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Evaluation of titanium release from titanium alloy implants in patients with spinal instrumentation

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Abstract

Objective: This study was performed to investigate the baseline serum titanium levels in patients with short-segment titanium alloy posterior instrumentation and to assess patient-, implant-, and surgery-related factors that might affect the serum titanium level.

Method: Two groups of patients were included in the study. The study group comprised 39 patients who had undergone short-segment posterior instrumentation from January 2013 to June 2016. The control group comprised 11 randomly selected patients who presented to the outpatient clinic with no history of orthopedic surgery. The serum titanium levels and inter-group differences were analyzed.

Results: The mean serum titanium level was significantly higher in the study group than in the control group. No significant difference was observed between patients with different etiologies, implants used for fusion, numbers of instrumented segments, or postoperative durations.

Conclusion: The serum titanium levels of patients with posterior lumbar spinal instrumentation are significantly higher than those of the normal population even after achievement of solid fusion. These levels are not affected by the use of transverse connectors, the use of cages, the operated segments, or the duration of implants.

Keywords

Spinal fusion, titanium, corrosion, posterior lumbar instrumentation, implant duration, cages

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Introduction

Since the introduction of the Harrington hook and rod constructs, posterior instrumentation has become the mainstay of surgical treatment for several spinal pathologies.[1] The last two decades have seen a surge in available implant designs, and the Harrington instrument has been replaced by newer and more versatile systems that incorporate polyaxial pedicle screws, hooks, rods, and transverse connectors. With the introduction of posterior and transforaminal lumbar interbody fusion cages, interbody fusion and segmental posterior instrumentation can now be achieved using a single posterior approach. These advances in surgical techniques and newer implant technologies have improved patient outcomes, triggering an upshift in the number of spinal surgeries performed annually. Each year, 500,000 spinal instrumentations and 250,000 posterior lumbar spinal fusion surgeries are performed in the United States.[2,3]

In most surgeries requiring posterior instrumentation, the ultimate goal is to achieve fusion of a certain spinal segment and thus provide enduring stability against deforming or degenerating forces. The main purpose of the rod and screw construct is to resist these forces and share the mechanical load until fusion occurs. An ideal spinal implant should be biocompatible and at the same time resist mechanical and corrosive stress. The biological environment predisposes the metal implants to oxidative stress, and the mechanical abrasion imposes further corrosion. Longer exposure of an implant to corrosive and mechanical forces might be expected to be associated with greater accumulation of metal ions. If fusion is not achieved, the implants will continue to share the mechanical load, making them more susceptible to implant wear. The resultant wear may range from visible metal debris around the implants to accumulation of metal ions in the bloodstream.

Titanium and its alloys have been used in orthopedic surgery for more than 50 years and are currently the materials of choice in spinal surgery. The effects of corrosion on orthopedic implants and accumulation of metal ions in knee and hip replacement surgery have been extensively researched because these implants are subject to constant abrasive wear.[4] Studies on corrosive wear of spinal instruments are relatively scarce, with the first article published in 1999. Although the factors that affect metal corrosion following hip and knee arthroplasty have been frequently investigated, factors affecting metal corrosion of spinal instrumentation or the relationship between the corrosion rate and clinical outcomes have been seldom reported.[5,6]

Achieving solid fusion reduces the mechanical load on posterior spinal instruments and implant corrosion. In contrast, inadequate fusion reportedly aggravates metal corrosion with a resultant increase in the serum titanium level.[7,8] Rising metal levels in the bloodstream may be of concern for two reasons. First, accumulation of metal ions may have toxic effects on surrounding tissues or distant organs. Second, rising levels may indicate increased implant wear and an increased risk of implant failure. Despite these concerns, the threshold of the serum titanium level and its correlation with clinical outcomes have not been clearly established.

This study was performed to investigate the baseline serum titanium levels in patients treated using short-segment posterior instrumentation made of titanium alloy-coated material and to assess patient-, implant-, and surgery-related factors that might affect the serum titanium level.

