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Blood metal levels after minimally invasive repair of pectus excavatum

Michele Torre [a,b,†], Luca Genova Gaia [b], Maria Grazia Calevo [c], Michela Wong [b], Maria Raso [d], Sebastiano Barco [e], Francesca Di Gaudio [d,*,†] and Giuliana Cangemi [e*]

[a] Pediatric Thoracic and Airway Surgery Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy
[b] Department of Pediatric Surgery, IRCCS Istituto Giannina Gaslini, Genova, Italy
[c] Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy
[d] Chromatography and Mass Spectrometry Section, Quality Control and Chemical Risk (CQRC), Department PROMISE, University Palermo, Palermo, Italy
[e] Chromatography and Mass Spectrometry Section, Central Laboratory of Analyses, IRCCS Istituto Giannina Gaslini, Genoa, Italy

* Corresponding authors. Department of Pediatric Surgery, Istituto Giannina Gaslini, Via G. Gaslini 5, 16147 Genova, Italy. Tel: +39-01056362217; e-mail: micheletorre@gaslini.org (M. Torre); Chromatography and Mass Spectrometry Section, Quality Control and Chemical Risk (CQRC), Department PROMISE, Policlinico Paolo Giaccone, Via del Vespro 133, Palermo 90127, Italy. Tel: +39-0916553652; e-mail: francesca.digaudio@unipa.it (F.D. Gaudio).

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Key question

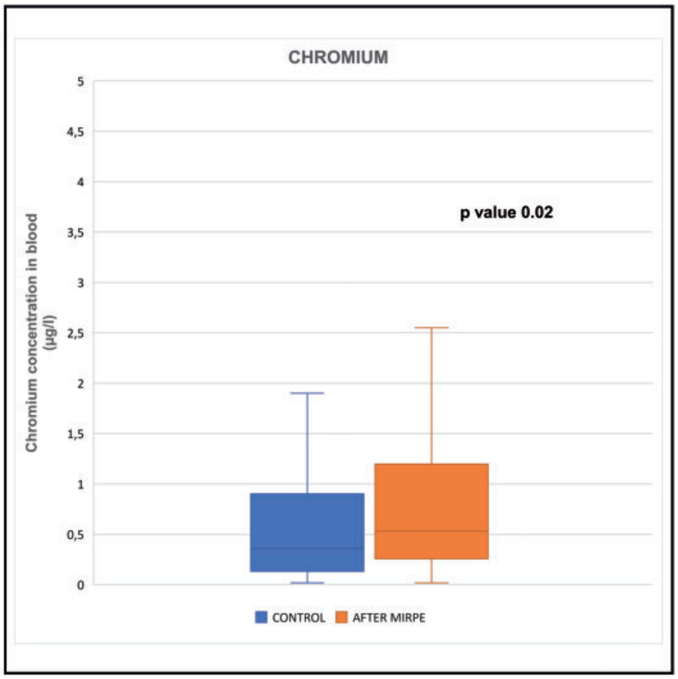
Are blood metal levels increased after minimally invasive repair of pectus excavatum (MIRPE) with substernal metallic bars?

Key finding(s)

Increased levels of chromium in the blood of patients who had MIRPE correlated with the number of bars and stabilizers used.

Take-home message

We should consider possible metal release in patients after MIRPE, which could influence our choice of bars and stabilizers.



Abstract

OBJECTIVES: Minimally invasive repair of pectus excavatum (MIRPE) is the most popular surgical approach for paediatric patients with pectus excavatum. A substernal stainless still bar is inserted and left in place for 3 years and then removed. Our goal was to investigate blood metal levels after MIRPE and to correlate them with surgical details, such as the numbers of bars and stabilizers and the length of time the bar was in place.

[†]These authors contributed equally to this work.

METHODS: Blood levels of iron, chromium, manganese, molybdenum and nickel were analysed in 130 teenagers (108 boys and 22 girls) who had MIRPE using inductively coupled plasma mass spectrometry. A total of 62 patients were operated on using MIRPE (study group) and 68 patients were evaluated at implant time (control group). Differences between the numbers of bars implanted and the presence or absence of stabilizers were also considered.

RESULTS: Significant increases in the levels of abnormal chromium were found in patients in the study group compared with the controls ($P = 0.02$). When we compared the group of patients with 2 or more bars with the group with 1 bar, the percentage of patients with a value above the threshold increased by 29 ($P = 0.05$). A significant increase in chromium levels was observed in patients with stabilizers ($P = 0.03$). Above-threshold levels of molybdenum were found in 5.1% of patients in the control group, but the number was not statistically significant ($P = 0.09$).

