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The mechanical aspect of titanium ion release after posterior instrumentation for early onset scoliosis

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Abstract: Surgical treatment of early onset scoliosis (EOS) is connected with the risk of early and late complications. The aim of the study is to assess influence of the rod fracture on the titanium ion release (TIR) in traditional growing rods instrumentation for EOS. 56 patients treated surgically due to EOS were divided into three groups: 1) a control-patients newly operated due to scoliosis, patients treated with the traditional growing rod (TGR) and TGR who had rod fracture (FGR) and required a surgical revision. Titanium quantification in blood sample, skin fragment (CT – clean tissue) and macroscopically contaminated tissue located near the implant (DT – dirty tissue) was performed using high-resolution emission spectrometry with excitation in inductively coupled plasma. The mean serum titanium level in control, TGR, and FGR groups were 1.93 ± 0.8, 5.61 ± 0.23, and 4.43 ± 0.1 μg/dm^3, respectively. The mean CT titanium level in control, TGR, and FGR groups were 0.0045 ± 0.001, 0.0035 ± 0.001 and 0.0065 ± 6.8 mg/g, respectively. The mean DT titanium level in TGR and FGR groups was 0.59 ± 0.02, and 1.022 ± 0.03 mg/g, respectively. Implant leads to the TIR into tissues and blood. Increasing the number of anchors increases the titanium content in the CT TGR group. Mechanical damage to the implant has no significant effect on the increase of TIR.

Keywords: scoliosis, metal ions, implant, titanium, mineralization

1. Introduction

The problem of scoliosis affects about 2-3% of the population (Stokes, 1994; Tambe et al., 2018; SRS Terminology, 2000; Bunnell, 1986), of which only 0.1% is in need of surgical treatment. Regardless of the etiology of the deformation, early onset scoliosis (EOS), i.e. before 10 years of age, is a challenge for a pediatric orthopedist, because the goal of the treatment is not the only correction of deformity but creating conditions for further proper growth of the chest and spine. The treatment allows preventing serious health consequences, with thoracic insufficiency syndrome (TIS - **T**horacic **I**nsufficiency **S**yndrome) at the forefront.

Apart from obvious benefits, the surgical treatment carries the risk of early and late complications. Mechanical problems or implant displacement, neurological damage, superficial and deep postoperative wound infections, secondary distortion, loss of correction, decompensation of curvature are widely described in the literature (Tambe et al., 2018). The risk of complications is accompanied by correction of spinal deformity regardless of its etiology, however, many studies agree that in the case of neuromuscular scoliosis the probability of complications is 35%, and in the case of EOS, this probability increases to 48% (Watanabe, et al., 2013, Weiss and Goodall, 2008).

However, due to the fact that the removal of implants seems controversial and it is not usually performed, remaining in the body for several or even several dozen years can bring about the effects of secretion of metal ions to the surrounding tissues and the blood.

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During the revision surgeries, metallosis contaminants around the implants are often observed. In addition to metal particles (insoluble) as a result of the use of orthopedic implants, impurities are also formed as metal ions (soluble) (Jacobs et al., 2001; Jacobs et al., 1994; Hallab and Sas, 2009). Jacobs (Jacobs et al., 2001) determined that there are two mechanisms for the release of metal from the implant - abrasion and corrosion. Abrasion is mechanical damage to a solid material, whereas corrosion is a chemical/electrochemical form of degradation. Of the two mechanisms, abrasion appears first. Despite the "abrasion-resistant" materials being marketed, it is not possible to completely eliminate these types of implant damage. According to Jacobs (Jacobs et al., 2001), stainless steel is more corrosive than cobalt or titanium alloys (Jacobs et al., 1998). Although Singh (Singh et al., 2018) in his work established in an *in vitro* model that in the case of titanium implants, the micro-rays in the sagittal plane cause more corrosion, we did not observe traces of corrosion on implants in our patients. Mu et al. (Mu et al., 2002) in the experiment on mice showed that the release of titanium particles also occurs in the absence of abrasion products. It is known that different types of pollutants cause inflammatory reactions of varying intensity, moreover, each of them can cause a different type of reaction. Despite many publications on the subject (Hallab et al., 2003), there is no consensus on the most the pro-inflammatory potential of specific particles. Another aspect of the threats was pointed out by Wick et al. (Wick et al., 2010). It showed *ex vivo* the possibility of crossing the TiO_2 across the blood-placenta barrier (Wick et al., 2010). Similarly, Takeda (Takeda, 2009) has shown that exposure of mice to titanium oxide particles may cause damage to the cranial nerves and the genital system in the offspring. The literature describes the effects associated with the use of total hip replacements, mainly with metal-metal articulation, while very few sources treat patients undergoing correction of spinal deformities, especially adolescents, treated in multiple stages using growth-friendly techniques.

