Systematic investigation of metallosis associated with magnetically controlled growing rod implantation for early onset scoliosis

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Abstract

Aims: To systematically investigate metallosis in patients with magnetically controlled growing rods (MCGRs) and reveal the complete metal particle profile of the tissues surrounding the rod.

Patients and Methods: This was a prospective observational study of patients with EOS treated with MCGRs and undergoing rod exchange consecutively recruited between 2/2019 to 1/2020. The configurations of the MCGR were studied to reveal the distraction mechanisms, with critical rod parts being the distractable piston rod and the magnetically driven rotor inside the barrel of the MCGR. Metal-on-metal contact in the form of ring-like wear marks on the piston was found on the distracted portion of the piston immediately outside the barrel opening through which the piston rod distracts. Biopsies of paraspinal muscles and control tissue samples were taken over and away from the wear marks, respectively. Spectrum analyses of the rod and biopsies were performed to reveal the metal components and concentrations. Histological analyses of the biopsies were performed with hematoxylin and eosin staining.

Results: Ten patients were recruited (mean age: 12±1.3; 80% female). Titanium (Ti), Vanadium (V) and Neodymium (Nd) concentrations in the biopsies taken near the wear marks were found to be significantly higher than those in the control tissue samples. Significantly increased Nd concentrations were also found in the tissues near the barrel of the MCGR. Chronic inflammation was revealed by the histological studies with fibrosis and macrophages infiltration. Black particles were present within the macrophages in the fibrotic tissues.

Conclusion: Ti and V were generated mainly at the barrel opening due to metal-on-metal contact, whereas the Nd from the rotor of the MCGR is likely released from the barrel opening during distraction sessions. Phagocytotic immune cells with black particles inside raise cautions of the long-term implications of metallosis.

Keywords: Early onset scoliosis; Magnetically controlled growing rod; MCGR; Metallosis; Spectrum analyses; Histological analyses

Introduction

Early onset scoliosis (EOS) requires early treatment as they occur in young children. If not treated timely, the spinal deformities may progress rapidly with growth leading to disfigurement and cardiopulmonary insufficiency.[1-7] The gold standard for surgical management of EOS is growing rods, which allow spinal growth while maintaining correction of the deformity.[8-10] Traditional growing rods (TGRs) require repetitive distraction surgeries around every 6 months.[8,9,11-15] However, repetitive surgeries have significant disadvantages including risk for anaesthetic and wound complications.[2] These patients also result in significantly lower health-related quality of life.[16]

Magnetically-controlled growing rods (MCGRs) with an external handset controller allowing for non-invasive out-patient distractions[17,18] has revolutionised EOS surgery. It allows for safe distractions with continuous neurological monitoring in conscious patients and has a reported clinical efficacy same as TGRs.[2,8,17,19,20] The MCGRs have additional benefits of 3-dimensional correction of the deformity and expanding potentials for correction of severe deformities.[21-30] Frequent distractions can be performed to mimic normal physiological growth[23], providing advantages of avoiding spine autofusion associated with forceful surgical distractions at irregular intervals.[22] However, complications are not uncommon[31,32], with a rate up to 40% including distraction failure and proximal anchor loosening, requiring reoperation,[33] which is similar to TGRs.

Unique complications associated with MCGRs have come to our attention, including the crooked rod[34] and metallosis.[22,28,35] Macroscopically, during revision surgery, metallosis manifests as a pseudo-capsule formation around the barrel opening and an accumulation of black/grey particles. A study reported wear particles from inside of the MCGR sleeve (barrel) are mainly titanium (size approximately 3μm).[36] The MCGR wear particles' components and concentrations in human tissues is unclear. Therefore, systematic investigations of the particles in the tissue surrounding the MCGR should be conducted.

A previous study[37] tested the blood of patients with MCGRs and observed raised vanadium (V), titanium (Ti) and aluminium (Al) in comparison with TGRs. The MCGRs are configured by Ti-6Al-4V ASTM F136 titanium alloy but also contain magnetic compounds in its rotor (magnet Neodymium alloy: $Nd_2Fe_{14}B$).[25] From our dissection of an explanted MCGR, we observed a possible design flaw in the piston rod portion of the MCGR causing distraction failure[34], and reported increased wear marks at the barrel opening. Along with the previously observed O-ring seal failure[38], we hypothesise that Nd should also be present in the soft tissues in addition to Ti and V, because the wear particles of the magnetic rotor can be released during rod distractions. Furthermore, one previous histological study[36] observed chronic inflammatory responses associated with metallosis for patients with the MCGRs under low magnification and we hypothesise that under high magnification, immune cells with phagocytic foreign particles will be discovered.

This study aims to systematically investigate the metallosis in patients with MCGR and to reveal the main metal particle profile of the patient tissues surrounding MCGR. Objectives include 1) quantitatively examining the metal profile from the tissue biopsies surrounding the implants; 2) revealing the phagocytotic immune response to the wear particles of the MCGR; and 3) exploring any factors that contribute to increased metal concentrations in tissue.