CONCLUSIONS: We demonstrated that stainless steel devices used in MIRPE can elevate blood metal levels in paediatric patients. Moreover, we demonstrated that the use of metal stabilizers is associated with higher metal levels, probably due to increased dispersion.

Keywords: Metal release • Metallosis • Metal toxicity • Pectus excavatum • MIRPE • Metallic bar

ABBREVIATIONS

ICP-MS	Inductively coupled plasma mass spectrometry
MIRPE	Minimally invasive repair of pectus excavatum
PE	Pectus excavatum

INTRODUCTION

Pectus excavatum (PE) is the most common anterior thoracic malformation, with an incidence of 1 in 300/400 live births [1]. Minimally invasive repair of PE (MIRPE), also known as the Nuss procedure [2], is the most popular surgical procedure for correcting PE, particularly in adolescents and young adults. One or more substernal bars are implanted and kept in place for an average period of 3 years (Fig. 1). In most cases, metal stabilizers are implanted to reduce the bar dislocation rate.

The local and systemic impacts of surgically implanted metal devices are an ongoing issue. The biocompatibility of such materials may be affected by corrosive events with both local and systemic dispersion of ions and metal particles, as demonstrated by several authors [3–5]. Systemic dispersion is usually studied by analysing the levels of metal in the blood and urine whereas local dispersion is determined by direct analysis of tissue surrounding the devices [4, 6, 7].

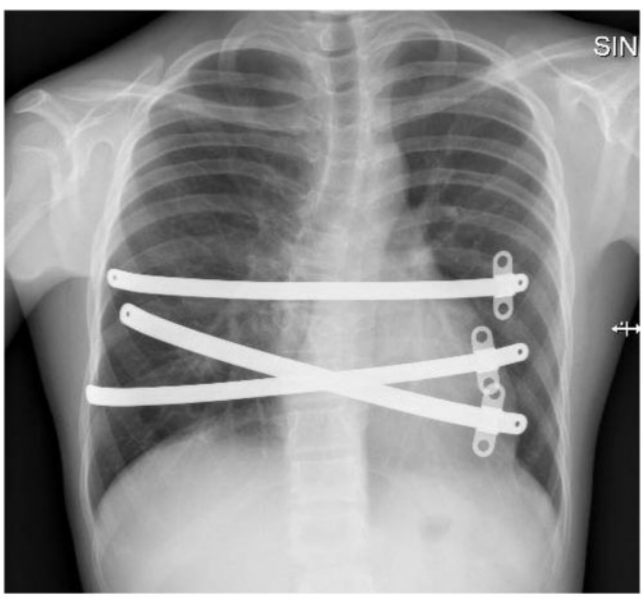


Figure 1: Chest radiograph showing 3 substernal bars and 3 stabilizers after minimally invasive repair of pectus excavatum.

It is know that, in patients undergoing orthopaedic surgery with metal-on-metal implants, the presence of 2 surfaces (metal-on-metal, metal-on-bone, metal-on-soft tissue) results in erosion and dissemination of the components, possibly leading to local and systemic adverse effects [8–10].

The clinical consequences of heavy metal dispersion related to the prosthesis are, however, not clearly explained in the literature. The reasons for this lack of evidence are in part related to the technical difficulties of analysing the metal levels, but also to the fact that the toxic action of metals, given that they are electron finders, is random and strictly correlated to the oxidative stress of the subject. More studies on long-term effects are warranted, in particular regarding chromium and cobalt toxicity, both of which are present in orthopaedic prostheses [11–13].

Metallosis could be clinically similar to a skin allergy. It can be difficult to distinguish between infection, metal allergy or metallosis [14, 15] in wound problems that occur after MIRPE.

For all these reasons, it is relevant to evaluate possible metal release after MIRPE, in particular the release of the elements comprising the outermost layers of the devices (chrome plating), because of the higher probability of mechanical and enzymatic electrochemical erosion.

To date, despite the relevance of the topic, few data are present in the literature [15, 16].

