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Chromium and Nickel Concentrations in Subjects with a Stainless Steel Metal-on-Metal Cervical Disc Arthroplasty: Results from a Prospective Longitudinal Study with 7 Years Follow-Up

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ABSTRACT

Background: Cervical disc arthroplasty (CDA) has emerged as an alternative to anterior cervical discectomy and fusion for degenerative cervical disc disease. The artificial discs provide intervertebral motion using multicomponent articulation and thus tend to generate particulate debris and soluble metal ions. Limited information is available on the long-term metal concentrations and associated systemic adverse events observed in metal-on-metal CDA. Serum chromium (Cr) and nickel (Ni) concentrations were assessed in patients implanted with ball-in-trough stainless steel-based cervical disc through 7 years.

Methods: A prospective, nonrandomized longitudinal study was conducted that included 25 patients following rigorous exclusion criteria that included no previous permanent metal implants and no professional exposure to metal particles. Blood serum Cr and Ni concentrations were assayed preoperatively and at 3, 6, 12, 24, 36, 60, and 84 months postoperatively using high-resolution inductively coupled plasma–mass spectrometry. Longitudinal statistical comparisons were made using the Friedman test with statistical significance at $P < .05$.

Results: Median serum concentrations determined preoperatively and at 3, 6, 12, 24, 36, 60, and 84 months postoperatively were 0.074, 0.106, 0.132, 0.170, 0.172, 0.274, 0.192, and 0.203 ng/mL for Cr and 0.085, 0.178, 0.222, 0.175, 0.205, 0.284, 0.181, and 0.194 ng/mL for Ni. The serum Cr concentrations were statistically higher for all postoperative time periods compared to preoperative concentration (Friedman $P < .01$), whereas serum Ni concentration was statistically higher at the 84-month postoperative time period than the preoperative concentration (Friedman $P < .01$) and then the concentration at 3, 12, 24, and 60 months postoperatively (Friedman $P < .03$).

Conclusions: The Cr concentrations detected at all postoperative times were statistically higher than preoperative concentrations, whereas Ni concentration was statistically higher than the preoperative concentration only at 84 months.

Research Article

Keywords: cervical disc, chromium, metal-on-metal, nickel, wear

INTRODUCTION

Anterior cervical discectomy and fusion (ACDF) is an effective modality to treat cervical degenerative disc disease by decompressing the neural elements and stabilizing the cervical spine. However, cervical disc arthroplasty (CDA) has emerged as an alternative treatment to ACDF for cervical degenerative disc disease with superior clinical outcomes.^{1,2} The CDA has the potential of reducing the incidence of adjacent level degeneration commonly associated with ACDF by preserving motion at the treated level.^{3–6} In addition, CDA mitigates nerve root compression by restoring both intervertebral disc and

foraminal height.⁷ Most commonly, the artificial cervical discs provide intervertebral motion using multicomponent articulation. However, the intervertebral articulation of these artificial disc components can generate in vivo wear in the form of particulate debris and soluble metal ions similar to any other large joint articulating implant. The clinical performance of the articulating implants have been observed to be dependent on the host response to the generated particulate debris and metal ions among other factors.^{8,9} Conventional ultra-high-molecular-weight polyethylene (UHMWPE)/metal-bearing couples for large joint

implants have exhibited evidence of limited survivorship with UHMWPE-induced osteolysis and aseptic loosening of the implants.^{10,11} Hard-on-hard bearing surfaces, such as metal-on-metal (MOM), have thus been explored for articulating applications, as the generated wear is expected to be less due to the superior wear properties of certain metallic materials in comparison to conventional UHMWPE. One such MOM cervical artificial disc, PRESTIGE Cervical Disc (Medtronic, Memphis, TN) was approved by the US Food and Drug Administration in July 2007. It is a 2-component ball-in-trough design made out of 316L stainless steel material consistent with the specifications of the American Society for Testing and Materials (ASTM F138). In a prospective, randomized, nonblinded clinical study with a total of 541 subjects, the noninferiority in overall success was confirmed for the investigational PRESTIGE disc group ($N = 276$).¹² The overall success rates were reported to be 75.0% and 63.7% for the investigational and ACDF control groups, respectively, at 84 months. The cervical disc maintained sagittal angular motion through 84 months averaging 6.75 degrees at the treated level at 84 months, while the second surgeries involving adjacent levels were reported to be 4.6% for the investigational group compared to 11.9% for the ACDF control group with statistical significance ($P = .008$).¹² The ball-in-trough articulation provides 4 independent degrees of freedom for the in vivo device mobility. Despite superior wear resistance of MOM articulating implants in comparison to metal-on-polyethylene, there have been concerns around the adverse local and systemic effects attributed to the elevated metal concentrations in local and remote sites as observed in association with MOM total hip implants.^{13,14}