Patients and Methods

All consecutive patients with EOS and MCGRs implanted undergoing rod exchange were recruited between 02/2019 to 01/2020. Ethics was approved by the local institutional review board (UW16-336). Written consent was obtained from parents or legal guardians. Patients were excluded if the consent process were not completed, or the patient had existing pathologies that could influence the study results, including previous TGRs implantations, metal implants for other purposes; traditional Chinese herbal medicine treatment, and had the MCGRs implanted for less than six months which might indicate a device failure. No patients were excluded according to these criteria.

Clinical data

Clinical parameters included gender, patient's age at initial implantation, duration of MCGRs implanted (days), body mass index (BMI) at the time of surgery, and the number of distraction sessions (DS: monthly 2mm distractions) before revision surgery. All patients had subfascial dual rods inserted in a standard and offset configuration. At implantation, all patients had rods inserted with just enough distraction over the concave rod to achieve a balanced spine. No additional distractions were performed intraoperatively. As rod wearing could be a result of combined effects from DS and BMI, the ratio of DS/BMI was also studied for its contribution. On X-rays, the amount of kyphotic bending (KB) and lordotic bending (LB) degrees in the rod was measured. Bending angles were measured by the angle between two tangents drawn from the midpoint of the barrel and the distal end of the MCGR. KB indicated the proximal thoracic rod bending and LB indicated the distal rod bending (Figure 1). All measurements were performed on PACS system by an investigator blinded to the results of the metallosis examination.

Biopsies obtained at rod exchange

For all patients included in this study, two biopsies were taken of the paraspinal muscles surrounding the portion of the barrel housing the magnets (BM) and the barrel opening (BO) (Figure 2A). These two biopsy sites were chosen because of the location of the metallosis during surgery and its relationship to the distraction mechanism of the MCGR (Figure 2B). We speculated increased wear particles could be accumulated at these two sites. MCGR has a thrust bearing (Figure 2C1) allowing the magnetic rotor (Figure 2C2) to rotate over it. The rod distraction was attained with the external remote controller by generating a rotating magnetic field which, in turns, rotates magnetic rotor and, thus, the threaded stud (Figure 2C3) inside the sleeve portion of the MCGR barrel (Figure 2C4). The threaded stud will be turned out of the piston rod which, not being able to rotate due to some geometric design features, go out of the barrel gradually through the BO (Figure 2C5-6). We suspected that the wearing is induced by the time-varying forces acting upon the MCRG due to the physical activities of the patient. After the coating of the piston rod at the BO is damaged, there is a metal-on-metal contact between the rod and the barrel, which may be prone to producing particles evidenced by the wear marks (Figure 2C7). A small volume of normal tissues (approximately 5mm^3 in size and 3cm distal to the piston rod) were taken from each patient as control.

Each biopsy sample was divided into two equal parts, one for spectrum analyses of the metal concentrations and another for histological study. The biopsy samples were placed in PBS (10X; ginco; ThermoFisher Scientific; US) immediately after collections and placed on dry ice before transfer to the -80°C fridge for storage and further analysis.

Spectrum analyses

We examined the major metal components of the piston rod using a Zeiss Sigma 300 FEG scanning electron microscope (SEM) equipped with an energy dispersive spectrometer (EDS; Oxford instruments; UK). Six samples were taken at the wear marks. The examination process followed the manual from EDS manufacturer (https://www.malvernpanalytical.com). Briefly, a recorded proportion of the collected particles was first mixed with lithium tetraborate. Then using a propane fluxer, the mixture was vitrified into circular glass disks. The discs were then irradiated by X-rays emitted from an internal X-ray tube. The characteristic fluorescence emission was unique for each element. The unique emission was then dispersed by a single crystal and measured by a scintillation detector or a flow detector, with the metal concentration expressed in wt%.

To systematically and quantitatively assess the MCGR wearing and metal particle release, metal concentrations in the human tissues were studied. The collected human tissue samples were heated under 450 °C in a muffle furnace (Thermolyne™; Thermo Scientific; US) for 1 hour, dissolved in acid (HCl + HNO_3) and then diluted 50 times. Finally, the concentrations of metals (mg/kg) in the sample were measured by inductively coupled plasma optical emission spectrometers (ICP-OES; Agilent 700 Series; Agilent Technologies, Inc.; US). The testing process followed the instructions from the manufacturer (https://www.agilent.com/cs/library/usermanuals) and for each sample triplicated tests were performed. For each metal element, the ICP produced excited atoms and ions that emitted electromagnetic radiation at different wavelengths. The intensity of the emissions from various wavelengths was proportional to the concentrations of the elements within the sample.