Our main goal was to study metal release after MIRPE in a large series of patients at the time of removal of the bar, to determine if relevant characteristics such as the number of bars or the presence of a metallic stabilizer on the surface of the bar influenced the results. Our hypothesis is that the metal-on-metal effect caused by the movement of the bar inside the stabilizer induced by chest wall motions could increase the release of metals into the tissues.

MATERIALS AND METHODS

A total of 130 patients undergoing surgery for PE at the Gaslini Institute (a paediatric tertiary care institution) were enrolled from May 2017 to July 2019. The study was approved by our internal review board (IRB, protocol number 0015221/20). Two patient groups were defined: the study group, which included 62 patients scheduled for bar removal, operated on 3 years before

Table 1: Parameters and operating conditions for the inductively coupled plasma mass spectrometry instrument

Parameter	Value
Radio frequency power (W)	1400
Nebulizer (carrier gas) flow rate (l/min)	0.95
Resolution (amu)	0.70
Detector	Dual
Speed of peristaltic pump (rpm)	30
Replicates	3
Dwell time	30 ms
Scan mode	Peak jump
Collision cell parameters	
He_2/H_2 reaction gas flow	4.0/0.35 ml/min
Isotopes monitored in standard mode	^{111}Cd, ^{121}Sb, ^{118}Sn, ^{200}Hg, ^{208}Pb
Isotopes monitored in collision mode	^{55}Mn, ^{56}Fe, ^{59}Co, ^{75}As, ^{52}Cr, ^{80}Se, ^{88}Sr, ^{51}V, ^{57}Fe, ^{60}Ni, ^{78}Se, ^{63}Cu, ^{65}Cu, ^{66}Zn, ^{68}Zn, ^{95}Mo, ^{121}Sb, ^{202}Hg, ^{137}Ba, ^{138}Ba

Amu: atomic mass unit; rpm: revolutions per min.

(from 2014 to 2017) by MIRPE, and a control group, which included 68 patients evaluated just before placement of the bar. Exclusion criteria included removal of the bar before 1.5 years, the use of a titanium bar for MIRPE or metal-free tubes not available at the time of surgery.

Allergies to metals and to other general substances were investigated in patients in whom surgery was scheduled and in their families. Titanium bars were used in patients who had suspected or positive test results to allergy tests for metals, and these patients were not included in the study. In the other cases, stainless steel bars were used. In the patients included in the study, 2 types of stainless steel bars were used: through February 2016, a bar manufactured by Biomet® (Zimmer Biomet Holdings, Warsaw, IN, USA) and since February 2016 a bar manufactured by Intrauma® (Intrauma, Torino, Italy). The 2 types of bars are made of surgical steel with almost identical metal compositions. The metal composition of the stabilizers is the same as that of the respective bars.

MIRPE was performed via right thoracoscopy. According to patient characteristics and age, 1 or more bars were inserted (Fig. 1). To stabilize the bar, sometimes 1 or more stabilizers were placed. The metallic stabilizer was avoided when the bar placed was estimated to be very stable. In all cases, other fixation systems were used (multiple pericostal fixation polydioxanone sutures were passed with an Endo Close needle under thoracoscopic vision). Patients were regularly followed up at our institute, and the bar was usually removed after 3 years.

The patients were placed under general anaesthesia for the operation; blood was collected via peripheral venous access. A 5- to 10-ml venous blood sample was obtained using a syringe without a needle and collected in metal-free tubes (Vacuette® Greiner Bio-One International) after discarding the first 3 ml, to limit any possible contamination.

Blood samples were then stored at -30°C until they were shipped to the reference laboratory [Haematology and Rare Disease Department, United Hospitals Villa Sofia-Cervello (Ospedali Riuniti Villa Sofia-Cervello) Hospital, Palermo, Italy] where the analyses were performed. The metals were quantified

Table 2: Numbers of bars and stabilizers in our study group

	Bars (*B*)			Total
	B = 1	*B* = 2	*B* = 3	
Stabilizers (*S*)				
S = 0	11	5	1	17
S = 1	24	4	0	28
S = 2	9	3	0	12
S = 3	0	1	1	2
S = 4	0	3	0	3
Total	44	16	2	

by inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Scientific X Series II, Thermo Fisher Scientific, Milan, Italy) equipped with a collision cell.

Before analysis, blood samples were digested and mineralized using a microwave oven (CEM Elettromeccanica Srl, Nonantola, Italy) with a high-pressure rotor. In particular, 2 ml of blood were transferred inside quartz vessels and treated with 3 ml of HNO_3 (69%), 2 ml of H_2O_2 (30%) and 100 µl of a solution containing Au 100 ng/l. ICP-MS analyses were performed in triplicate using the instrumental parameters shown in Table 1.

