Levels of systemic metal ions in patients with intramedullary nails

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Background **It is being increasingly recognized that orthopedic implants are associated with adverse tissue responses, mediated by degradation products. Recent interest has been focused on the production of metal ions from hip arthroplasty. Few studies have reviewed fracture fixation devices and their metal ion production.**

Methods **61 subjects were enlisted into the study, with 3 subgroups. 21 subjects had Russell-Taylor intramedullary tibial nails in situ for 26 (21–32) months (316LVm stainless steel), 20 subjects had TriGen intramedullary tibial nails in situ for 43 (35–51) months (Ti-6Al-4V titanium alloy), and the remaining 20 subjects did not have any implant in situ and served as controls. Blood samples were taken and serum chromium, molybdenum, titanium, aluminium, and vanadium concentrations were measured using inductively coupled plasma (ICP) techniques.**

Results **The 3 groups were matched for age, sex, and BMI. The subjects with Russell-Taylor nails had elevated levels of chromium (0.10 µg/L) with median concentrations 2.5 times higher than those of the control group. The subjects with TriGen nails had less significantly elevated levels of titanium (6.5 µg/L).**

Interpretation **Stainless steel implants show significant differences from titanium implants in the dissemination of metal ions. Although the levels of chromium were elevated, the overall levels were modest when compared to published data regarding metal ion release and hip arthroplasty. Intramedullary nails are, however, often used in younger patients. If not removed, they may result in prolonged exposure to metal ions.**

The materials used in modern fixation of fractures are well tolerated by the body; however, it is incorrect to call them "biologically inert". All metal implants in vivo may undergo corrosion and wear, which will result in the production of metal ions and surface degradation particles (Case et al. 1994, Jacobs et al. 1998a). In fracture fixation devices such as intramedullary nails, this phenomenon may be facilitated further by movement and micromotion of the implant, galvanic corrosion between materials of different composition in close proximity, and fretting corrosion between the nail-locking screw interface (Jacobs et al. 1998a).

The shedding of metal ions and degradation particles greatly increases the total surface area of contact between the implanted material and the biological environment. This facilitates the exchange of potentially toxic elements, both at the local and the systemic levels. Locally, metal ions enter the cells and may alter intracellular processes. Systemically, they undergo wider dissemination as both free ions and ingested particles that are transported to sites remote from the implant. These sites include regional lymph nodes, the lungs, and the spleen, the functions of which may be affected (Rae 1975).

To date, most of the research within this field has dealt with metal ion release in relation to hip arthroplasty. There has been very little research into dissemination of metal ions from fracture fixation devices. We believe that the study of fracture fixation devices is warranted, as they are often used in a younger cohort of patients who commonly sus-

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tain long bone fractures from road traffic accidents and sporting pursuits.

We determined metal ion levels in patients who had undergone intramedullary nailing for tibial shaft fractures, either with a stainless steel or a titanium intramedullary nail.

Patients and methods

Study groups

The study was approved by the Grampian Research Ethics Committee and all patients recruited signed an informed consent form. In order to meet the criteria for enrollment in this cohort study, patients had to have had their tibial intramedullary nail inserted between 2000 and 2002. In addition, the patients were required to have had no other metal implants in situ and no systemic disease that might alter their systemic metal ion levels.

61 patients were enrolled in the study. 20 did not have an implant in situ and had no systemic disease, and they served as the control group. The remaining 41 patients had had an intramedullary nail inserted for the treatment of a tibial shaft fracture; all had clinically and radiologically progressed to union. The 41 patients were divided into 2 groups on the basis of the composition of the intramedullary nail. No metal implant other than the intramedullary nail had been used in any patient.

Group 1 consisted of 21 patients who had had a stainless steel Russell-Taylor intramedullary nail inserted. The nails had been in situ for a mean duration of 26 (21–329) months. The Russell-Taylor nail (manufactured by Smith and Nephew) is a 316LVm stainless steel nail. Its composition is carbon 0.03%, manganese 2.0%, phosphorus 0.025%, sulfur 0.01%, silicon 1.0%, chromium 17–19%, nickel 13–15%, molybdenum 2.25–3.5%, copper 0.5%, and nitrogen 0.1%. The nails included in this study were locked proximally and distally with the appropriate stainless steel cortical screws.

Group 2 consisted of 20 patients who had had a titanium TriGen intramedullary nail inserted. The nails had been in situ for a mean duration of 43 (35–51) months. The TriGen nail (also manufactured by Smith and Nephew) is a Ti-6Al-4V titanium nail, with a composition of titanium 88%, aluminium 6%, vanadium 4%, and additional trace metals 2% (none of which was greater than 0.5%). Again, the nails were locked proximally and distally with titanium cortical screws.