Histology analyses

All samples under histological examinations went through the standard protocol of hematoxylin and eosin (H&E) staining. Briefly, the samples were embedded in paraffin and sectioned to 5-micron thickness by a microtome. Prior to any staining, the samples were dewaxed and in xylene for 3 minutes each for 3 times. Then the sections were processed using H&E stains (sigma 230251) and mounted with DPX mounting medium (Fisher 10050080). Images were obtained using Nikon Digital Microscope (Eclipse 80*i*).

Statistical analysis

Statistical inferences (GraphPrism 6) on the effect of biopsy sites with different metal concentrations were made through Student's paired *t*-test. Absolute metal concentrations were calculated by the difference between the concentrations in each sample taken at the BO and the concentrations in the control sample. Linear regression analysis was used to discover any association with duration of implant in-situ, DS, BMI, DS/BMI, and average KB and LB, on absolute metal concentrations. The average KB and LB per patient was calculated between the bending degrees of the two rods in the same patient. All data are presented as mean ± standard error (SE). A $P<0.05$ was considered statistically significant. 95% confidence intervals (95% CIs) were reported where appropriate.

Results

In total, biopsy samples were collected from 10 patients (average age 12±1.3 years, 80% females). All patients were ambulatory. The summary of clinical data is illustrated in Table 1, with average implant age (time since rod implanted) of 1431±230 days, average 22±1 distractions, average patient BMI of 17±1 kg/m^2, average KB of 29±4° and average LB of 9±2°. Pseudo-membrane formation around the BO and BM with black pus-like material (Figure 2A) was observed during surgery.

The metal component of the rods tested using EDS showed that the majority of metals within the piston rod were common Titanium (Ti) alloy with Aluminum (Al), Vanadium (V) and Carbon (C). Six samples were tested and the average concentration (wt/wt) of Ti was 88±0.6%; Al was 4.9±0.2%; V was 4±1.0% (Figure 3).

ICP-OES results of biopsy samples collected from the ten patients revealed (Figure 4), in the samples taken at the BO, the concentrations of Ti (54361.34±17467.98 vs control: 301.56±110.39 mg/kg; *P*=0.017) and V (1287.65±407.02 vs control: 17.28±4.37mg/kg; *P*=0.016) were significantly higher than controls. These concentrations were also significantly higher than the two metal concentrations from the samples taken at the BM (Ti: 24141.55±10585.42mg/kg; *P*=0.028 and V: 587.27±271.44mg/kg; *P*=0.043). However, concentrations of these two metals in the samples taken at BM were not significantly increased than the controls. For Al, no significant differences in the concentrations were discovered between samples taken at different sites of the implant. The concentration at BO was 4789.47±1994.81mg/kg versus 1333.46±611.11mg/kg at BM (p=0.14) and 171.6±23.16mg/kg for controls (p=0.06 comparing with BO; p=0.14 comparing with BM). A significantly increased concentration of Nd was detected from the samples taken at the BO (34.30±3.94mg/kg; *P*=0.0003) and the BM (17.03±5.22mg/kg; *P*=0.024) as compared with the controls (9.50±2.52mg/kg). The Nd concentration in the samples from BO was also significantly higher than the samples taken from the BM (*P*=0.015).

Microscopic examination of the H&E stains revealed the samples were mainly fibromuscular tissues with some atrophic skeletal muscle. Accumulation of black and fine particles was discovered in the dense fibrotic areas (Figure 5A). A mild active and moderate chronic inflammatory cell infiltration was seen in the most slides near the black particles (Figure 5B). Macrophages containing black pigmentations were observed under high magnification (Figure 5C).

No observations of local neoplasia were made.

DS/BMI was found to be significantly associated with increased Ti (*P*=0.049; R^2=0.40; 95% CI=511.1-230733) and V (*P*=0.032; R^2=0.46; 95% CI=327.1-5419) concentrations. No associations were observed with Nd concentrations. No other individual clinical parameters were significantly associated with any metal concentrations detected in the human tissue.

Discussion

This study utilised human tissue biopsies of paraspinal muscles from 10 patients with EOS undergoing MCGR rod exchange. Spectrum and histological analyses were made and revealed increased Ti, V, and Nd concentration in the biopsies along with mild to moderate chronic inflammation. To our knowledge, this is the first study systematically examining the metallosis of EOS patients with MCGRs.

We directly examined the metal concentrations of the tissues near the implantations to provide more reliable evidence of the accumulation of wear particles. A previous study reported Ti as wear particles inside the barrel of the MCGR after cutting the barrel open, but according to their protocol, some of the metal particles may have been generated from the process of opening the barrel of the MCGR[36], rather than wearing particles generated from the time-varying loading experienced by MCGRs in a patient's daily activities. Our spectrum analyses of the piston rod revealed metal components of mainly Ti, Al and V. This is consistent with the increased Ti and V found in the biopsies of the paraspinal muscles at the BO (also near the wear marks) of the MCGR when compared with the normal tissues taken from the same patient. No statistically significantly increase in Al was found likely due to the sample size but also may be because Al is also commonly presented in normal human tissues unlike the other metal ions (Ti, V and Nd) involved in this study.[39] Nevertheless, the overall value appeared higher than the control specimens. We observed increased Ti and V concentrations mainly at the piston rod but not at the BM, indicating that these metal particles were generated by the metal-on-metal wearing between the piston rod after coating of the piston rod was damaged at the BO.

