Serum metal ion levels following spinal deformity surgery: a case-control study of 182 individuals

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Abstract
Purpose The aim of this study is to evaluate the levels of chromium (Cr), cobalt (Co), and titanium (Ti) after instrumented fusion for scoliosis.

Methods Serum samples were collected at median 2.24 (range 0.1–38.8) years after fusion surgery for scoliosis in 91 individuals, of which 71 had been treated with steel implants and 20 with titanium implants. 91 sex and age-matched non-surgically treated individuals with scoliosis were used as controls. Levels of Cr, Co, and Ti were measured.

Results In the 91 surgically treated individuals median levels of Cr were 0.54 µg/l vs 0 µg/l in the 91 controls, \( p < 0.001 \).

Corresponding results for Co were 0.29 µg/l vs. 0.24 µg/l, \( p = 0.19 \), and for Ti were 0 µg/l vs. 0 µg/l, \( p < 0.001 \).

In the individuals with steel implants and their corresponding controls median Cr levels were 0.63 µg/l vs. 0.00 µg/l, \( p < 0.001 \) and Co levels 0.27 µg/l vs. 0.23 µg/l, \( p = 0.36 \). No Ti was detected.

In the individuals with titanium implants, median Cr levels were 0 µg/l vs. 0 µg/l in their corresponding controls, \( p = 0.38 \).

Corresponding results for Co was 0.39 µg/l vs. 0.31 µg/l, \( p = 0.27 \) and for Ti 4.31 µg/l vs. 0 µg/l, \( p < 0.001 \).

In the individuals with steel implants a negative correlation between implant time in situ and levels of Cr was found (\( \rho = -0.52, p < 0.001 \)) but not with Co (\( \rho = -0.14, p = 0.23 \)). Ti was not detected.

In the individuals with titanium implants, there was no correlation between implant time in situ and levels of Cr (\( \rho = 0.36, p = 0.12 \), Co (\( \rho = -0.12, p = 0.60 \)) or Ti (\( \rho = 0.22, p = 0.35 \)).

Conclusion The use of stainless steel and titanium implants in spinal fusion surgery is associated with elevated metal ion concentrations several years after surgery.

Keywords Scoliosis · Metal ions · Spinal fusion · Spine surgery · Spinal deformity

Introduction

The use of surgical implants is a key element in modern orthopedic surgery. A wide variety of implants has been introduced and is widely used for joint replacement, fracture fixation, and spinal fusion.

Historically orthopedic implants have been manufactured from 316L stainless steel, i.e. iron, chromium and nickel or from cobalt-chromium alloys. Implants made of titanium alloys have become more widely used during the last decades.

Liberation of metal particles from these implants may be due to mechanical or chemical reasons [1]. High levels of metal ions have been detected several years after joint replacement and spinal surgery and possibly the level of metal ion concentration in blood samples may be associated with implant loosening or failure [2, 3].
Numerous publications have highlighted possible consequences of dissolved metal particles including pseudotumor formation, local tissue reactions, end-organ deposition, or systemic effects [4, 5]. Little is known about adverse health effects, disturbance of fertility and association with neoplasms [6].

In a recently published systematic review of the literature on metal ion concentrations after instrumented spinal fusion, Siddiqi et al. found elevated levels of chromium (Cr) from stainless steel and titanium (Ti) from titanium implants but no certain association between metal ion concentrations and clinical or radiological outcomes [7]. Sorensen et al. found similar levels of Cr or cobalt (Co) in 67 patients with stainless steel implants compared to 48 non-surgical patients with a mean follow-up of 24 years [8].

The purpose of this study is to compare serum concentrations in a large group of patients after instrumented spinal fusion with non-surgically treated patients with a long follow-up. The second purpose is to clarify whether there is an association between implant time in situ and metal ion levels.

Materials and methods

We used serum samples collected at the Malmö site of the study Scoliosis and Genetics in Scandinavia (ScolioGeneS). Details of the this study have been published elsewhere [9, 10].

Study groups

Originally enrolled at the Malmö site were 506 idiopathic scoliosis patients (425 female, 81 male). In this group, we identified 91 surgically treated individuals (78 female, 13 male), that had serum samples available. These individuals were age and sex-matched to 91 individuals from the same site that had not been treated with surgery and served as controls.

