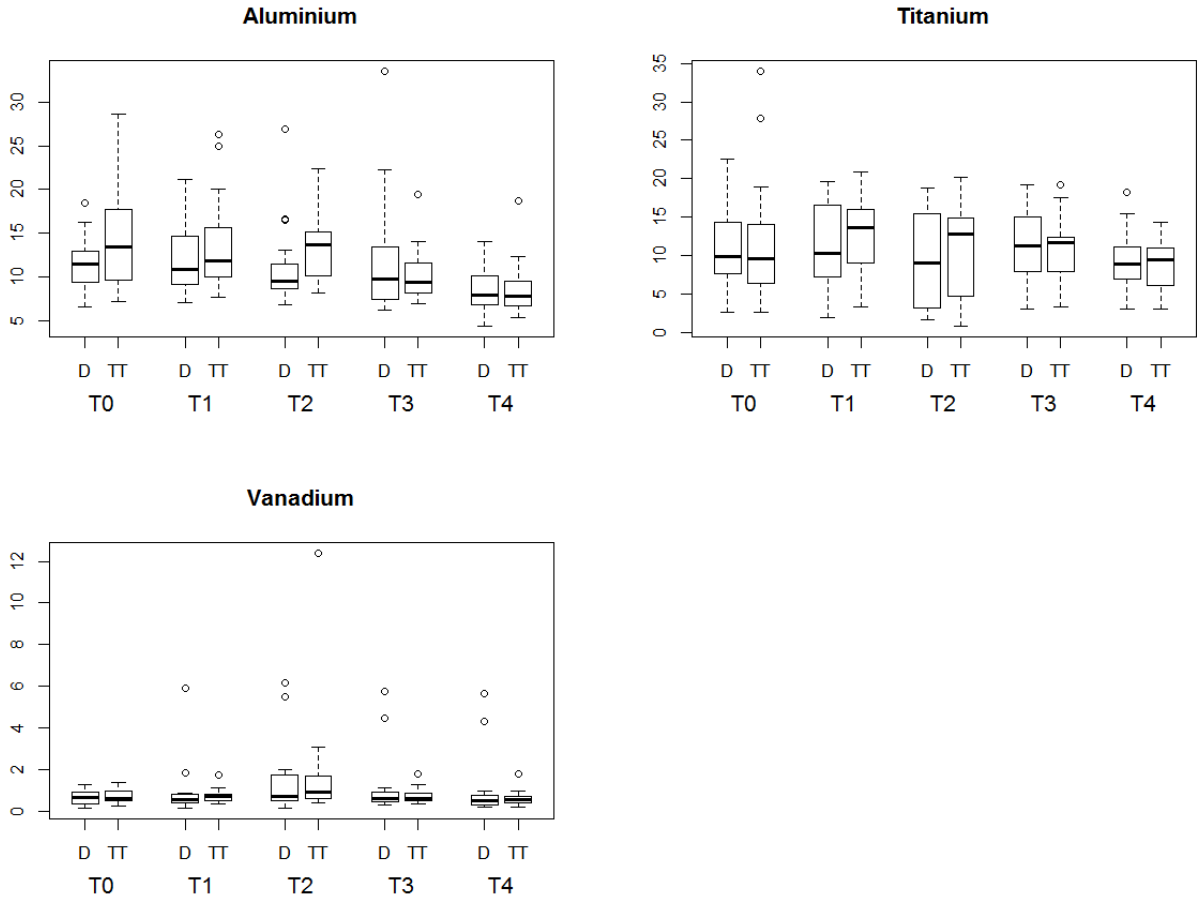

Figure 3. Metal concentration in urine by group over time. The Titanium concentrations are reported in µg/L. Aluminum and Vanadium concentrations are expressed µg/g creatinine (in relation to the creatinine excretion). D = Group-D (control group), Delta PF cup (conventional cup); TT = Group-TT (study group), Delta TT cup (trabecular cup).