Another previous study tested the blood of patients with MCGR and reported increased Ti and V[37], but no examination of the tissue metal concentrations was reported. The increased Ti and V in the blood cannot be confirmed to be generated from the MCGR, because the fixation screws are of Ti alloy and may also be associated with the increased metal concentrations in the blood. Furthermore Ti particles can be introduced into humans via food and personal care products.[40] It is important to note these Ti particles may differ in content depending on the tissue. The normal average concentration in the normal liver is less than 0.146mg/kg and is comparable in cirrhotic livers,[41] while muscles with a Ti alloy implant may yield over 100 higher concentration of Ti than normal muscles.[42] However, it is important to note that these are results focused on the elderly population and has not been established in the paediatric population. Ti is still important for study as its debris activates fibroblasts and macrophages consistent with the histological findings reported in this study.[43] Thus, specific biopsy sites are critical to revealing the specific metal particle generations from the MCGR.

Increased Nd concentrations at the samples taken both at the BO and at the BM of the MCGRs were found, which is possibly associated with a releasing of Nd wear particles during the rod distraction and/or O-ring failure from the barrel, as well as possible migration of the magnet wear particles from the BO to the BM. This may indicate that an improved sealer design should be developed to isolate the magnets within the barrel from the human environment and prevent leakage.

Previous histological examinations also showed fibrosis and immune cell infiltration[36] of the tissues near the MCGR, but this is the first time to observe black particles inside the phagocytotic immune cells. There is a lack of understanding of the long-term effects of metallosis associated with MCGR. This is because the implant has only been in use for a decade.[17] Patients requiring the MCGR are at a young age. Long-term implications of metallosis have yet to manifest. However, the potential health risk of metallosis with orthopaedic implants is not new. In arthroplasty research with metal-on-metal bearing total hip replacements, studies have long-term risks related to complicated pregnancies, potential risks of malignancy and higher rates of mortality, and nationwide registries of hip replacements have shown an increased risk of stillbirth, children who are small for gestational age, low birth-weight and pre-term birth.[44,45] Additionally, previous studies on the toxicity of magnetic metal particles (Nd) in adults have indicated that the particles can result in embolisms and liver damage[46], but there is a lack of long-term investigation of the potential risk and toxicity of Nd in the pediatric population. Especially with females, there may be a concern for child-bearing and teratogenic risks with long-term exposure to these metals.

To put into perspective, the appearance of metallosis in other scoliosis surgeries is a rare event.[47] It has only been presented as case reports for explantation of spinal instrumentation in scoliosis surgery[47-49] and has not been reported in large-scale traditional growing rod cohorts[2,50]. One study did report 5 patients with metallosis with the Shilla operation[51] and found raised Ti (1300mg/kg, range 103-5750mg/kg), Al (18mg/kg, range 2-106 mg/kg) and V (11mg/kg, range 2-109mg/kg) in the tissues using the similar spectrometry method as we have. In our patients, we found vastly greater amounts of Ti (54361.34±17467.98mg/kg), Al (4789.47±1994.81mg/kg) and V (1287.65±407.02mg/kg) as well as Nd. Long-term follow-up of these patients is necessary to identify any potential health risk with metallosis, especially in the presence of the uncommon Nd.

This is especially important since metallosis is common in MCGR surgery with up to 60% in one series.[35] Systematic investigations of the effect of Nd to pediatric population should also be carried out, with an analysis of the dose and time effect. Investigations of the material components of the black particles inside of the phagocytotic immune cells should be investigated, in the context of systematic investigation of any cytotoxicity effect.

There is a significant positive association between DS/BMI and metal elements that consist of the piston rod (Ti and V) of MCGR. This is an expected finding as increased DS indicating both longer implant duration and more distraction sessions leads to increased wearing of the piston rod. It was interesting to find the BMI may have a role in predicting rod wearing. Studies have shown that increased BMI is positively associated with a sedentary lifestyle (i.e. TV watching)[52,53], whereas low BMI is significantly associated with increased physical activities in the paediatric population and not diet.[52] Therefore, in this study, we used BMI as an indirect parameter to assess the patients' activity level and presumed increased physical activities with low BMI. Hence, DS/BMI was positively associated with the increased wearing of the implants at the BO, indicating increased Ti and V concentrations (components of the piston rod). Nd (a component of the magnet rotor) was not associated with DS/BMI, because it is sealed in the barrel and the leaking of Nd is more relevant to the design of the MCGR. Nevertheless, the relationship of DS/BMI with implant wearing and metallosis is an assumption. An objective measurement of activity level should be employed in future study. Due to the small sample size, the results may not be conclusive, but provided a possible direction for the future large-scale. We need to acknowledge due to the small number of the patients participated, significant associations between the implant duration, DS, BMI and the concentrations of the metals in biopsy samples were not established. Further multi-centre studies could benefit the establishment of these associations.