Group 3 consisted of the 20 control patients who did not have an implant or systemic disease.

The 3 groups were matched for age, sex, and BMI. The Russell-Taylor group (group 1) had a mean age of 38 years (SD 14) and was composed of 13 males and 8 females. This group had a mean BMI of 25 (SD 3.7). The TriGen group (group 2) had a mean age of 36 years (SD 12) and was composed of 14 males and 6 females. This group had a mean BMI of 25 (SD 6). The control group had a mean age of 36 years (SD 9) and was composed of 13 males and 7 females. This group had a mean BMI of 25 (SD 4).

Collection of specimens

Blood samples were obtained from all patients at the Orthopaedic Research Clinic, Aberdeen Royal Infirmary. 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 and utensils that were used for the collection of specimens were verified to be free of metal contamination. Blood samples were obtained using a 14-gauge Adsyte BD cannula (Becton Dickinson, Oxford, UK) and duplicate polypropylene syringes. The cannula was inserted into the antecubital fossa; on removal of the metal stylus, the first syringe was used to flush the system, and was subsequently discarded. Metal-ion analysis was performed on the contents of the second syringe. The blood was separated and frozen at –80ºC as serum and clot fractions.

Metal ion analysis

Metal ion analysis was done blind. The concentrations of serum chromium and vanadium were measured on a Perkin Elmer Elan ICPMS with DRC. The concentration of serum molybdenum was measured on a Perkin Elmer Elan 6000 ICPMS. The concentration of serum titanium was measured with a Thermo Electron x-Series ICPMS fitted with high-sensitivity Xs cones and a Burgener AriMist nebulizer. The instrument was operated in collision mode using 1% NH_3/He as the collision gas. Serum aluminium was analyzed on a

Median serum ion concentrations (interquartile values: Q_1; Q_3) for the control group, the Russell-Taylor (stainless steel) group, and the TriGen (titanium) intramedullary nail group

	Control group (n = 20)			Russell-Taylor group (n = 21)			p-value
	Q_1	median	Q_3	Q_1	median	Q_3	
Chromium	0.04	0.04	0.04	0.04	0.10	0.22	0.005
Molybdenum	0.40	0.88	1.26	0.35	0.75	1.25	0.6
	Control group (n = 20)			TriGen group (n = 20)			p-value
	Q_1	median	Q_3	Q_1	median	Q_3	
Titanium	2.73	4.70	6.10	3.38	6.45	7.65	0.04
Aluminium	0.50	2.20	3.45	0.73	2.55	4.05	0.4
Vanadium	0.015	0.015	0.015	0.015	0.015	0.038	0.7

All measurements are expressed in μg/L. The limits of detection, in μg/L, were 0.08 for serum chromium, 0.06 for serum molybdenum, 0.4 for serum titanium, 1.0 for serum aluminium, and 0.03 for serum vanadium.

Varian ICP Vista optical emission spectrometer.

The detection limits, in μg/L, were 0.08 for serum chromium, 0.06 for serum molybdenum, 0.4 for serum titanium, 1.0 for serum aluminium, and 0.03 for serum vanadium. Concentrations below the detection level were approximated to be one-half of the detection level in order to permit statistical analysis (Jacobs et al. 1998b, Grubl et al. 2006).

Statistics

All statistical analyses were performed using SPSS version 14.0. Initially, descriptive analyses were employed and data are reported as the median and interquartile range for each group. The groups were found to be non-parametric; thus, intergroup comparisons between each of the two experimental groups and the control group were made using the Wilcoxon-Mann-Whitney test. Values were considered significant at $p < 0.05$.

Results

We found highly significant elevation in serum chromium in the Russell-Taylor nails, with median concentrations that were 2.5 times higher than those in the control group.

The elevation of serum titanium levels in patients with TriGen nails, when compared with controls, were less statistically significant ($p = 0.04$).

There were no statistically significant differences in serum levels of molybdenum, aluminium, and vanadium between groups, the median level of vanadium being below the level of detection (Table).

Discussion

Much of the interest in long-term biocompatibility of orthopedic implant materials has concentrated on the metal components of joint arthroplasty, because of their tendency to undergo corrosion and wear.

Despite this current interest in metal ion dissemination, there have been no widely accepted standardized protocols for metal ion analysis. This has resulted in considerable variation in the protocols and analytical techniques that various laboratories have used and reported.

Despite this variability, however, the levels of serum chromium reported for patients with metal-on-metal hip arthroplasties have been reasonably consistent, averaging 2.0 μg/L (Jacobs et al. 1996, Brodner et al. 1997, 2003, MacDonald et al. 2003, Savarino et al. 2003, MacDonald 2004, Dunstan et al. 2005, Heisel et al. 2005). Despite the recent interest in metal ion release from arthroplasty, few studies dealing with metal ion release from fracture fixation devices have been published. In the present study, the levels of chromium were sig-

nificantly elevated in the stainless steel nail group (0.10 µg/L) relative to the control group; however, this figure is considerably lower, by about 20-fold, than the levels reported for modern metal-on-metal hip arthroplasties.