Descriptive statistics were generated for the whole cohort. Data were expressed as mean and standard deviation, as median and range for continuous variables and as absolute or relative frequencies for categorical variables. The distribution of the data was analysed using the Kolmogorov–Smirnov test. Non-parametric statistics were considered as appropriate. Differences between groups were evaluated using the Mann–Whitney test for continuous variables and the χ^2 or Fisher exact test for categorical variables. A *P*-value of <0.05 was considered statistically significant; all *P*-values were based on two-tailed tests. Statistical analyses were performed using SPSS for Windows version 20 (SPSS Inc, Chicago, IL, USA). The reference values for tolerable blood metal concentrations published by the Italian National Institute of Health (Istituto Superiore di Sanità) were used [17].

RESULTS

The study group included 54 (87.1%) boys and 8 girls (12.9%); the control group included 54 (79.4%) boys and 14 (20.6%) girls. The median age was 18.7 years (range 7.1–22 years) for the study group and 15 years (range 0.6–23.2 years) for the control group. The median age of the patients in the study group at the time of bar placement was 15.8 years (range 4.5–19.1 years). The median time elapsed from MIRPE to removal of the bar in the study group was 2.9 years (range 1.6–3.5 years).

In the study group, 44 (71%) patients had 1 bar and 18 (29%) patients had 2 or more bars; 45 patients (72.6%) had 1 or more stabilizers and the remaining 17 (27.4%) had no stabilizers (Table 2).

The results of the ICP-MS analyses in both groups are summarized in Table 3.

Chromium levels in the study group were significantly higher than those found in the control group ($P = 0.02$), with an increase of 10.4% of patients presenting a value above the physiological upper threshold. Although not statistically significant, in 5.1% of

Table 3: Comparison between control group and study group

	Control (*n* = 68)	After MIRPE (*n* = 62)	*P*-value
Cr			
Mean ± SD Median (range)	0.50 ± 0.43 0.36 (0.02–1.9)	27.75 ± 143.4 0.53 (0.02–1070.8)	0.022
Percent above threshold	41.2% (28/68)	51.6% (32/62)	0.29
Ni			
Mean ± SD Median (range)	227.65 ± 1476.57 2.01 (0.1–11725)	14.70 ± 50.60 2.13 (0.09–340.15)	0.72
Percent above threshold	45.6% (31/68)	50% (31/62)	0.72
Mo			
Mean ± SD Median (range)	0.36 ± 0.40 0.17 (0.01–1.41)	1.77 ± 7.86 0.33 (0.01–59.54)	0.33
Percent above threshold	0	5.1% (3/62)	0.099
Mn			
Mean ± SD Median (range)	12.13 ± 7.80 8.43 (3.78–39.75)	13.07 ± 9.76 9.83 (1.30–48.31)	0.89
Percent above threshold	54.4% (37/68)	58.1% (36/62)	0.72
Fe			
Mean ± SD Median (range)	332.99 ± 72.92 340.93 (37.51–535.5)	359.39 ± 118 377.69 (2.1–584.08)	0.001
Percent above threshold	0	0	

MIRPE: minimally invasive repair of pectus excavatum; SD: standard deviation.