In the surgical group, 71 patients had implants made of stainless steel (28 Harrington, 33 Kaneda anterior spinal system, 9 Isola, 1 Isola combined with anterior Zielke system) and 20 patients had received implants made of titanium alloy (18 Expedium, 2 Frontier). All individuals answered a questionnaire, including questions on smoking status, chronic illnesses, and occupational strain [11].

Serum metal analysis

Blood samples were obtained in a standardized setting at the research ward at Malmö University Hospital, Sweden between the years 2005 and 2010. After separation, serum samples were stored at −80 degrees C.

All samples were analyzed at the same time in January 2021 at a commercial laboratory (ALS Scandinavia AB, Luleå, Sweden). Samples were dissolved with HNO₃ and/or HNO₃ + HF in a microwave. Serum levels of chrome (Cr), cobalt (Co), and titanium (Ti) were measured using inductively coupled plasma sector field mass spectrometry (ICP-SFMS) in accordance with SS-EN ISO 17294–1, 2(mod) and EPA-method 200.8(mod).

Reference levels for the metal ions are 0.05–0.48 µg/L for Cr, 0.03–0.18 µg/L for Co, and 0.1–0.28 µg/L for Ti, respectively. Detection limits are 0.40 µg/L for Cr, 0.022 µg/L for Co, and 0.17 µg/L for Ti [12]. Results under the detection limit were set to "0".

Statistical analysis

Visual estimation of the serum levels for each of the metal ions revealed a non-normal distribution. Descriptive data are therefore shown as median (lower quartile, upper quartile and/or range). Group differences were analyzed using the Wilcoxon–Mann–Whitney test and correlations using the Spearman non-parametric rank correlation test with “rho” used as correlation coefficient. For statistical analysis RStudio 1.4.1106 © RStudio, PBC was used.

Results

Descriptive data for surgically treated individuals and controls is shown in Table 1.

Levels of metal ions

Chromium

In our study 65 of 182 individuals (36%) showed Cr levels above the reference range (0.05–0.48 µg/l). In the 91 surgically treated individuals, levels of Cr were higher than in the 91 non-surgical controls (p < 0.001).

In the 71 individuals with steel implants levels of Cr were higher than in their 71 controls (p < 0.001) (Fig. 1). In the individuals with steel implants, there was no difference in Cr levels when comparing anterior (n = 33) to posterior fixation (n = 37), (p = 0.36). When comparing individuals treated with Harrington implants (n = 28) to individuals treated with the Kaneda anterior spinal system (n = 33) a significant difference was found in Cr levels (median 0.00 µg/l vs. 0.70 µg/l; p = 0.003), but the implant time in situ in the Harrington subgroup was significantly longer compared to that in the Kaneda subgroup (median 29.3 years vs. 2.2 years; p < 0.001).

In the 20 individuals with titanium implants, Cr did not differ significantly when compared to their controls (p = 0.38).
Table 1 Descriptive data of 91 surgically treated and 91 non-surgically treated controls with idiopathic scoliosis. Data shown as number or median and 25th; 75th percentile

|                          | Surgical treatment | Controls | Total  |
|--------------------------|--------------------|----------|--------|
| No of individuals        | 91                 | 91       | 182    |
| Male                     | 13                 | 13       | 26     |
| Female                   | 78                 | 78       | 156    |
| No of patient with steel implants | 71               |          |        |
| No of patient with titanium implants | 20               |          |        |
| Age at blood sampling    | 21.2 (16.6; 41.8)  | 20.8 (16.6; 41.6) | 21.2 (16.6; 41.6) |
| Age at surgery (median)  | 15.6 (14.2; 18.8)  |          |        |
| Follow-up/implant time in situ (years) | 2.2 (0.2; 18.7) |          |        |
| Cobb angle, before surgery (median) | 56 (50; 63)       |          |        |
| Cobb angle, latest (median) | 33 (21; 41)       | 30 (22; 37) |        |
| Levels fused             | 10 (7; 12)         |          |        |
| Smokers                  | 12                 | 7        | 19     |
| Chronic illness          | 18                 | 14       | 32     |
| Occupational strain\(^a\) | 40                | 43       | 83     |
| Predominantly sedentary, sitting | 8                 | 8        | 16     |
| Sitting and standing, some walking | 21               | 15       | 36     |
| Walking, some handling of material | 7                 | 11       | 18     |
| Heavy manual work        | 4                  | 9        | 13     |