The potential of particulate debris generation in the PRESTIGE disc was assessed in an in vitro long-term durability and wear test, and the wear patterns were characterized from the retrieved and in vitro tested discs.¹⁵ In this study, Kurtz et al observed that the in vitro evaluation of the disc represented a more severe wear scenario than would be encountered in vivo. Even though this study provides some insight into the potential of MOM cervical discs to generate in vivo wear, information about the distribution of wear debris in the bloodstream is still not available. Elevated blood metal concentrations have been associated with adverse local and systemic effects observed in

MOM total hip implants.¹⁶ Most commonly, MOM articulating devices have been associated with the elevated metal concentrations, but this has also been observed for the non-MOM articulating devices, including metal-on-polyethylene and ceramic-on-polyethylene, because of various mechanical phenomena, including tribocorrosion at modular junction metal interfaces.^{17,18} The long-term clinical implications of elevated metal concentrations are still not well understood and require long-term patient surveillance for metal concentrations and any related adverse events. Previous studies have reported on the long-term cobalt (Co), chromium (Cr), nickel (Ni), and titanium metal concentrations for various articulating large joints¹⁷⁻²⁰ and Cr and Ni concentrations in pediatric and adult subjects implanted with stainless steel-based nonarticulating posterior spinal instrumentation.²¹⁻²⁶ However, no information is available on the long-term metal concentrations in the articulating stainless steel spinal implants. The metal concentrations reported for stainless steel-based posterior fixation spinal instrumentation provide some indications about the metal concentrations in spinal implants but may not truly represent the metal concentrations resulting from an articulating device, as the fundamental mechanism of wear (and thus the resulting debris and metal serum concentrations) is different between the 2 types of devices. Wear generated by posterior spinal instrumentation is primarily from fretting micromotion accompanied by corrosion²⁷ compared with the abrasive wear and microscopic surface fatigue observed in articulating MOM discs.²⁸

The objective of the present study was to assess the blood metal concentrations in the subjects implanted with stainless steel-based cervical disc.

METHODS

A prospective, nonrandomized longitudinal study was conducted that included 25 subjects implanted with the PRESTIGE Cervical Disc System. This study measuring serum metal concentrations was conducted under a US Food and Drug Administration-approved investigational device exemption (G010188) and was a part of the PRESTIGE cervical disc system postapproval study ($N = 59$). The study was approved by the institutional review board of each participating site, and all participants signed an informed consent prior to their inclusion in the study. The subjects in this study were enrolled

Table 1. Patient demographics.

Age (y), mean \pm SD	48.2 \pm 6.4
Height (in.), mean \pm SD	67.4 \pm 4.4
Weight (lbs), mean \pm SD	180 \pm 35.5
% Male	36%
% Caucasian	88%

at 2 investigational sites in the United States and consisted of 9 males and 16 females with an average age at implantation of 48.2 years (range 36.0–58.0 years). Fourteen subjects were treated at C5–C6 and 11 at C6–C7. Subject demographic data are shown in Table 1.

The subjects enrolled in the continued access arm of the trial were screened for eligibility based on the protocol-specified inclusion and exclusion criteria of the trial. The exclusion criteria was specifically expanded for the study of metal concentrations to reduce additional sources of metal exposure and included exclusion for patients:

- With any prior procedure requiring the use of permanent metal implants (ie, stents, joint replacement, and/or dental implants [does not include fillings, crowns, or braces])
- Working in a profession with increased exposure to metal particles (ie, jewelry making, construction, ironworking, metal grinding, welding, etc.).