Table 4: Comparisons of types of bars with and without stabilizers

	Bar = 1 (*n* = 44)	Bars ≥2 (*n* = 18)	*P*-value	No stabilizers (*n* = 17)	Stabilizers (*n* = 45)	*P*-value
Cr						
Mean ± SD Median (range)	30.76 ± 163.15 0.48 (0.02–1070.8)	20.40 ± 80.18 0.70 (0.02–341.56)	0.19	0.49 ± 0.46 0.44 (0.02–1.31)	38.06 ± 167.73 0.58 (0.02-1070.8)	0.031
Percent above threshold	43.2% (19/44)	72.2% (13/18)	0.051	35.3% (6/17)	57.8% (26/45)	0.16
Ni						
Mean ± SD Median (range)	15.83 ± 54.24 2.06 (0.09–340.15)	11.91 ± 41.67 2.14 (0.10– 178.80)	0.979	2.52 ± 4.10 1.38 (0.10 –17.41)	19.30 ± 58.86 2.28 (0.09– 340.15)	0.13
Percent above threshold	50% (22/44)	50% (9/18)	1	35.3% (6/17)	55.6% (25/45)	0.25
Mo						
Mean ± SD Median (range)	1.93 ± 9.06 0.22 (0.01–59.54)	1.39 ± 3.73 0.58 (0.01–16.18)	0.17	0.44 ± 0.32 0.49 (0.01–0.97)	2.27 ± 9.21 0.13 (0.01–59.54)	0.48
Percent above threshold	4.7% (2/44)	6.2% (1/18)	1	0	7.1% (3/45)	0.55
Mn						
Mean ± SD Median (range)	12.35 ± 9.41 9.83 (1.30–48.31)	14.84 ± 10.63 9.58 (4.52–40.24)	0.35	15.94 ± 8.18 16.93 (2.43– 27.81)	11.99 ± 10.16 8.84 (1.30–48.31)	0.051
Percent above threshold	56.8% (25/44)	61.1% (11/18)		70.6% (12/17)	53.3% (24/45)	0.26
Fe						
Mean ± SD Median (range)	347.3 ± 118.76 374.96 (2.1–525.44)	388.8 ± 114 411.39 (7.51–584.08)	0.16	372.73 ± 81.14 383.99 (101.1–477.24)	354.34 ± 129.67 376.33 (2.10–584.08)	0.89
Percent above threshold	0	0		0	0	

SD: standard deviation.

the patients in the study group, molybdenum levels were above the threshold ($P = 0.09$). No significant differences were observed in nickel levels between the 2 groups. No patients in either the control group or the study group had iron values above the threshold; nevertheless, the study group had significantly higher mean concentrations of iron ($P = 0.001$). Table 4 shows the results according to the number of bars and stabilizers: 43.2% of patients with 1 bar and 72.2% of patients with 2 bars had chromium levels above the threshold with a significant difference ($P = 0.05$). No differences in molybdenum and nickel levels were found in relation to the number of bars.

When comparing patients with or without stabilizers, we observed that chromium levels were higher in patients with stabilizers ($P = 0.03$). Patients with stabilizers had an increase of 22.5% in cases with chromium above the threshold and of 20.3% for nickel (even if not statistically significant).

Levels of molybdenum above the threshold were found in 5% of patients in the study group, but only in patients with stabilizers (7%). No patients without stabilizers had abnormal molybdenum levels. No influence on metal levels was found when we considered the time elapsed from bar implant to removal or the patients' gender.

We noted some abnormal values: In particular, 3 patients had extremely high concentrations of chromium (1070, 341 and 196 µg/l), nickel (340, 178 and 71 µg/l) and molybdenum (59, 16 and 12 µg/l), and very low levels of iron (6, 7 and 2 mg/l) after MIRPE. Two other patients presented extremely high values of nickel (11725 and 3480 µg/l).

To date, no clinical symptoms have been observed in any of the patients during the follow-up period that could be attributed to heavy metal dispersion.

DISCUSSION

We have reported the results of the largest study ever conducted on metal dispersion after MIRPE and the first on an Italian population. Given the high frequency of MIRPE, it is essential to investigate any aspect that may affect patient safety, in particular in paediatrics. To the best of our knowledge, only 2 studies on blood metal levels after MIRPE have been published, both demonstrating metal release in a small series of patients. Cundy and Kirby [16] in 2012 reported a significant increase in serum chromium levels and a non-significant increase in serum nickel levels in 11 patients in whom a Biomet bar was implanted, with a significant difference in the number of metallic wire sutures used. Fortmann *et al.* [15] in 2017 demonstrated significantly increased levels of nickel, chromium and cobalt in tissues, of chromium and nickel in plasma and of chromium in urine in 20 patients in whom a MedXpert bar (MedXpert, Eschbach, Germany) was implanted. MIRPE is a general definition describing a variety of techniques that differ in surgical details such as types and numbers of bars, the use of metal stabilizers and other fixation mechanisms. To further investigate the possible mechanism of metal release after MIRPE, we evaluated in a larger series the role of surgical details on metal release. Our results demonstrate that metal levels tended to increase after MIRPE, even if a statistically significant difference was reached only for chromium. The increase in metal levels in patients with stabilizers reinforces our hypothesis that the metal-on-metal effect of the bar against the stabilizer can play a crucial role in determining amount of metal released. Our results could lead to reflections on the future choice of bar type and stabilization technique. Titanium is generally considered to be more resistant to corrosion, so titanium bars would theoretically release fewer metallic ions than steel bars would. However, titanium implants may also be related to the release of particles and ions; further studies on these metal alloys are needed [18–21].