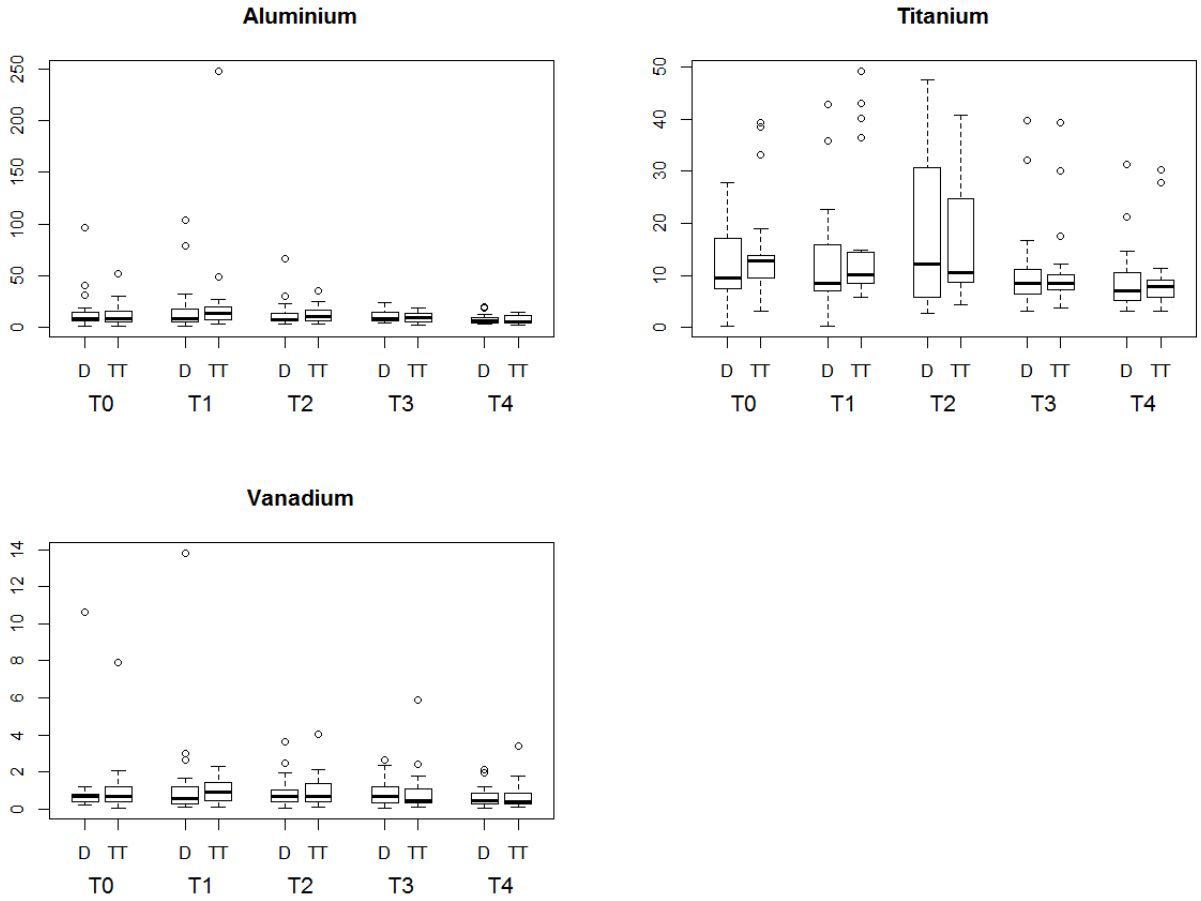

Table 1. Patients demographic and HHS results.