Hence the idea of this research, which aims to assess the level of release of trace metal ions into the peripheral tissues and the bloodstream in children treated for scoliosis with the use of the growth-friendly technique and the answer to the question whether the mechanical damage to the implant increases the concentration of metal ions in the tissues.

2. Materials and methods

The study included 56 patients treated surgically in one center due to EOS in the years 2015-2016. 43 patients were girls (74.13%) and 15 were boys (25.83%). The average age of patients was 13.5 ± 3.54 years. The average follow-up time was 4 years ± 2.8 years. Patients were divided into three groups - TGR – which was the phased correction with final spondylodesis (Fig. 1.), and a group of patients treated with TGR who required a revision procedure due to the fracture of the device (FTGR). The control group included 20 patients (patients newly operated due to scoliosis). The average age of surgery was 13.6 years ± 3.6. (5.6 years, - 17.75 years.) The average BMI of patients was 20.1. There were 22 patients in the TGR group, 17 girls and 5 boys. The average time of treatment is 2.9 years. The average age of surgery during the study was 13.5 ± 3.8 years. The patient's BMI was 16.5. The mean number of implanted anchors was 7.9 ± 4.5, 11 patients underwent single rod treatment, and in others – double rod. Stabilization included an average of 14 segments. The group in which the rod was broken during multi-stage treatment was 14 patients, 6 boys and 8 girls, and middle-aged 12.6 ± 2.7 years. The follow-up time was 5.7 ± 3.6 years. The BMI was 16. Six had one rod implanted, eight had two rods. The average number of anchors is 7, and the stabilization range was 13.5 segments.

A peripheral blood sample was collected for each patient before surgery, by min. 3 cm^3 volume into a sterile test tube made of polypropylene, with EDTA, containing no trace elements (S-Monovette, SARSTEDT AG & Co. KG). During the surgery, before the insertion of the implants, the skin fragment were taken from the surgical cutting site (CT). Patients from the study groups had additionally collected macroscopically contaminated tissue, located near the implants (DT). Each time a parent and a patient expressed their consent to participate in the study if he was 16 years old. The project obtained consent no. KE-0254/105/2015 of the Bioethics Committee of the Medical University of Lublin.

Statistical analysis of experimental data was carried out using the Statistica 13.0 program. Differentiation of titanium content in clean and contaminated tissues was made using the Wilcoxon pair test. To assess the correlation of the content of titanium in the blood and tissues with BMI, age, time of observation of the number of implanted elements, the analysis of Spearman's rank correlation was used. For gender correlation, a gamma coefficient was applied due to the presence of related observations.