There have been few orthopedic studies dealing with titanium and aluminium levels. Jacobs et al. (1998b) reviewed the serum concentrations of titanium and aluminium in groups of patients with various combinations of uncemented and cemented femoral and acetabular components of titanium alloy. There was no statistically significant difference in serum aluminium concentration in any particular group, but the titanium levels were elevated 3-fold in the group with uncemented acetabular and femoral components, with a mean concentration of 4.1 µg/L. Again, titanium levels were elevated in patients with loose prostheses as compared to patients with stable prostheses and control patients. The mean serum titanium levels (8.1 µg/L) were approximately twice as high as corresponding levels in patients with stable prostheses and controls (Jacobs et al. 1991). The levels of titanium described in this study are similar to levels reported for control subjects in previous studies (Jacobs et al. 1991, 1998b). Although there were elevated titanium levels in the TriGen nail group (at 6.5 µg/L on average) as compared to the control group, the relatively small increase suggests either that low levels of metal ion are released or that there is efficient excretion by the body.

Levels of the trace metals molybdenum, aluminium, and vanadium were not significantly elevated in any group, and this appears to reflect the results of other studies that have quoted values for these trace elements in relation to hip arthroplasty (Savarino et al. 2003).

It is important to realise that concentrations of metal ions detected in the blood may be distinctly different from those actually found at the level of local tissue adjacent to the implant. Several studies have demonstrated accumulation of metal particles in tissues adjacent to implants, including arthroplasties and fracture fixation devices. Elevated levels of chromium, iron, nickel, and aluminium have also been found in the regional lymph nodes, the distant lymph nodes, the liver, and the spleen of post-mortem subjects, and further increases were found when the implants were loose (Case et al. 1994, Urban et al. 2000). To date, there have been no publications comparing local tissue levels of metal ions with those levels found in the circulation.

The dissemination of metal ions has been linked to alterations in the immune system and hypersensitivity reactions (Hallab et al. 2001). Studies into possible carcinogenic effects have shown a correlation between chromosomal damage and elevations in degradation products and metal ions, in both in vitro and in vivo studies. This appears to be dose-dependent and specific to the type of metal (Heath et al. 1971, Daley et al. 2004, Davies et al. 2005).

Large epidemiological studies reviewing correlation between cancer incidence and hip arthroplasty have failed to show a causal link. However, several studies have noted moderate elevations in hemopoietic malignancies (myeloma and leukemia) in patients with hip arthroplasties (Paavolainen et al. 2000, Signorella et al. 2001, Tharani et al. 2001). This is of some concern, because intramedullary nails may well disseminate unknown quantities of metal ions into the intramedullary canal, and thus directly into the hemopoietic system. This is supported by animal studies, which have demonstrated increases in neoplasia adjacent to intramedullary metal rods (Sinibaldi et al. 1976).

Unlike arthroplasty, however, it is possible to remove fracture fixation devices after fracture union. This is not universally performed because of the possibility of complications. These complications can include incomplete removal, infection, and refracture. One phenomenon specific to tibial nails is that there is an increased incidence of subsequent anterior knee pain in previously asymptomatic patients following removal of metalwork (Sanderson et al. 1992, Boerger et al. 1999). One alternative to removal is modification of the alloys and materials that are inserted in patients. It is quite clear that stainless steel implants have a substantial degree of corrosive load, which is greater than that of titanium implants. However, even these could be modified to reduce the shedding of metal ions. Recent studies have demonstrated that the titanium alloy Ti-15Zr-4Nb-4Ta has a significantly lower degree of metal ion release (approximately 30% less) than the standard titanium alloy (Ti-6Al-4V), both in vitro and when inserted into animal tibias (Okazaki et al. 2004, Okazaki and Gotoh 2005).

Of course, these alloys must also fulfill the other mechanical requirements for the fixation of fractures.

Dissemination of metal ions is not isolated to hip arthroplasty, but also extends to other implants in vivo. Fracture fixation devices such as intramedullary nails show continued release of metal ions, as demonstrated in this study, and are often used in younger patients. The extent and effect of this low-level exposure reported in this study are not known. Further studies are required to assess changes in ion release over time, and to measure both local tissue levels and cellular changes at the site of the implant. This may have implications for surgeons and patients, in deciding whether all fracture fixation devices should be removed once the fracture has united.

MSP and GPA: design of study, collection of specimens, and writing of the manuscript. TDBL: serum analysis performed blind.

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