Original Article

Concentration of Chromium and Nickel in Serum of Patients with Orthopedic Implant: An Analysis

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Abstract

Introduction: Surgical corrections of fracture using fixation devices made from various alloys (stainless steel, cobalt-chromium alloys, and titanium) carry a risk of these alloys leaching into circulation, potentially causing undesired health effects. Hence, monitoring the levels of metal ions in the serum of postoperative patients with metal implants is mandated. **Materials and Methods:** Blood samples from seventy patients with orthopedic metal implants was collected after a minimum postoperative period of 1 year. The samples were subjected to triple acid digestion and serum levels of chromium and nickel were analyzed using inductively coupled plasma-mass spectrometry. **Results:** The concentration of chromium (0.13 ± 0.06 μg/L) and nickel (0.39 ± 0.28 μg/L) in serum was within the reference range (chromium: 0.05–0.15 μg/L; nickel: 0.05–1.0 μg/L). Although a relatively high variability in the concentration of nickel was observed compared to chromium. In a subgroup analysis, the concentrations of both metal ions were not influenced by either gender, age groups, site of intramedullary nail, or postoperative duration. **Conclusion:** The concentration of chromium and nickel in serum of patients with orthopedic metal implants was within the normal reference levels at over 1-year post implant. The concentration of these metal ions was not influenced by gender, age groups, site of intramedullary nail, or postoperative duration.

KEYWORDS: 316L stainless steel, chromium, implants, inductively coupled plasma-mass spectrometry, intramedullary nail, nickel

Introduction

Metal implants are integral part of orthopedic fracture fixation surgeries. Recent advances in metallurgy together with better understanding of the biomechanics of metals have led to several combinations of alloys (stainless steel, cobalt-chromium, and titanium) being used to develop implants (plates, intramedullary nails, bone screws, and prosthesis) for fracture fixation in orthopedics.[1] The most commonly observed fracture in orthopedic practice is of long bones of lower limbs which require surgical fixation using metal implants. Intramedullary nail made from 316L stainless steel is the most common implant used globally for internal fixation of fractured shaft of femur and tibia.[2] The 316L stainless steel has the following composition: iron (61%–68%), chromium (17%–19%), nickel (10%–15%), molybdenum (2%–4%), and carbon (<0.06%) with variable traces of copper, nitrogen, and silicon.[3] All metal implants although designed to be inert, invariably undergo biochemical reactions once inside the human system, resulting in adverse biological reactions including the loss of its structural integrity.[4] The adverse effect of metal ions leaching from the orthopedic implants is of concern as these implants remain *in situ* for life time, and most of the constituent metal ions are recognized as potential carcinogens.[3,4] Hence, there is a need to analyze the levels of the relevant metal ions in the circulation and evaluate the risk of the associated adverse effects. In this study, we have analyzed the serum levels of chromium and nickel in patients who had undergone fracture fixation with intramedullary nails made of 316L stainless steel after a minimum postoperative period of 1 year. The serum levels of chromium and nickel in relation to gender, age groups, site of intramedullary nail, and duration of postoperative period were also analyzed.

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Materials and Methods

This study included seventy orthopedic patients (aged 18–75 years), who had undergone internal fixation with intramedullary nail made of 316L stainless steel at Coimbatore Medical College Hospital during the period from January 2018 to December 2019. The study was reviewed and approved by the Institutional Ethics Committee, and the informed consent was obtained from all patients. Patients who have completed a postoperative period of minimum 1 year after being operated with 316L stainless steel intramedullary nail for tibia or femur fracture were included in this study. Patients with postoperative period of <1 year, presence of other metallic implant in the body, history of any implant removal, occupational exposure to metals, and chronic renal or hepatic disorders were excluded from this study.

Five milliliters of blood samples were collected under sterile conditions. The blood collected was transferred to sterile tubes containing anticoagulant (ethylenediaminetetraacetic acid) and then stored in cold storage (−10°C). Prior to analysis, the blood samples were thawed and serum separated by centrifugation at 3000 rpm for 20 min. Two milliliters of the supernatant serum was collected in a test tube and subjected to triple acid digestion. The triple acid was prepared by the mixture of nitric acid, sulfuric acid, and perchloric acid in the ratio of 9:2:1. The acid digested sample solution was then heated in a heating mantle at a temperature of 80°C until the solution was completely vaporized. Later, distilled water of 10 ml was added to the test tube and filtered to remove any solid impurities. The filtered sample was collected in a sterile container and kept in cold storage. The sample was then subjected to metal analysis using the inductively coupled plasma-mass spectrometry. The results obtained were calculated taking into consideration the dilution ratio and the concentration of the metal ions were expressed as micrograms per liter.