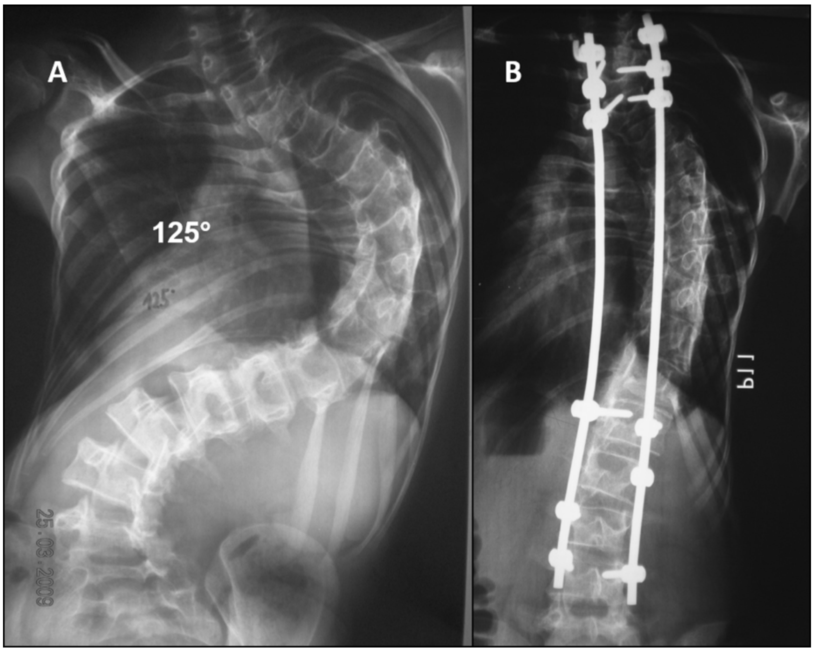

Fig. 1. An X-ray of the patient treated with TGR: A – pre-operatively, B – after first surgery

2.1. Methodology of the tissues titanium level marking

In the case of tissue and blood analysis, it was necessary to pre-mineralize them, consisting in the distribution of a given biological material to simple inorganic compounds. The TOPWave apparatus (Analytik Jena) was used to prepare the samples, enabling pressure mineralization supported by microwave radiation at elevated temperature. The biological material was mineralized in a mixture of nitric(V) acid Suprapur and deionized water. Titanium quantification was performed using inductively coupled plasma induction emission spectrometry (ICP-OES) using PlasmaQuant® PQ 9000 (Analytik Jena AG). The obtained values of titanium concentrations in mineralization were converted into titanium content in mili or micrograms per gram of the tested material.

3. Results and discussion

The mean serum titanium level in control, TGR, and FGR groups were 1.93 ± 0.8, 2.64 ± 0.23, and 4.19 ± 0.1 μg/dm^3, respectively. The mean CT titanium level in control, TGR, and FGR groups were 0.0045 ± 0.001, 0.0035 ± 0.001 and 0.0065±6.8 mg/g,, respectively. The mean DT titanium level in TGR, and FGR groups were 0.59 ± 0.02, and 1.022 ± 0.03 mg/g, respectively.

3.1. Tissue correlations

3.1.1. With sex

Significantly, the negative correlation only occurs in the case of the control group ($p<0.05$). According to data presented in Table 1 it can be concluded that in this group there is a strong relationship between gender and TI content in the tissue. A negative sign indicates that Ti content is lower for women. This means that the titanium content in the clean tissue in the control group is lower in women.

3.1.2. With the observation time

No significant differences were observed between observation time and Ti content in tissue in any group. One can only notice that the longer the observation time, the Ti content in the pure tissue is smaller in the TGR_ fracture group. The relationship, however, does not show statistical significance (Table 2).

Table 1. The gamma correlation coefficient for the dependence of Ti content in tissues on sex

Correlation coefficient	DT	CT
FGR	-0.3333	0.4999
TGR	-0.2273	0.0303
Control	----	-0.833

Table 2. Correlation coefficient for dependence of Ti content with observation time

Correlation coefficient	DT	CT
FGR	0.05406	-0.6324
TGR	-0.0127	-0.1518

3.1.3. With BMI

There was no statistically significant relationship between BMI and Ti content in tissue in any group (Table 3). One can only assume that the larger the BMI, the Ti content in the pure tissue is smaller in the TGR group.

Table 3. Correlation coefficient for dependence of Ti content with BMI

Correlation coefficient	DT	CT
FGR	-0.2500	0.1999
TGR	-0.3326	-0.4681
control	---	0.2883

3.1.4. With the number of anchors

Only in the TGR group, there was a statistically significant correlation between the Ti content in the pure tissue and the number of anchors. A positive value of the correlation coefficient indicates that the more anchors, the higher the Ti content in the pure tissue in the TGR group (Table 4).