Blood samples were collected preoperatively and at 3, 6, 12, 24, 36, 60, and 84 months postsurgery. Venipuncture using a butterfly needle in triplicate S-Monovette (Sarstedt, Nümbrecht, Germany) syringes was used to collect the blood. The first collected vial served to rinse the needle, tubing, and multi-adaptor and thus was discarded, while second and third vials were used only for the metal concentration analysis. To avoid potential contamination, all the laboratory supplies, including storage tubes, pipette tips, and vessels in contact with the samples, were acid washed prior to their use in the blood collection procedure. The blood samples were left at room temperature to clot before these were centrifuged to separate into serum and cell fraction, and then these serum samples were stored at -80°C until analyzed. To minimize any atmospheric and manual contamination, all the postcollection sample handling was carried out in a class 100 clean room environment. The Rush University Medical Center Trace Metal Analysis Laboratory has used the blood collection procedure adopted in the current

Table 2. Median Cr and Ni concentrations in ng/mL.

Time Point	Cr Concentration	Ni Concentration
Preoperative	0.074	0.085
3 months	0.106	0.178
6 months	0.132	0.222
12 months	0.170	0.175
24 months	0.172	0.205
36 months	0.274	0.284
60 months	0.192	0.181
84 months	0.203	0.194

study as a standard practice for nearly 2 decades.^{29–33}

A high-resolution inductively coupled plasma–mass spectrometer (Element 2, Thermo-Finnigan MAT, Bremen, Germany) was used to assay serum for Cr and Ni. The testing was conducted using the method of additions, and the detection limits for Cr and Ni in serum were 0.015 and 0.17 ng/mL, respectively. The Rush University Medical Center Trace Metal Analysis Laboratory ensured the accuracy and performance for Cr and Ni by analyzing Seronorm Trace Elements Serum L-1 and L-2 (Sero, Billingstad, Norway).

Any concentration values below the detection limit were assigned a value of one-half the detection limit: 0.008 ng/mL for Cr and 0.085 ng/mL for Ni.

STATISTICAL METHODS

Longitudinal statistical comparisons were made using the Friedman test with statistical significance at $P < .05$.

RESULTS

Twenty-five subjects were enrolled in the study; however, a few were lost to follow-up until the 84-month interval. Two subjects missed their 24-month appointments, whereas 4 subjects missed their 36- and 60-month appointments. In addition, 7 subjects missed their 84-month appointments. This resulted in a sample size of 25 at the preoperative through 12 months, 23 at 24 months, 21 at 36 and 60 months, and 18 at 84 months.

The preoperative median serum Cr and Ni concentrations and those at 3, 6, 12, 24, 36, 60, and 84 months postoperation are provided in Table 2. A box plot distribution of serum Cr and Ni concentrations is presented in Figures 1 and 2, respectively. Serum Cr concentrations were statistically higher for all postoperative time periods compared to preoperative concentration (Friedman $P < .01$). In addition, the concentrations at 6, 12,

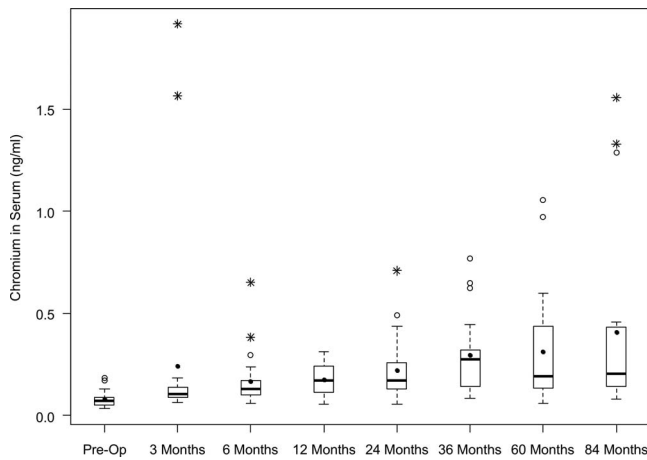


Figure 1. Cr serum metal concentrations. Solid line dividing the interquartile box represents the median and (•) represents the mean. Extended whiskers from each side of the box represent lowest and highest observations. Extreme cases (*) are defined as values more than 3 interquartile ranges from the upper or lower edge of the interquartile box, while outliers (o) are defined as cases with values between 1.5 and 3 interquartile ranges from the upper or lower edge of the box.

