



## Pmma body injection and hypercalcemia correlation: a cross-sectional observational study on the comprehensive analysis of variables

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DOI: <https://doi.org/10.54448/ijn23301>

Received: 05-18-2023; Revised: 07-19-2023; Accepted: 07-21-2023; Published: 07-27-2023; IJN-id: e23301

### Abstract

**Introduction:** Hypercalcemia related to aesthetic intramuscular implants exclusively made of PMMA (polymethylmethacrylate) is a very rare condition. Late complications of these implants are related to poorly understood inflammatory triggers, which may reactivate stabilized implants, increase calcitriol production, and lead to hypercalcemia. **Methods:** Records of patients seen between 2022 and 2023 with a PMMA microsphere body implant and a subsequent diagnosis of hypercalcemia were searched. Medical history, medication use, data on PMMA implantation, and laboratory tests related to calcium metabolism were described and subjected to variable correlation analysis. The instituted treatments were described. **Results:** A total of 17 female patients with exclusive body PMMA implants confirmed by ultrasonography or MRI (Magnetic Resonance Image) developed hypercalcemia between 2017 and 2022. Prior renal disease, COVID-19 infection, vitamin D use, and anabolic steroid use correlated with laboratory changes in hypercalcemia. Larger PMMA implant volumes led to parathyroid hormone suppression. **Conclusion:** Patients with PMMA body implants may rarely present with hypercalcemia when variables such as renal disease before implantation, high doses of vitamin D or anabolic steroids are present. Based on the data presented and the available scientific literature, recommendations for patient investigation, implant volume limit, and patient follow-up after the procedure were made.

**Keywords:** Hypercalcemia. PMMA. COVID-19. Vitamin D. Anabolic steroids.

### Introduction

The worldwide demand for aesthetic body procedures has increased in recent years. Approximately 25 million aesthetic medical procedures were performed worldwide in 2021, and Brazil accounted for 7% of this number [1]. The reasons are driven by several factors, such as growing awareness of health and well-being, increased life expectancy of the population, popularization of safe aesthetic treatments, less invasive and with shorter recovery time, and increased exposure to images of "ideal" bodies in social media.

The intramuscular implantation of PMMA (polymethylmethacrylate) microspheres for body contouring treatment, which has been performed for more than 20 years in Brazil [2], also followed this trend. Its use is widely recognized in addressing the aesthetic and functional problems associated with HIV-related lipodystrophy and use of antiretroviral drugs [3,4]. ANVISA (National Health Surveillance Agency) regulates the aesthetic use of PMMA for treating lipodystrophy related to the use of antiretroviral drugs in HIV (Human Immunodeficiency Virus) and in the aesthetic facial and body volumetric correction in healthy patients, provided the volume of the product is determined by qualified physicians [5].

A report of two cases of hypercalcemia in patients with PMMA body implants [6] generated alert among physicians because this complication had not been reported on the national scene until 2018 [7]. It is possible that the volumes of PMMA implanted in patients increased after 2018 as a reflection of the low rate of complications associated with the procedure [8].

Therefore, evaluating the technical aspects of body PMMA implantation in patients with hypercalcemia is a scope of this study.

There are no studies on hypercalcemia that include patients with only PMMA body implantation. The most frequent material in the literature related to hypercalcemia is injectable silicon. The lack of specificity about the nature of implanted material was pointed out by Manfro et al [6], mentioning that other materials concomitant to PMMA in fillers may produce different biological reactions leading to distinct laboratory phenotypes. There is marked confusion in the literature between PMMA, a solid product that produces a fixed tissue where it is implanted, and silicon oil, which suffers the action of gravity, moving down and presenting a perennial risk of necrosis and embolism. Thus, the diagnosis of the implanted material is fundamental for the therapeutic choice and follow-up of patients and is another objective proposed in this study.

The objective evaluation of the characteristics of patients seeking body aesthetic treatments, preexisting diseases, SARS-CoV-2 infection (COVID-19), as well as the use of medications such as vitamin D and Anabolic Androgenic Steroids (AAS) is also analyzed. Accordingly, was conducted in this study to investigate the set of variables that may be correlated with hypercalcemia in patients with PMMA body implants.