Metallosis with MCGR is not uncommon in patients with EOS. Increased Ti, V and Nd metal concentrations in muscle tissues surrounding the MCGR are found with chronic inflammations and phagocytotic black particles. Ti and V are generated mainly at the barrel openings due to metal-on-metal contact, whereas the Nd from the magnet rotor within the barrel is likely released from the BO during distractions. Cautions should be raised due to potential long-term implications of these metals in the pediatric population.

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Table 1: Summary of patient and rod demographics

Patient number	Diagnosis	Duration of implant (days)	DS	BMI (kg/m^2)	Average KB (°)	Average LB (°)
01	JIS	718	15	16.8	25.7	9.1
02	Arthrogryposis	1113	21	12.5	22.9	12.7
03	CS	1373	27	21.8	48.1	18.1
04	JIS	1249	23	20.3	37.6	13.8
05	JIS	2399	21	18.5	9.0	0.7
06	JIS	2464	22	22.3	23.6	0.4
07	JIS	1110	21	15.5	25.3	11.4
08	Scimitar syndrome with CS	847	22	11.9	39.0	8.4
09	EDS	2429	29	18.8	44.2	8.8
10	NF	603	14	14.1	16.5	9.8
Average	-	1431	22	17.0	29.2	9.3
SE	-	230.36	1.44	1.2	4.0	1.7

JIS: juvenile idiopathic scoliosis; CS: congenital scoliosis; EDS: Ehlers-Danlos syndrome; NF: neurofibromatosis; SE: standard error; DS: number of distraction sessions; BMI: body mass index; KB: kyphotic bending; LB: lordotic bending

Figure Legends

Figure 1: MCGR bending angles. The kyphotic bending (KB) and the lordotic bending (LB) angles was measured by the angle between the two tangents drawn to the barrel and the proximal and distal end of the MCGR correspondingly.