24, 36, 60, and 84 months were statistically higher than the 3-month concentrations (Friedman $P < .01$); the concentrations at 12, 36, 60, and 84 months were statistically higher than the 6-month concentrations (Friedman $P \leq .05$), and the concentration at 36 months was statistically higher than the 12-month concentration (Friedman $P < .05$). The concentrations at 60 and 84 months were not statistically different than what was observed at 36 months, which appeared to be the peak value.

Serum Ni concentrations were statistically higher at the 84-month postoperative time period than were preoperative concentrations (Friedman $P < .01$) and statistically higher than the 3-, 12-, 24-, and 60-month postoperative time periods (Friedman $P < .03$). Additionally, the concentration at the 6-month postoperative time period was higher than the 3-month postoperative time period (Friedman $P < .02$), and the concentrations at the 36-month postoperative time period were statistically higher than those at the 3- and 12-month postoperative time periods (Friedman $P < .02$). Even for Ni, the concentration appeared to peak at 36 months with no statistical difference when compared to concentrations at 60 and 84 months.

There were 7 subjects for Cr and 6 subjects for Ni that were identified as having either outlier or extreme concentrations at 1 or more time periods. (Subjects with values between 1.5 and 3 box lengths from the upper or lower edge of the box are defined as outliers. The box length is the interquartile range [25%–75%] [SPSS ver. 15.0]. Subjects with values

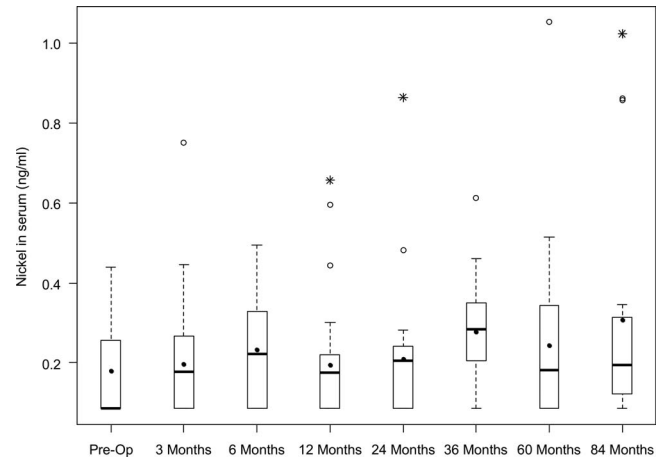


Figure 2. Ni serum metal concentrations. Solid line dividing the interquartile box represents the median and (•) represents the mean. Extended whiskers from each side of the box represent lowest and highest observations. Extreme cases (*) are defined as values more than 3 interquartile ranges from the upper or lower edge of the interquartile box, while outliers (o) are defined as cases with values between 1.5 and 3 interquartile ranges from the upper or lower edge of the box.

more than 3 box lengths from the upper or lower edge of the box are defined as extreme. The box length is the interquartile range [25%–75%] [SPSS ver. 15.0].) These included 4 common subjects that had both Cr and Ni outlier or extreme concentrations. Table 3 presents subjects with extreme and outlier concentrations at various time periods.

It is interesting to note that with an exception of 2 subjects (subject III at the 60-month postoperative period and VIII at the 84-month postoperative period in Table 3), the remaining subjects had Ni concentrations below the laboratory's normal reference range for Ni (<1 ng/mL).

The detection limits for Cr and Ni were changed to 0.010 and 0.088 ng/mL, respectively, at the 84-month testing cycle as a result of the improved sample handling and testing techniques introduced at this testing cycle. There were no undetectable Cr values in serum; hence, there was no impact on the reported Cr concentrations at 84 months due to this change. However, the lower detection limit resulted in 8 subjects having Ni concentrations higher than 0.085 ng/mL (the value which would have been assigned with the previous detection limit of 0.17 ng/mL) and therefore resulted in a higher median for the 84-month time period.