Table 4. Correlation coefficient for dependence of Ti content with the number of anchors

Correlation coefficient	DT	CT
FGR	-0.3671	0.3999
TGR	0.0384	0.5597

3.1.5. With the number of rods

There was no statistically significant relationship between the number of rods and the Ti content in the tissue in any of the groups. One can only assume that the more rods, the Ti content in the pure tissue are greater in the TGR_ fracture group (Table 5).

Table 5. Correlation coefficient for dependence of Ti content with the number of bars

Correlation coefficient	DT	CT
FGR	-0.0770	0.4472
TGR	0.3396	0.1687

3.1.6. With the number of segments

In the case of the study of the correlation of the titanium content in tissues with the length of stabilization, expressed by the number of stabilized segments, no statistically significant relationship was found (Table 6).

Table 6. Correlation coefficient for dependence of Ti content with the number of stabilized segments

Correlation coefficient	DT	CT
FGR	0.0187	0.2582
TGR	0.0251	0.3399
Control	---	0.2477

3.2. Serum correlations (Spearman's rank correlation coefficient)

3.2.1. With observation time

There was no significant relationship between observation time and titanium content in the serum in any group. It can only be noted that the longer the observation time, the lower the concentration of Ti in the blood in the TGR_ fracture group. This relationship, however, does not show statistical significance. Correlation coefficient for dependence of Ti content with observation time FGR vs. TGR were -0.5389 vs. -0.1116.

3.2.2. With BMI

There was no statistically significant relationship between BMI and the content of Ti in the serum in any group. Correlation coefficient for dependence of Ti content with BMI FGR vs. TGR vs. control were -0.4047, -0.3123, -0.2857, respectively.

3.2.3. With the number of anchors

There was no statistically significant relationship between the number of anchors and the content of Ti in the serum in any group. Correlation coefficient for dependence of Ti content with the number of anchors FGR vs. TGR were 0.0199 vs. -0.0416.

3.2.4. With the number of rods

In the TGR group, a statistically significant ($p<0.05$) relation between the number of rods and the content of Ti in the serum was demonstrated. Based on the positive value of the Spearman's rank correlation coefficient, it may be assumed that the content of Ti in the blood increases with an increasing number of rods. Correlation coefficient for dependence of Ti content with the number of rods FGR vs. TGR were 0.1826 vs. 0.4779.

3.2.5. With the number of segments

There was no significant correlation between the number of stabilized segments and the content of titanium in the blood in any group. No relationship is statistically significant ($p>0.05$). Correlation coefficient for the Ti content dependence with the number of segments FGR vs. TGR and control were -0.2223, 0.2898, 0.2229, respectively.

4. Discussion

In the light of these studies, the problem associated with the passage of metal ions across the blood-barrier of the placenta can be disturbing real despite the fact that in clinical cases the existence of such hazards has not been demonstrated. However, these publications are based on descriptions of individual patients (de Souza et al., 2012; Johnson et al., 2013; Novak et al., 2014). An additional aspect is a fact that this work concerns adult patients with implanted joint prostheses with metal-metal articulation and not patients after spine stabilization in childhood. Certainly, the consequences of the prolonged presence of elevated levels of metal ions in the blood should still be investigated. In the animal model Sarmiento-Gonzalez et al. (Sarmiento-Gonzalez et al., 2009) studied rats after implantation of titanium wires in the femur up to 18 months, analyzing the levels of titanium in the blood and distant organs (DR-ICP-MS-double focusing inductively coupled plasma mass spectrometry). The concentration of titanium in the blood was around 2.5 $\mu g/dm^3$, (vs. 2.3 $\mu g/dm^3$ in the third month of observation, increasing after another 15 months to an average of 7 $\mu g/dm^3$).