\(^a\)Reported by 40 surgically treated individuals and 43 controls

Fig. 1 Shows the levels of each of the three metal ions. The midline of the box indicates the median. The upper and lower borders of the box indicate the first and third quartile. The lower whisker indicates the first quartile minus 1.5 times the interquartile range. The upper whisker indicates the third quartile plus 1.5 times the interquartile range. Outliers are marked. a: Cr levels were significantly higher in individuals with steel implants compared to non-surgical controls \((p<0.001)\) but not in individuals with Ti implants compared to their controls \((p=0.38)\). b: There was no significant difference in Co levels comparing individuals with either Steel \((p=0.36)\) or Ti \((p=0.27)\) implants with their respective controls. c: Ti was found only in individuals with Ti implants

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Cobalt

We found that 132 of the 182 individuals (73%) in our study group showed Co levels higher than the reference range (0.03–0.18 µg/l) (Fig. 1). However, there was no significant difference in Co levels between the steel implant subgroup or the Ti implant subgroup compared to their respective control groups, all \( p > 0.27 \).

Titanium

Titanium could be found only in the 20 individuals that had been operated with titanium implants and not in any other individuals (\( p < 0.001 \)) (Fig. 1).

Correlation of metal ion levels and implant time in situ

In the subgroup of individuals with steel implants a significant correlation between implant time in situ and levels of Cr was found (\( \rho = -0.51, p < 0.001 \)) (Fig. 2) but not with Co (\( \rho = -0.14, p = 0.23 \)). Ti was not detected.

In the subgroup of individuals with titanium implants, there was no significant correlation between implant time in situ and levels of Cr (\( \rho = 0.36, p = 0.12 \)), Co (\( \rho = -0.12, p = 0.60 \)), or Ti (\( \rho = 0.22, p = 0.35 \)).

Correlation of metal ion levels and patient age

In the whole surgical group, there was a significant negative correlation between age and Ti levels (\( \rho = -0.40, p < 0.001 \)), but not in the group of patients with Titanium implants (\( p = 0.80 \)). In the subgroup of individuals with stainless steel implants, there was a negative correlation between age and Cr levels (\( \rho = -0.33, p = 0.005 \)). In the whole surgical group, the correlation between age and Co was \( \rho = -0.18, p = 0.08 \), and between age and Cr \( \rho = -0.17, p = 0.11 \). In the 91 controls the correlation between age at the time of blood sampling and levels of metal ions for Cr was \( \rho = 0.05, p = 0.62 \) and for Co was \( \rho = -0.32, p = 0.002 \). Ti could not be traced in these subjects.

Discussion

Deformity correction with instrumented fusion has been an established treatment for severe cases of scoliosis for decades [13]. Implants are usually inserted during childhood or adolescence and left in place for the remainder of the patient’s life.

Metal used in orthopedic implants is not an inert material but is exposed to wear, fracture and biologic corrosion. This corrosion has been divided into three kinds: Galvanic corrosion occurs in the high-saline environment of the body and especially in the interface between different metals. Fretting corrosion is due to micromovements causing mechanical abrasion of the outside layer. Crevice corrosion may occur in cracks and similar crevices on the implant surface [14, 15].

When discussing temporary changes of metal liberation or accumulation two phenomena have been discussed. The “putting in” theory implies that a large amount of metal ions is liberated during surgery and the early postoperative period. Cundy et al. investigated intraoperative samples from the fluid used for wound irrigation and reduction tab washing as well as cell saver blood and found detectable levels of Ti. In consecutive blood samples, the two patients showed a rapid increase in serum Ti levels up to one month after surgery [16].

The “wearing in” theory means that the liberation of metal ions takes place during the early postoperative period.
and decreases when bony fusion is seen. Villarraga et al. examined 57 implants they retrieved after an implantation time from 2 months to 13.5 years and found signs of wear in 75% and corrosion in 39% of cases. Wear was present at all implantation times and there was no significant correlation between presence of wear and duration of implantation. Noteworthy is the fact, that retrieved Ti implants showed signs of wear but no corrosion was present [17]. Wang et al. examined tissue samples from revision surgery and found significantly higher levels of Ti in local tissue samples in patients with a pseudarthrosis compared to patients that had achieved solid fusion [18].