DISCUSSION

In this study, we looked at the long-term serum Cr and Ni concentrations for subjects implanted with stainless steel-based cervical disc replacement.

Table 3. Subjects with statistically identified extreme and outlier concentrations at various time points (out, outlier; ext, extreme).

Subject	Preoperative	3 Mo	6 Mo	12 Mo	24 Mo	36 Mo	60 Mo	84 Mo
I			Cr _{out}		Ni _{ext} Cr _{ext}	Cr _{out}	Cr _{out}	Ni _{out} Cr _{ext}
II				Ni _{out}	Ni _{out} Cr _{out}	Ni _{out} Cr _{out}	Ni _{out} Cr _{out}	Ni _{out} Cr _{ext}
IV		Cr _{ext}	Cr _{ext}					
V				Ni _{out}				
VI	Cr _{out}	Ni _{out} Cr _{ext}	Cr _{ext}					
VII	Cr _{out}							
VIII				Ni _{ext}				Ni _{ext} Cr _{out}
IX						Cr _{out}		

The Cr concentrations at all time periods were statistically higher than the preoperative concentration, whereas the Ni concentration was statistically higher than the preoperative concentration only at 84 months. The Cr concentration continued to increase until 36 months, at which time it reached the steady state. Time periods after 36 months were not statistically different from the 36-month concentration. For Ni, the highest concentration was observed at 36 months, and there was no statistical difference observed between the concentrations at 36 months and those at 60 and 84 months. The Ni concentration at 84 months was observed to be statistically higher than 60 months, but this was a result of change in the Ni detection limit at 84 months. These concentrations were still very low compared to the laboratory's normal reference range for Ni (<1 ng/mL). The stabilization of concentrations observed after 36 months suggests a steady state where the 2 device components had accommodated each other and were generating metal concentrations at a constant rate.

The median serum Cr and Ni concentrations reported for the artificial cervical disc in the current study are lower than serum Cr and Ni concentrations reported in subjects with stainless steel implants for single- or multilevel posterior lumbar arthrodesis. Table 4 presents reported Cr and Ni concentrations for the stainless steel-based posterior instrumentation for adult and pediatric patient populations and for articulating metal-on-polyethylene and MOM hip joints. It is important to use caution when comparing serum metal concentrations in the current study with the reported values for spinal instruments and large joint arthroplasty, as the measurement of metal in blood or serum is a sensitive process and very susceptible to potential contaminations. It has been shown that variables

such as analytic methodology, blood collection techniques, and time of collection can cause significant variation in the detection limits and subsequent results of a study measuring metal concentrations.³⁴⁻³⁶ In addition, in large joint arthroplasty, CoCrMo alloy is utilized (not stainless steel), which differs in its Cr and Ni content from the stainless steel used in the disc arthroplasty of the present study and in the spinal instrumentation studies (Cr 27%–30%, Ni <0.5% for CoCrMo alloy; Cr 17%–19%, Ni 13%–15% for 316L stainless steel).

There currently is no consensus on either the threshold level of metal concentrations in the blood at which adverse systemic effects begin appearing or the threshold concentration that should serve as a trigger for intervention.³⁷ To assess the possible impact of serum metal concentrations on patients receiving the cervical disc replacement under study, an assessment of systemic adverse events in our study population was performed by chart review. Case histories were reviewed for systemic events reported during the period of device implantation. Those events were compared with systemic events previously reported in MOM hip implant literature. Some case reports and articles in the medical literature suggest that subjects with a MOM hip implant may be at risk for certain chronic metal ion toxicity syndromes (systemic reactions), including general hypersensitivity reaction (skin rash), cardiomyopathy, neurological changes including sensory changes (auditory or visual impairments), psychological status changes (including depression or cognitive impairment), renal function impairment, and thyroid dysfunction (including neck discomfort, fatigue, weight gain, or feeling cold).^{38,39} An evaluation of systemic events during cervical disc implantation with the device under study demon-

Table 4. Cr and Ni concentrations reported for posterior spinal instrumentation and hip joint arthroplasty.