Richardson et al. (Richardson et al., 2008) evaluated, on average, after 26 months the serum Ti level in adult patients undergoing spinal surgery. The metal content was determined using HR-ICP-MS (high resolution inductively coupled plasma-mass spectrometry). In 2/3 of patients, elevated serum Ti (mean 2.6 μg/dm^3), presence of up to 4 screws, and stabilization of 1 segment generated lower serum Ti concentration, stabilization of the structure with a cross-link also reduced the release of ions into the serum. The level of titanium ions is comparable to the results of our research. However, in contrast to Richardson et al. (Richardson et al., 2008), in our observations, the length of stabilization did not affect the level of released serum. However, a statistically significant correlation was found between the Ti content in the pure tissue and the number of anchors – the more anchors, the higher the Ti content in the pure tissue in the TGR group. In another work, Rackham (Rackham et al., 2010) studied chromium levels in patients treated for scoliosis using stainless steel implants with primary spondylodesis for more than 5 years, stabilizing an average of 10.5 segments. The author found a positive relationship between the level of Cr in serum and sex (increased level of Cr in men), which was also confirmed in our research, but it related to titanium ions. Cundy (Cundy et al., 2010) has similar observations. In the group of patients operated with steel implants, the author observed a positive correlation of blood Cr concentration with the patient's gender – men had on average 1.77 times higher Cr levels than women.

In another study (Cundy et al., 2014) the correlation between the level of titanium and the number of implanted implants and the range of stabilization was described, which we did not show in our work. The authors evaluated 33 patients treated for spinal deformities, treated by posterior and frontal stabilization with titanium implants (Ti6Al7Nb, titanium serum metal levels), with simultaneous spondylodesis. Each patient received a blood sample before surgery, one week after, 1.6, 12 and 24 months after. With each segment, the level of titanium increased by 10% and 62% in every 5 segments. Another factor influencing the release of metal ions was the number of bolts. The level of titanium increased by 4.2% with the implantation of each screw. The use of each additional 10 cm rods resulted in a 17% increase in the level of titanium. Increasing the total implant surface obviously increases the release of Ti into the tissues. No positive correlation was found in titanium level growth using cross connectors, cables or staples. In the case of Ti, each 100 after the surgery caused an increase in its concentration by 2.3%. The niobium concentration dropped by 4.3% every 100 days. In the group of posterior stabilization involving an average of 11 segments vs. front (4 segments), a higher average level of Ti was observed - 1.79 vs. 1.1 ppb. McCarthy (McCarthy, 2014) did not report metalosis during a two-year follow-up, although he did two searches due to surgical site infections. However, in the next work (McCarthy, 2016), he observed local metastases with no general symptoms in patients among complications associated with the treatment (Morell and McCarthy, 2016). In an animal model study, McCarthy (McCarthy, 2016) observed similar macroscopic impurities in the stabilization range without spondylodesis and in the histopathological examination of acquired periaortic lymph nodes (McCarthy et al., 2010). The Shilla system used by the author was made of steel. In the case of mechanical damage to the implant, which is associated with a certain destabilization of the system and the appearance of additional movable property between the elements of the structure, one would expect it to increase the release of ions (Kasai, 2003). The authors assessed the content of Ti, Al, and V in the hair and blood of adolescents and adults undergoing spine stabilization procedures. The method of determining ICP-MS with a detection limit of 20 ppb was applied. In 1/3 of the patients with implant damage, increased metal concentration in the blood (80-90 ppb) and in the hair (in 1 patient, 21 μg/g) after the mean 5 years after surgery, was noted. In two patients, implants were removed to normalize the level of metal ions in the first year after surgery. In the group with intact implants, similarly, 1/3 of patients showed increased levels of titanium in the blood (60-90 ppb), while in the hair only 25% (11-21 μg/g). After a year, these values have not changed significantly. The authors did not observe the relationship between the additional increase in the level of ions and the mechanical damage of the implant. This is consistent with the results of our research.

5. Conclusions

According to presented study, following conclusions were marked:

- implanted implants lead to the release of metal ions into tissues and blood,

- the time of the presence of implants in the child's body, the range of stabilization, BMI does not affect the content of Ti in the tissues and blood,
- the titanium content in the clean tissue in the control group is lower in women,
- increasing the number of anchors increases the Ti content in the pure tissue in the TGR group,
- mechanical damage to the implant, destabilizing the structure, has no significant effect on the increase of titanium content in the blood and tissues.

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