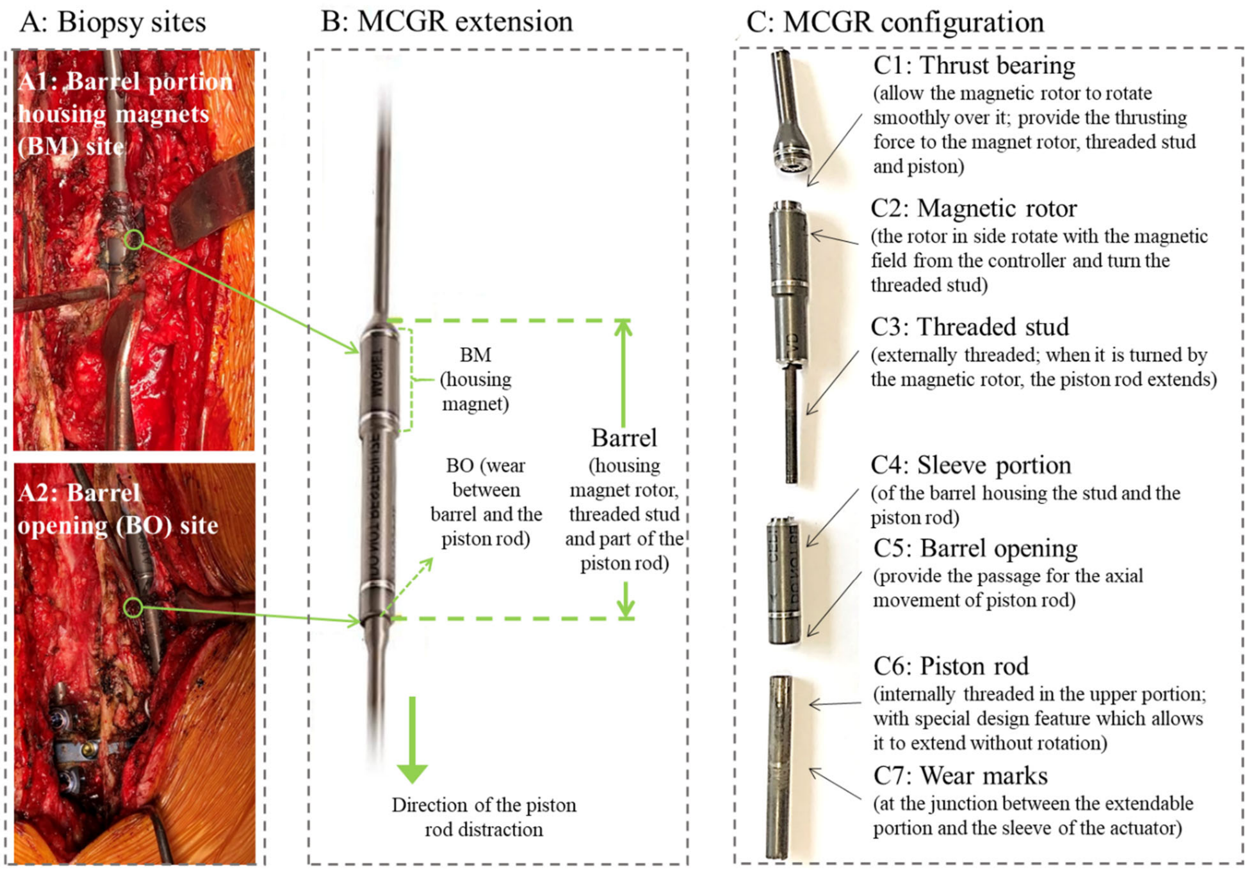

Figure 2: Biopsy sites and MCGR distraction mechanism. Two biopsy sites were chosen during surgery including the soft tissues surrounding the barrel portion housing the magnets (A1: BM) and barrel opening (A2: BO). The MCGR distracts because it has a magnet rotor and threaded stud inside its barrel (B). The thrust bearing (C1) allows the rotor to rotate smoothly over the closed-end of the barrel and provides the thrust to counteract the compressive force experienced by the MCGR, when the external remote controller rotates the magnetic rotor (C2). The magnetic rotor is coupled with the threaded stud (C3). Before distraction, the stud has been turned into the upper portion of the piston rod within the sleeve (C4-6). When the stud is being turned out of the piston rod, thru the barrel opening (C5), part of the piston (C6) will go out of barrel gradually and lead to the MCGR distraction. Wear marks (C7) are seen on the distracted portion of the piston rod close to the barrel opening.