Parameters (Mean; SD)	T0			T1			T2			T3			T4	
	D	TT	P	D	TT	P	D	TT	P	D	TT	P	D	TT
Age (years)	69 ± 12 y	65 ± 8 y	n.s	–	–	–	–	–	–	–	–	–	–	–
Sex	9M–10F	10M– 9F	n.s	–	–	–	–	–	–	–	–	–	–	–
Diagnosis	12 Arthritis 5 necrosis 2 post-traumatic arthritis	15 Arthritis 4 necrosis	n.s	–	–	–	–	–	–	–	–	–	–	–
BMI	< 40	< 40	n.s	–	–	–	–	–	–	–	–	–	–	–
Total Score	53.2	53.5	n.s	84.6	85.2	n.s	88.2	88.3	n.s	88.6	88.8	n.s	89.1	89.2
Pain	20	20	n.s	42.3	42.1	n.s	43.3	43.4	n.s	43.3	43.4	n.s	43.3	43.4
Limp	6.4	6.4	n.s	9.4	9.4	n.s	10.2	10.1	n.s	10.5	10.5	n.s	10.6	10.7
Support	8.1	8.1	n.s	9.0	9.0	n.s	10.7	10.7	n.s	10.8	10.8	n.s	10.8	10.8
Distance	6.9	7	n.s	9.5	9.5	n.s	9.7	9.7	n.s	10.6	10.6	n.s	10.8	10.8
Stairs	2.1	2.1	n.s	3.2	3.1	n.s	3.7	3.7	n.s	3.8	3.8	n.s	3.9	3.9
Shoes, socks	2.2	2.2	n.s	3.0	3.0	n.s	3.7	3.7	n.s	3,7	3,8	n.s	3.8	3.7
Sitting	3.9	3.9	n.s	4.7	4.7	n.s	4.7	4.7	n.s	4.9	4.9	n.s	4.9	4.9
Pub. Transp.	0.7	0.7	n.s	1.0	0.9	n.s	1.0	1.0	n.s	1.0	1.0	n.s	1.0	1.0
Flexion	73°	73°	n.s	106°	107°	n.s	117°	117°	n.s	117°	118°	n.s	118°	118°
Abduction	18°	18°	n.s	32°	31°	n.s	33°	34°	n.s	36°	36°	n.s	36°	36°
Adduction	11°	11°	n.s.	20°	20°	n.s	21°	21°	n.s.	23°	23°	n.s.	23°	23°
Ext. rotation	13°	13°	n.s.	27°	26°	n.s	27°	27°	n.s.	28°	28°	n.s.	28°	28°
Int. rotation	5°	5°	n.s.	16°	16°	n.s	16°	16°	n.s.	17°	17°	n.s.	17°	17°

Table 2. Differences in metal concentration over time between groups in blood. Values reported are I quartile/ median/III quartile

Time	N	delta	tt	p-value		
		(N=19)	(N=19)	Group	Time	Group x time
Aluminium						
T0	38	9.35/11.50/12.95	9.60/13.40/17.75			
T1	38	9.10/10.90/14.60	9.95/11.80/15.60			
T2	37	8.60/ 9.50/11.35	10.17/13.70/15.15	0.063		<0.001
T3	38	7.35/ 9.80/13.43	8.09/ 9.40/11.55			
T4	38	6.75/ 7.90/10.05	6.67/ 7.73/ 9.45			
Titanium						
T0	38	7.70/ 9.90/14.40	6.45/ 9.60/14.10			
T1	38	7.25/10.29/16.55	9.10/13.60/15.95			
T2	37	3.30/ 9.05/14.63	4.75/12.78/14.86	0.912		0.035
T3	38	7.95/11.34/15.05	7.93/11.70/12.35			
T4	38	6.92/ 8.90/11.15	6.10/ 9.43/10.94			
Vanadium						
T0	38	0.37/0.67/0.94	0.51/0.64/0.96			

T1	38	0.41/0.55/0.83	0.54/0.72/0.82		
T2	37	0.50/0.71/1.55	0.62/0.92/1.69	0.988	0.662
T3	38	0.49/0.60/0.95	0.53/0.63/0.88		
T4	38	0.33/0.49/0.77	0.43/0.56/0.72		

Table 2. Differences in metal concentration over time between groups in urine. Values reported are I quartile/ median/III quartile

Time	N	delta	tt	p-value		
		(N=19)	(N=19)	Group	Time	Group x time
Aluminium						
T0	38	7.03/ 8.76/14.63	5.42/ 9.22/16.28			
T1	38	5.91/ 9.01/17.65	8.3/14.38/19.99			
T2	37	6.75/ 7.56/13.67	6.72/10.31/16.67	0.823		0.025
T3	38	6.28/ 8.42/15.30	5.89/10.0/14.08			
T4	38	4.78/ 6.78/ 9.72	4.59/ 5.98/12.10			
Titanium						
T0	38	7.42/ 9.56/17.04	9.53/12.7/13.86			
T1	38	6.96/ 8.4/15.78	8.54/10.2/14.36			
T2	37	6.23/12.15/30.33	8.65/10.65/23.64	0.251		0.026
T3	38	6.42/ 8.56/11.09	7.20/ 8.51/10.06			
T4	38	5.25/ 7.12/10.56	5.90/ 7.79/ 9.01			
Vanadium						
T0	38	0.37/0.67/0.83	0.38/0.70/1.22			
T1	38	0.30/0.58/1.20	0.49/0.93/1.44			
T2	37	0.43/0.67/1.00	0.37/0.70/1.28	0.275		0.107
T3	38	0.34/0.70/1.19	0.34/0.47/1.12			
T4	38	0.28/0.48/0.87	0.25/0.39/0.87			