Materials and methods

Following approval from the institutional review board (Decision number: 2017-13/70, Bursa Uludag University Faculty of

Medicine Clinical Research Ethics Committee/TURKEY), the medical records of patients who had undergone posterior instrumentation from January 2013 to June 2016 were retrieved and analyzed. The inclusion criteria were an age of >18 years, posterior instrumentation of the lumbar spine, achievement of solid interbody or posterolateral fusion, and willingness to participate in the study. Patients with posterior instrumentation extending beyond five levels, combined anterior instrumentation, fixation of the cervical or thoracic region, revision, liver or kidney disease that may affect removal of metal ions from the bloodstream, and a postoperative period shorter than 12 months were excluded. A control group was established by random inclusion of patients who presented to the outpatient clinic with no history of orthopedic surgery and with willingness to participate in the study. Written informed consent was obtained from all included patients.

Whole blood samples were drawn, and the first 10 mL was discarded to minimize contamination. The remaining samples were centrifuged at 1410 $\times g$ for 8 minutes to precipitate the cellular components. The obtained serum was transferred to dry tubes and stored at −20°C. An inductively coupled plasma–optical emission spectrometry atomic mass spectrometer (PerkinElmer, Inc., Waltham, MA, USA) was used to assess the trace element levels of titanium. The minimum detectable level of titanium for this device was 0.02 μg/L. The patients' serum titanium levels and the difference between the study and control groups were analyzed. The effects of the etiology, patient demographics, time span between instrumentation and blood tests, type of instrument, rod length, instrumentation level, number of screws, and fusion types on the serum titanium levels were evaluated.

Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation, median (range), or n (%). The variable distribution was determined using the Kolmogorov–Smirnov test. The Mann–Whitney U-test was performed to analyze quantitative independent data. A *P*-value of <0.05 was considered statistically significant. Spearman's correlation analysis was performed for the correlation analysis. Multiple linear regression analysis was performed to determine factors that were correlated with the serum titanium level. IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

The medical records of 139 patients were analyzed. Forty-six patients were deemed suitable for inclusion in the study and were called for a final follow-up and evaluation of the serum titanium concentration. Seven patients refused to participate, and the remaining 39 patients presented for the follow-up. Their radiographs and blood samples were obtained. These 39 patients comprised the study group, whereas 11 patients were included in the control group (Table 1). In the study group, 21 (53.8%) patients were male and 18 (46.2%) were female. Their mean age at the time of surgery was 59.2 ± 13.3 years (range, 18–78 years), and their median body mass index was 33.2 kg/m^2 (range, 27.1–43.2 kg/m^2). In the control group, seven (63.6%) patients were male and four (36.4%) were female. Their mean age was 53.8 ± 11.1 years (range, 28–65 years) and median body mass index was 32.3 kg/m^2 (range, 29.4–39.0 kg/m^2). There was no significant difference in sex, age, or body mass index between the two groups. The patients' demographics are outlined in Table 1.

Table 1. Patient demographics and intergroup analysis.

Group	Patients	Sex		Age, years	Body mass index, kg/m^2
		Male	Female		
Study group	39	21 (53.8)	18 (46.2)	59.2 (18–78)	33.2 (27.1–43.2)
Control group	11	7 (63.6)	4 (36.4)	53.8 (28–65)	32.3 (29.4–39.0)
P		**0.74**	**0.96**	**0.089**	**0.094**

Data are presented as n, n (%), or median (range).

The etiology of spinal instrumentation was spinal stenosis in 25 (64%) patients, spondylolisthesis in 6 (15%), and vertebral fracture in 8 (21%). The EXPEDIUM posterior instrumentation system (DePuy Spine, Raynham, MA, USA) was used in 20 (51.2%) patients, whereas the Legacy posterior instrumentation system (Medtronic Sofamor Danek, Memphis, TN, USA) was used in the remaining 19 (48.8%) patients. The median number of screws used for patients with EXPEDIUM implants was 5.2 (range, 4–8), and the mean rod length was 13.1 cm (range, 7–18). Transverse rod connectors were used in five (25.0%) of these patients. The median number of screws used for patients with Legacy implants was 5.1 (range, 4–8), and the median rod length was 13.2 cm (range, 7.5–19). Transverse rod connectors were used in five (26.3%) of these cases.