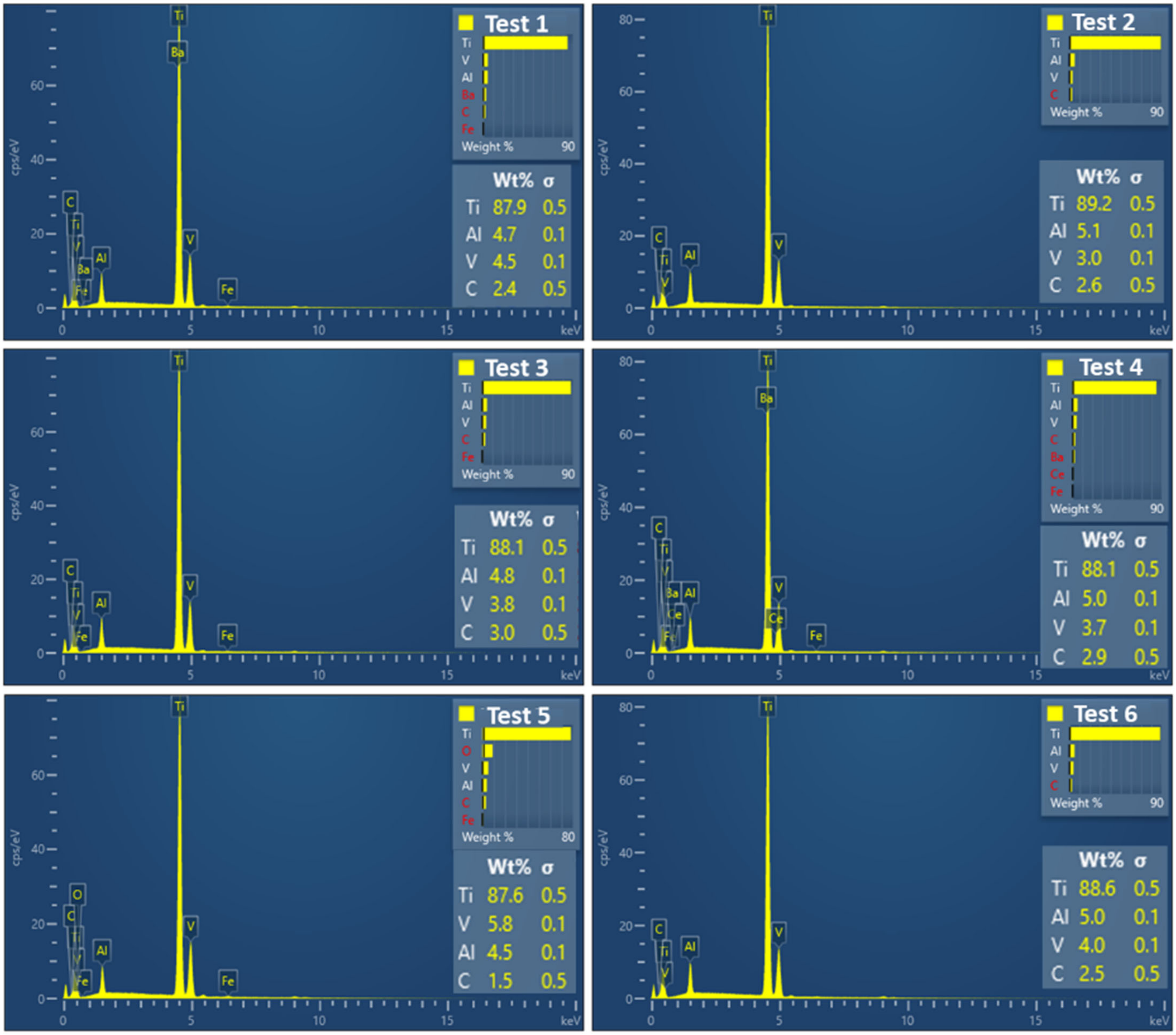

Figure 3: Analysis of the MCGR metal components in vitro. The six repetitive EDS studies on the same extendable portion samples showed that the majority components of the metal particles were Ti (>87%) and followed by Al (>4.5%) and V (>3%) in all six replicated tests (detailed results summarised in tables in the right bottom corner of each spectrum panel).

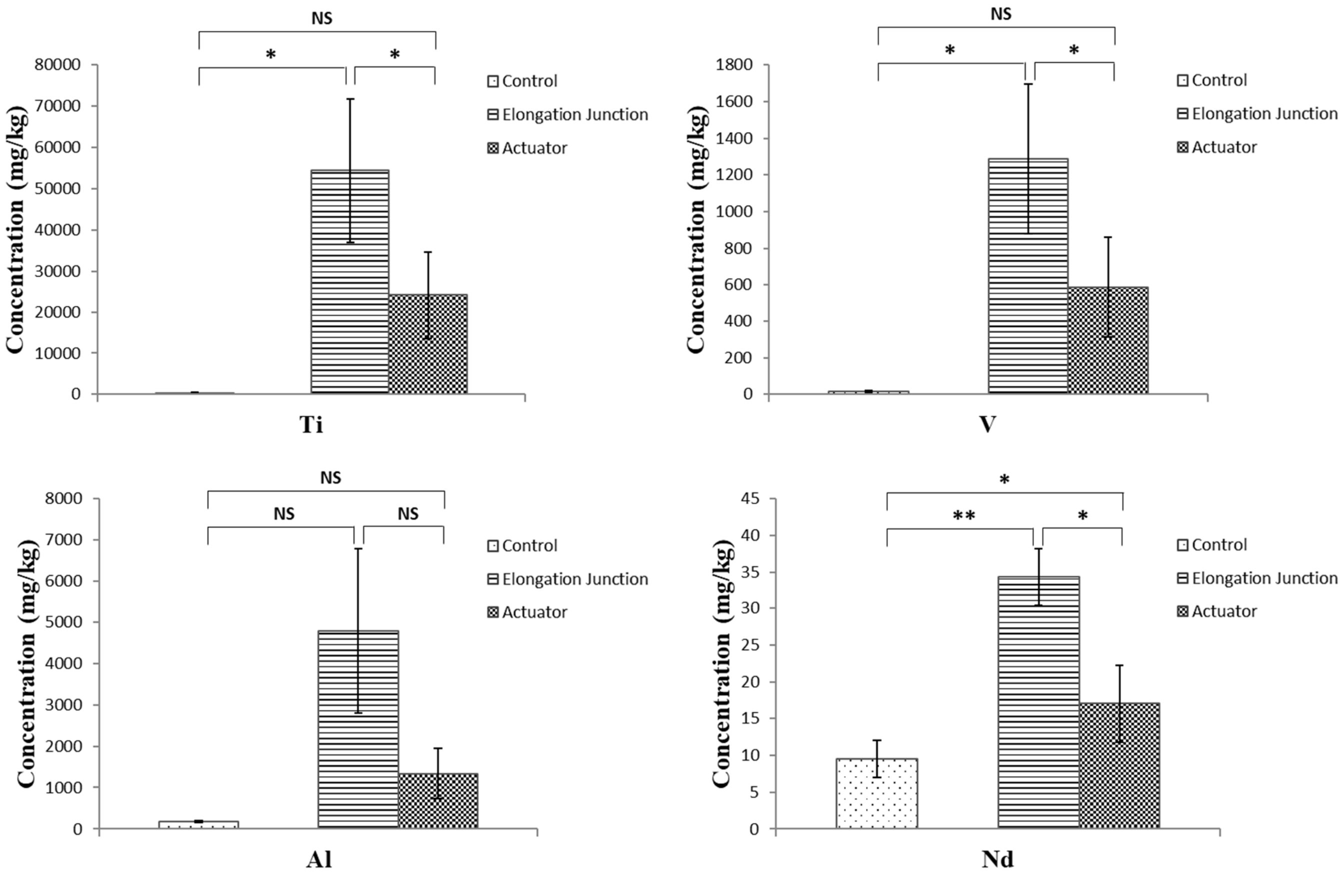

Figure 4: Analyses of the metal concentrations in human biopsy samples. Significantly increased Ti, V, and Nd were detected from the samples taken at the elongation junction comparing with the controls and the samples taken near the actuator. No significantly increased Ti and V were detected from the samples taken at the actuator than the controls. No significant differences in Al concentration were found between samples taken at different sites. Significantly increased Nd was discovered from the samples taken around the actuator than controls. * P value <0.05; ** P value <0.01; NS=No Significance.