Statistical analysis

The data are presented as mean ± standard deviation (SD) of all participants in each category. The data were analyzed by either *t*-test or two-way ANOVA using GraphPad Prism software (version 8).

Results

This study included seventy patients with 316L stainless steel intramedullary nails, among which 51 were males and 19 were females. Twenty-three patients received intramedullary femur nails, while 47 patients received intramedullary tibia nails. The age group distribution of this study subjects was as follows: 18–30 years (20 patients), 31–40 years (18 patients), 41–50 years (10 patients), 51–60 years (16 patients), and 61–70 years (6 patients). A majority (48 patients) of these study cohorts were under 50 years of age. The postoperative follow period category in this study were as follows: 12–17 months (26 patients), 18–23 months (30 patients), over 24 months (14 patients). A majority (56 patients) of this study subjects were followed up from 12 to 24 months.

The average serum chromium concentration in this study cohort was observed to be 0.13 ± 0.06 μg/L and was within the reference range of 0.05–1.05 μg/L reported by previous studies conducted on unexposed individuals.[5] The average serum nickel concentration in this study cohort was observed to be 0.39 ± 0.28 μg/L, which was also within the reference safe levels of 0.05–1.0 μg/L.[6-8] In a subgroup analysis, this study did not observe any statistical differences in the serum concentration of either chromium or nickel between gender [Figure 1a], age groups [Figure 1b], site of implant [Figure 1c], or duration of follow-up [Figure 1d]. Although a higher variability (higher SD values) in the concentration of nickel was observed compared to that of chromium concentration.

Discussion

Metal alloys such as stainless steel, cobalt-chromium alloys, and titanium alloys are commonly used in the manufacturing of orthopedic implants. Surgical stainless steel is strong, corrosion free, and has low carbon content, which makes it a desired material for developing orthopedic implants.[9] Despite these desirable features, the risk of metal ions leaching from the implants into the circulation prevails. Hence, studies to assess the concentration of the relevant metal ions in various populations are necessary. The present study adds a valuable information on Indian population to the literature in this context.

As most often, the surgical implants are retained in the patients for their lifetime, studies looking at the metal ion concentrations on a longer duration postimplant surgery are seen as necessary. In this study, we did not observe any progressive changes in the metal ion concentration on a follow-up duration beyond 2 years, reflecting the safety of the implants used in this study. However if such a feature holds good for implants made from other alloys merits to be evaluated in future studies. Although this study observed concentration of chromium or nickel in the circulation to be within the reference range, it is likely that these metal ions released gradually may accumulate in the local tissue and cause tissue-specific undesired effects. Detailed studies to explore such tissue-specific pathophysiology are warranted in future as WHO has classified both chromium and nickel as potential human carcinogens.[10] Besides Cr(+6) being a strong oxidizing agent, both chromium and nickel when internalized into the human cells can induce cytotoxicity, chromosomal damages, and oxidative stress, leading to a wider damage to the DNA, proteins, and lipids.[4,5] Nickel is specifically known to directly damage the mitochondria and induce apoptosis and is reported to accumulate selectively within the neurons in the brain.[11]

In this study, the serum levels of chromium and nickel ions which are the major constituents of the 316L stainless steel alloy were observed to be within the normal reference levels but closer to the upper limits. Further, a considerable variability in the concentration of nickel was observed compared to the