Thirteen patients with spinal stenosis and four patients with spondylolisthesis underwent interbody fusion using titanium cages. Transverse rod connectors were used in two of these patients. The mean duration from surgery to blood sampling was 30.4 months (range, 18–57 months) [EXPEDIUM, 34.7 months (range, 18–59 months) and Legacy, 25.9 months (range, 18–42 months)]. This duration was shorter than 28 months in 13 patients and longer than 28 months in 26 patients. Eighteen (46.1%) patients underwent 2-level instrumentation, 19 (48.7%) patients underwent 3-level instrumentation, and 2 (10.5%) patients underwent 4-level instrumentation.

At the final follow-up, the mean serum titanium level of patients in the study group was 0.048 ± 0.009 μg/L (range, 0.023–0.067 μg/L), which was significantly higher than that of patients in the control group (0.020 ± 0.000 μg/L (range, 0.000–0.020 μg/L)) ($P < 0.001$). Tables 2 and 3 show the serum titanium levels of patients in the study group with respect to the etiology, use of an interbody cage or transverse connectors, rod length, level of instrumentation, and implant duration. There was no significant difference in the serum titanium level according to the etiology, use of interbody cages or transverse connectors, rod length (shorter vs. longer than 13 cm), level of instrumentation, or duration of implant use (shorter vs. longer than 28 months postoperatively).

Discussion

With the improvements in life expectancy, the increased demand for a more active lifestyle, and increased patient expectations related to quality of life, orthopedic implants have become key components of musculoskeletal surgery to enhance support and stability. Designation of the first decade of the 21st century as the "Bone and Joint Decade" by the World Health Organization can be considered an indicator of their large-scale use.[9] However, limited numbers of implications related to spinal surgery have been studied since the beginning of the 2000s. Furthermore, no study has been performed to investigate

Table 2. Serum titanium levels among patients with different etiologies.

Etiology	Serum titanium level	Significance
Spinal stenosis	0.045 ± 0.003 μg/L	$P > 0.05$
Spondylolisthesis	0.055 ± 0.004 μg/L	
Fracture	0.052 ± 0.004 μg/L	

Data are presented as mean ± standard deviation.

Table 3. Effect of certain factors on serum titanium levels.

Analyzed parameters		Serum titanium level, μg/L	Significance
Cage	Yes	0.046 ± 0.008	$P > 0.05$
	No	0.050 ± 0.010	
Transverse connector	Yes	0.046 ± 0.10	$P > 0.05$
	No	0.049 ± 0.009	
Rod length	< 13 cm	0.0487 ± 0.008	$P > 0.05$
	> 13 cm	0467 ± 0.007	
Level of segments	2	0.0398 ± 0.008	$P > 0.05$
	> 2	0453 ± 0.007	
Implant duration	< 28 months	0.0546 ± 0.003	$P > 0.05$
	> 28 months	0.0423 ± 0.006	

Data are presented as mean ± standard deviation.

the threshold for the corrosion rate and its related factors. The results of our study indicate that the use of titanium alloy implants for posterior instrumentation causes a significant increase in titanium ions in the serum. Patients' etiology, level of instrumentation, use of interbody or posterolateral fusion, rod length, transverse connectors, and length of postoperative period do not have a significant impact on ion release.