Study	Instrumentation	No. of Subjects	Mean Follow-Up (y)	Metal Evaluated	Mean Concentration (ng/mL)	Median Concentration (ng/mL)	Technique
Savarino et al ²⁶	Stainless steel instrumentation for scoliosis correction	22	19.4	Cr Ni	—	0.36 0.56	Graphite furnace atomic absorption spectrometer
del Rio et al ²²	Posterior spinal arthrodesis with stainless steel instrumentation with and without evidence of corrosion	11 (corrosion group), 22 (noncorrosion group)	31.8 (corrosion group), 24.5 (noncorrosion group)	Cr Ni	—	0.50 (corrosion group), 1.00 (noncorrosion group) 3.80 (corrosion group), 1.00 (noncorrosion group)	Atomic absorption spectrophotometry
McPhee et al ²⁴	Stainless steel posterior instrumentation for deformity or fracture	32	9.3	Cr Ni	0.94 0.88	—	Atomic absorption spectrometer Inductively coupled plasma mass spectrometry
Kim et al ²³	Posterior spinal arthrodesis with stainless steel instrumentation	37	3.9	Cr Ni	For <2 y from surgery: 2.7. For >4 y from surgery: 0.3 For <2 y from surgery: 3.8. For >4 y from surgery: 0.9	—	Inductively coupled plasma mass spectrometry
Cundy et al ²¹	Posterior spinal surgery for scoliosis with stainless steel instrumentation	30	5.7	Cr	0.97	—	Graphite furnace atomic absorption spectrometry
Levine et al ¹⁷	Metal-on-polyethylene hip with Co allow based modular stem and femoral head	10	7	Cr	—	0.184	Inductively coupled plasma mass spectrometry
Savarino et al ²⁰	Metal-on-metal hip resurfacing	19	5	Cr Ni	—	1.63 0.93	Graphite furnace atomic absorption spectrometry

strated that there are no trending clinical symptoms or events suggestive of chronic metal toxicity syndrome in 335 study patients from the initial clinical study and the continued access arm. This chart review includes patients with explanted devices ($N = 10$) and patients with extreme or outlier concentrations in the present study ($N = 9$).

To evaluate the possible clinical implications of local debris, the case histories as well as the available histological data of the explanted patients (8/10) were assessed. Histological examination of the explanted devices demonstrated absence of ALTR/osteolysis in the periprosthetic tissue. Additionally, the assessment of those patients' case histories suggested that device removal was most likely caused by patient or surgery-related factors, including traumatic events (3/10), surgical technical causes (ie, inadequate decompression followed by early removal) (2/10), multiple work-related injuries (1/10), or adjacent segment disease (2/10). The combination of clinical data and histological analysis does not suggest that a biological reaction to local debris was the reason for device removal. It is important to mention that none of the explanted patients had serum metal concentration data, and therefore the correlation between histology and serum data was not feasible.

Local and systemic reactions to wear debris have been frequently reported in large joint implants.^{40,41} While reviewing the adverse events related to wear debris, it has been found that Co may be synergistic with Cr in eliciting adverse local and systemic reactions in large joint replacement patients.⁴²⁻⁴⁴ However, as noted above, the cervical disc arthroplasty in this study is made out of 316L stainless steel, which does not include Co. Furthermore, none of the disc arthroplasty patients had systemic clinical symptoms or events suggestive of chronic metal toxicity.

This was a long-term prospective, longitudinal study presenting the Cr and Ni concentrations up to 84 months for the stainless steel-based MOM cervical disc arthroplasty. When compared with preoperative concentrations, higher serum Cr concentrations were detected at all postoperative time points, whereas Ni concentration only at 84 months was statistically higher than the preoperative concentration. The detected serum Cr and Ni concentrations were an order of magnitude lower than the concentrations reported for stainless steel-based posterior instrumentation without any signs of

corrosion. A chart review revealed no clinical symptoms or events indicative of systemic metal toxicity in 335 study patients, including patients with explanted devices and patients with statistically identified extreme or outlier concentrations in the present study.

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