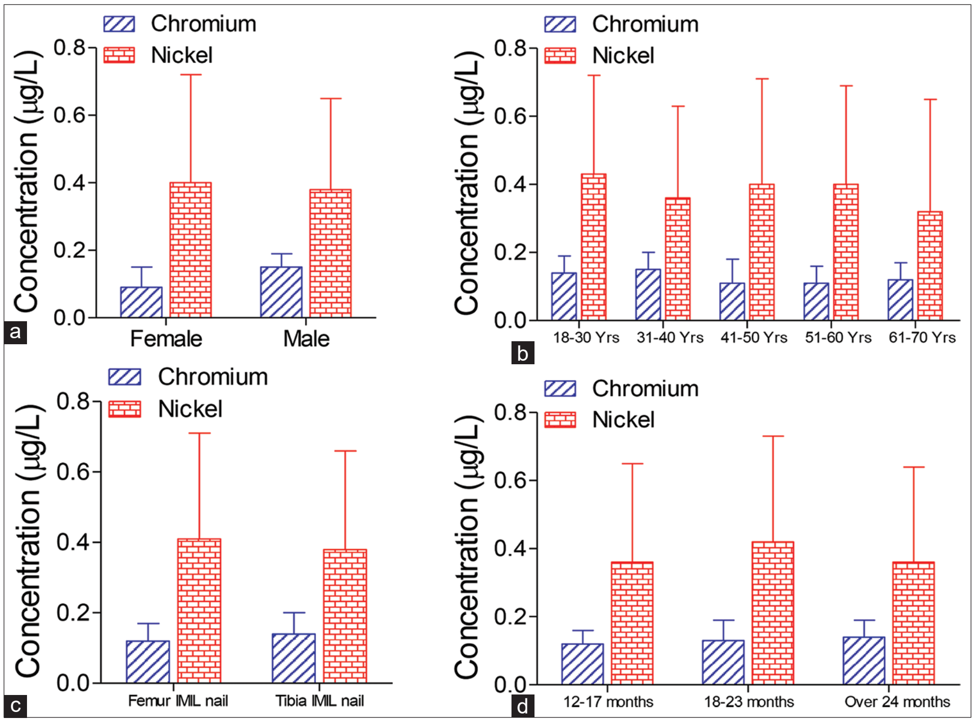

Figure 1: (a) Mean concentrations of serum chromium and nickel in males and females. (b) Mean concentration of serum chromium and nickel in different age groups. (c) Mean concentration of serum chromium and nickel in patients with femur and tibia intramedullary nail. (d) Mean concentrations of serum chromium and nickel in different postoperative periods

variability in the concentration of chromium. The observations from this study are consistent with previous reports on concentration of chromium following hip implants.[12] The concentration of chromium and nickel among males and females did not show any significant variation. Neither were any differences in the concentration of the metal ions observed between different age groups, site of implant, or duration of follow-up, which tends to suggest that these variables are unlikely to influence the concentration of the metal ions and hence may be valuable for the design of similar clinical trial in future. Further, these findings are also relevant to the routine orthopedic clinical practice, as in our opinion gender, age of the individual, or site of the implant cannot be considered as a risk factor. Alternatively, the quantity of ion release also cannot be predicted based on the age or gender of the patient. It was also interesting to note that, despite the femur nail being relatively larger (mass and surface area), we did not observe differences in the concentration of chromium and nickel between femur and tibial implants, which suggests against the common notion that larger implants will release more metal ions into circulation. Nevertheless, this paradox remains to be scientifically and clinically addressed. Although as mentioned above, lack of changes in the circulatory concentration of metal ions does not rule out the accumulation of the metal ions in the local tissues. Although this study did observe considerable variations in the concentrations of nickel, from a study design aspects, such variations can be optimally addressed by serial analysis of ion levels within the individual patient. Hence, future studies should consider address this limitation in their study design. Another studies have reported much higher levels of serum chromium[15] and nickel concentration[13] compared to that observed in this study or other reports[13-15] [Table 1]. Such discrepancies may be attributed to differences in the sample size, population variances, and implant locations. The presence of mobile parts in arthroplasty prosthesis which undergo continuous and higher wear and tear can potentially lead to higher metal ions leaching from the implants into the circulation. Some studies have reported that maximum concentration of metal ions is detected in tissues vicinity to the metal implant. Consistent with this observation, moderately higher incidence of hemopoietic malignancies are reported in patients with metal prosthesis.[16,17] Hence, despite the release of metal ions from intramedullary nails being lower than that of arthroplasty implants, considering the closer association of intramedullary nails with hemopoietic tissues, the chronic consequence of the continuous exposure to metal ions warrants necessary investigations. However, unlike arthroplasties, the intramedullary nails can be removed after complete healing of the fracture, the merit of which should be considered in clinical practice.

Conclusion

This study reports that the serum concentrations of chromium and nickel in the patients with 316L stainless steel intramedullary nail implants were within the reference range. Although a higher variability in the concentrations of nickel was observed. A subgroup analysis showed that serum

Table 1: Serum concentration of chromium and nickel in patients with orthopedic implants reported by various studies

Literature	Chromium (μg/L)	Nickel (μg/L)
Dahlstrand *et al*. (Sweden)[13]	1.15	2.16
Imanishi *et al*. (Japan)[15]	0.4	-
Linden *et al*. (USA)[14]	-	0.30
Patton *et al*. (Scotland)[12]	0.1	-
This study (India)	0.13±0.06	0.39±0.28
Normal reference levels[5-8]	0.05–0.15	0.05–1.0

concentrations of chromium or nickel were not influenced by gender, age groups, site of implant, or postoperative duration.

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Conflicts of interest

There are no conflicts of interest.

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