Even though our analyses of other metals found no statistical significance, we observed an upwards trend in the number of patients above the thresholds for metals after MIRPE. Further studies with larger sample sizes are warranted to further elucidate the differences found in the quantities of these metals in the blood.

Some important meta-analyses of these metals in relation to carcinogenesis found no differences in short- and medium-term follow-up compared to the general population; nevertheless, given the long possible latency, further studies and screening are necessary, especially concerning chromium, a known carcinogenic agent, particularly for respiratory tract tumours [22, 23]. There are many correlations between oncological diseases and neurological and neuro-developmental disorders and oxidative stress and metals. Few clinical and epidemiological data are available regarding the correlations with the specific ionization states of metals (speciation).

Metal dispersion may also occur from nonarticular surfaces and metal implants that release ions and nanoparticles [18, 19]. It is important to emphasize that nanoparticles will cause long-term, greater effects due to their high surface area. Given the difficulty of quantifying the actual prevalence and bioaccumulation of these materials, patients should be followed up in the medium to long term to determine blood metal levels associated with specific toxicological tests and biomarkers.

Due to the complex interactions between the organism and implanted metal devices, it is difficult to make a quantitative estimate of the risk based on blood levels of metal ions, especially regarding alloys containing multiple elements.

An important difference between MIRPE and lifetime orthopaedic implants is the fact that the MIRPE implant is temporary, which could limit the pathological effects of the systemic dispersion of metal ions. In fact, in patients with PE, the toxicity effects of metallosis have never been demonstrated. However, the release of metal around the bar and the stabilizer could induce local reactions. Many skin reactions after MIRPE are considered to be allergies or infections. The diagnosis of a metal allergy is usually performed through epicutaneous tests before the bar is implanted; titanium bars are recommended for patients with a positive result from a skin test [24–26]. A conversion from non-allergic to metal-allergic status following the implant could be possible [27]. An allergic reaction should not be confused with an infectious event or metallosis. Local tissue reactions in patients with negative epicutaneous allergy tests and without clear signs of infection are also described in literature: Such reactions, therefore, should not be considered as purely allergic or infective complications with little knowledge about their actual origin [14, 15]. One of the most reliable hypotheses is based on a potential inflammatory reaction caused by local and/or systemic dispersion of metal from the devices implanted.

A point of strength of our study is the method of analysis: We used whole blood instead of plasma (used in other previously published studies), thus including cells with the potential to accumulate metals. Despite our rigorous methods for sample collection and analysis, we cannot rule out a possible contamination of some abnormal samples. However, we thought it appropriate to consider these values as valid by including them in our statistical analysis but also to use the variability of patients above the threshold as a parameter to limit the weight of these abnormal values.

Limitations

This study has several limitations. They include the small sample size and the large number of statistical comparisons that are prone to multiple testing biases. Another limitation of the study is the lack of standardized blood metal threshold values for the Italian paediatric population; in fact, the values used in this study are referred to the general population.

Because we found considerable variability in the blood values of metals in our control group (>50% of the patients were over the threshold for manganese; 46%, for nickel; and 41%, for chromium), a longitudinal study of the same group of patients at the moment of positioning and at the time of removal is necessary. This comparison will reduce to a minimum the influence of external factors such as the area of residence and diet: A coeliac diet was shown to be associated with metal trace elements [28].

CONCLUSION

Given the popularity of MIRPE, the hypothesis of the possible release of metals from the devices used should lead to research on even better biocompatibility in order to exclude the risk of possible complications related to the implanted materials.

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Author contributions

Michele Torre: Conceptualization; Writing—original draft. **Luca Genova Gaia:** Conceptualization; Data curation; Writing—original draft. **Maria Grazia Calevo:** Formal analysis; Methodology; Supervision; Writing—review & editing. **Michela Wong:** Conceptualization; Data curation; Writing—review & editing. **Maria Raso:** Formal analysis. **Sebastiano Barco:** Data curation. **Francesca Di Gaudio:** Formal analysis; Methodology; Supervision; Writing—review & editing. **Giuliana Cangemi:** Conceptualization; Methodology; Supervision; Writing—review & editing.

Reviewer information

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