The threshold of the serum titanium level that indicates increased wear, corrosion, and possible implant-related problems has not been established. Determination of such a validated ion level could warn the surgeon about implant loosening or failed fusion before clinical symptoms arise, or symptoms with no clear identifiable cause could be attributed to implant-related factors. However, such a reference value for the rate or cumulative release of titanium in spinal surgery does not exist.[7,8] Richardson et al.[10] reported an average serum titanium level of 2.60 μg/L (range, 0.48–12.97 μg/L) at the end of a 26-month follow-up in 30 patients with degenerative discs with posterior instrumentation who experienced no problems during this period. Similarly, in their study of 32 patients with spinal deformity with instrumentation, Cundy et al.[11] noted an average serum titanium level of 1.69 ng/L (range, 0.84–12.70 ng/L) at the end of a 12-month follow-up period; this was 2.4 times higher than the preoperative value, and this increase was observed in all patients. Conversely, in another study, only 2 of 18 patients with spinal instrumentation had higher-than-normal serum titanium levels.[7]

Consistent with the increase in serum titanium levels, metal accumulation in the surrounding soft tissues may also occur.[7,8] Wang et al.[8] performed tissue sampling in patients who developed fusion complications after lumbar decompression and

fusion using titanium implants, and they found significant accumulation of titanium ions around the implants. Further, they compared these titanium ion concentrations with those in patients who achieved solid fusion. The measured titanium levels of 0.616 μg/g around the rod and 2.148 μg/g around the pedicle screws in patients with solid fusion were dramatically higher than the levels in patients with fusion complications.[8]

Although an uncertain increase in the serum titanium level has been demonstrated in most of the studies on this subject, only pseudoarthrosis and delayed fusion have been investigated as possible factors that might affect metal release.[11] Richardson et al.[10] compared patients with and without an interbody fusion cage and found that the average serum titanium level was 3.30 and 1.98 μg/L, respectively, with a significant difference. Although this was not a direct evaluation of the effect of fusion on metal ion release, the reason for the low serum titanium levels in patients with interbody fusion cages may be attributed to the possibility that cage use enhances stability and shortens the time needed for spinal fusion. In our study, we found no significant difference between patients with and without an interbody fusion cage. This may be because only patients with solid fusion were included and that blood samples were taken at a minimum of 12 months of follow-up. Any changes in the serum levels prior to fusion might have been diminished by the time the serum titanium levels were evaluated.

Richardson et al.[10] found that the mean serum titanium level was lower in eight patients with than without interconnection devices (2.44 vs. 2.70 μg/L), but the difference was not statistically significant. Similarly, in our study, the average serum titanium level was lower in 10 patients with transverse connectors without reaching statistical significance. We had expected that using interconnection devices and interbody cages would enhance stability until fusion occurred and would reduce corrosion. There may be several reasons for our results failing to support our hypothesis. Our sample size might have been too small to detect a significant difference. Another explanation is that decreased metal wear and corrosion due to increased stability provided by the additional implants may have been counterbalanced by metal release from the increased implant surface of the connectors.

In studies by Kasai et al.[7] and Richardson et al.,[10] the average duration of implant use was 2.2 and 5 years, respectively. The serum titanium levels throughout this period were 4.2 and 3.6 times higher than the preoperative level, respectively.[7,10] In a prospective study by Cundy et al.,[11] blood analysis performed on postoperative day 7 revealed increased serum titanium levels, which remained significantly high for up to 12 months. The median duration of implant use in our patients was approximately 2.5 years (30.4 months), which is about 2.5 times higher than the threshold.

Limitations of this study include its small sample size, absence of preoperative serum titanium level measurement, and lack of correlation of metal release with time by repeated-measure analysis as part of follow-up. However, all included patients underwent operations by a single surgeon using a single technique, and this ensured homogeneity during data assessment. Monitoring for corrosion using repeated measurements, which makes it possible to compare the relationship between metal release until solid fusion is achieved and the release measured during follow-up, might be helpful for projecting possible complications that can be encountered during follow-up. It is possible to reveal the cut-off metal corrosion rate and its relationship with clinical outcomes by repeated-measure analysis as part of well-designed,

prospective, multicenter studies with an adequate number of patients and sufficiently long follow-up period.

In conclusion, the serum titanium levels of patients with posterior lumbar spinal instrumentation are significantly higher than those in the normal population even after achievement of solid fusion. These levels are not affected by the use of transverse connectors, the use of cages, the operated segments, or the duration of implants. The establishment of a cutoff value will guide clinicians in more accurately determining the prognosis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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