Cundy et al. showed that also other factors, namely electro-surgery electrode tips, may contribute to Cr deposition in the surgical site [19].

The main findings in the present study are significantly higher levels of Ti after insertion of Ti implants and significantly higher levels of Cr after insertion of stainless steel implants.

Another important finding is the negative correlation between implant time in situ and Cr levels in individuals with stainless steel implants. This supports the theories presented above, that liberation of metal particles occurs during surgery and the initial postoperative period before fusion is achieved. During this period inserted implants are exposed to high mechanical stress that is thought to result in micro-motion and wear. Over time, as arthrodesis gradually is achieved, stress and resulting motion decreases. Our data are also supported by a recent long-term follow-up by Sorensen et al. with a mean implant time in situ of 24 years, that showed no difference in Cr and Co levels between individuals with Harrington rods compared to individuals treated with a Boston brace [8].

In our study, no significant correlation between implant time in situ and Ti levels was observed in individuals with Ti implants, as opposed to the negative correlation we observed for Cr levels in individuals with steel implants. This could be explained by the difference in follow-up between these subgroups. Whereas the implant time in situ in the steel group was up to 38 years it was only up to 2 years in the Ti group. A fall in Ti levels might have been seen if follow-up time in Ti patients had been longer.

A negative correlation between Co levels and age at sampling was seen, although not significant in the surgical group. This contradicts any suspicions, that in the studied population there was an accumulation of metal ions due to environmental exposure.

The negative correlation between patient age and Ti levels in the surgical group but not in the titanium subgroup is due to the fact that Ti was found only in individuals with titanium implants and at the time of sampling these were significantly younger than the ones with steel implants.

The significantly higher levels of Cr in the Kaneda subgroup compared to the Harrington subgroup could be interpreted in a way, that anterior fusion causes higher levels of Cr than posterior fusion, but another explanation would be the difference in implant time in situ between these two subgroups.

One limitation is that we do not have any blood samples taken at baseline, i.e. preoperatively and immediately postoperatively as well as the fact, that the time span between surgery and blood sampling, i.e. the implant time in situ, varies between our patients and was particularly short in individuals with Ti implants. Especially for this group, it is important with longer follow-ups.

Another limitation is the lack of radiological data at the time of blood sample collection. Therefore, we cannot conclude whether implant loosening or rod breakage was associated with higher metal ion levels.

In addition, we cannot provide any estimate of mass or surface area of the implants used, which could be a reason for difference in metal ion levels.

The strengths of the current study are the large sample size (N = 182) from one single center and a control group which is matched for both sex and age. Although the follow-up time in Ti patients was only 2 years, in the steel group we had a follow-up ranging up to 38 years.

The total number of patients in the review of Siddiqi et al. mentioned earlier was 623 out of which 187 were treated with stainless steel implants and 275 with titanium implants. The total number of non-surgical patients or healthy controls was 158. The largest referred study in that review comprised 46 subjects and the study with the longest follow-up covered a period of 14 years [7]. The study by Sorensen et al. mentioned earlier followed 67 surgically and 48 conservatively treated individuals with a mean follow-up of 24 years [8].

In summary, we conclude that metal ion levels are increased in patients after spinal deformity surgery with instrumentation, but our findings contradict concerns, that metal ions from stainless steel or titanium implants would accumulate in patients’ blood over time.

Author contributions All of the authors made substantial contributions to the conception or design of the work, drafted the work and revised it critically for important intellectual content, approved the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and material  Not applicable.

Code availability  R and RStudio is available for download on https://www.rstudio.com/products/rstudio/download/

Declarations

Conflicts of interest  All authors declare no conflict of interest.

Ethics approval  The protocol was approved by the Ethics Committee of Lund University (LU363-02 and LU290/2006) and the Swedish Ethical Review Authority (2020–02297 and 2020–03756).

Consent to participate  All individuals provided informed consent prior to study participation.

Consent for publication  All individuals provided informed consent prior to study participation.

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