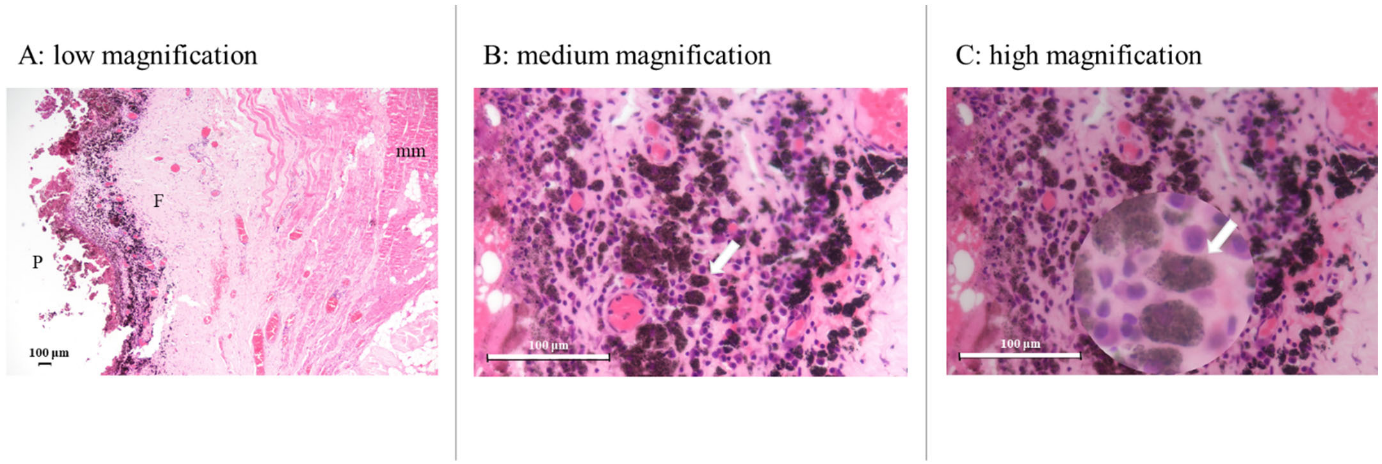

Figure 5: Examples of microscopic examinations of the soft tissues. The section showed accumulation of black and grey granular particles (A: low magnification), hyalinised fibrous stroma, and chronic inflammation reaction with macrophages infiltrates (B: medium magnification). High magnification (E: high magnification) investigations revealed possible multinucleated immune cells with black particle accumulated inside, whereas mm = muscles; F = fibrosis; P = particles; and the white arrows pointing at the macrophages.

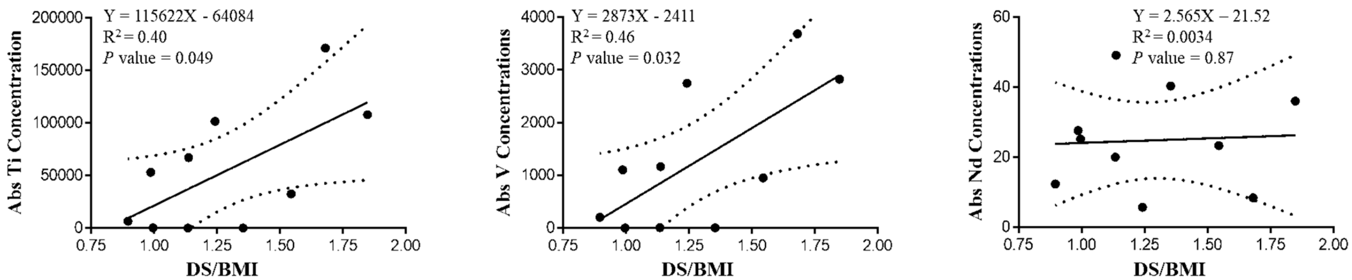

Figure 6: Regression analysis to predict the metal concentrations. In the three panels all X axes were DS/BMI (m^2/kg), and the Y axes were absolute metal concentrations (Abs Ti or V or Nd concentrations; mg/kg). The correlation between Ti and V concentrations with the metal concentrations in biopsy samples were both significant (*P* value being 0.049 and 0.032 correspondingly), but the predictive strength of the linear models were moderate (R^2 being 0.40 and 0.46 correspondingly). No significant association between Nd concentrations and the combined parameter was established.