## Methods

### Study Design

This observational, transversal study was elaborated according to the rules of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology, <https://www.strobe-statement.org/>). Medical records were selected in sequence from patients who consulted with the authors between January 2022 and March 2023 with a diagnosis of hypercalcemia and who had previously undergone intramuscular body implantation of PMMA microspheres.

### Inclusion Criteria:

#### Primary:

- Laboratory examination of total calcium equal or greater than 10.2 mg/dL (a rigorous laboratory test criteria);
- Affirmative information about having PMMA microspheres implanted into the body by a physician;
- Negative information about silicon prosthesis inclusion surgery in PMMA-implanted regions and the implantation of injectable products other than PMMA performed by any professional;

### Secondary:

- Doppler ultrasound or Nuclear Magnetic Resonance Imaging (MRI) diagnosing the exclusive presence of PMMA in the implanted area;
- Biopsy of the implanted area confirming the presence of microspheres compatible with PMMA and absence of reactive areas characteristic of hydrogel or oil implants;

### Exclusion Criteria:

- Failure to meet all primary inclusion criteria and at least one secondary criterion.

### Qualitative and Quantitative Variables:

- Medical history: sex, age, presence of hypercalcemia symptoms at diagnosis, chronic diseases, family history of diseases, surgeries, silicon prostheses, ultraviolet light lamp tanning habit;
- COVID-19: date of infection prior to hypercalcemia, vaccination;
- Medications: continuous use drugs, vitamin D, AAS, another prescription or over-the-counter;
- PMMA implant: total volume, the number of regions, the number of interventions, date of implantation preceding the hypercalcemia;
- Serum laboratory tests: total calcium, albumin, ionic calcium, calcitriol, cholecalciferol, parathyroid hormone (PTH), creatinine, urea, sodium, potassium, phosphorus;
- Treatments: drug and nondrug therapy.

### Data Analysis

Qualitative data were described. IBM SPSS Statistics - v29 was used to perform the statistical analyses. Descriptive statistics were used to express absolute values and frequencies of variables. Continuous variables were presented with mean, minimum, maximum, and standard deviation ( $\pm$ ). A correlation test was performed between variables, considering statistical significance when  $p < 0.05$ . Due to the small sample size, marginal significance was also considered, with  $p < 0.06$ . For these cases, the 95% confidence interval (CI) and effect size were calculated (Fischer's r-to-z transformation). Statistically significant differences between magnitudes of correlations were considered when  $p < 0.05$ . Data normality was assessed using the asymmetry, kurtosis, Kolmogorov-Smirnov and Shapiro-Wilk tests. The variables did not show a normal distribution. Then, Spearman's correlation ( $\rho$ ) was used to analyze the data.

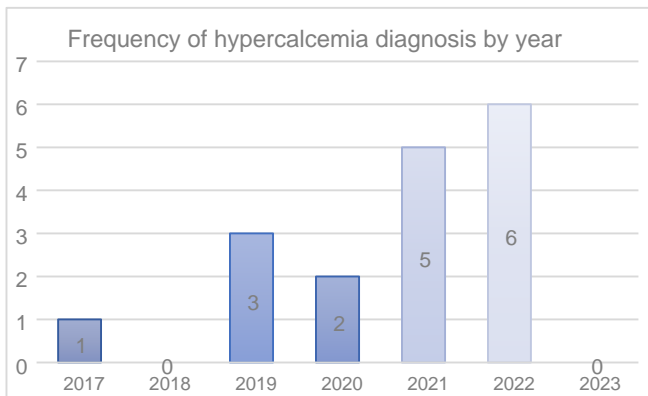
**Ethical Approval**

This study was approved by the National Research Ethics Committee (CONEP) under number 5.158.889 and is in accordance with the 1975 Declaration of Helsinki, revised in 2013.

**Results**

Of the 18 selected patients, all females, 17 met the inclusion and exclusion criteria. One patient was excluded from the study because she presented with an ultrasound image of liquid silicon in gluteus. Hypercalcemia was diagnosed between 2017 and 2022 (Graph 1) in patients with a mean age of  $47.9 \pm 9.56$  years, ranging from 31 to 62 years.

Graph 1. Frequency of hypercalcemia diagnosis by year.



The variables vaccination for COVID-19, surgeries, silicon prostheses, and artificial tanning were not described in the medical records.

Diseases before PMMA implantation and hypercalcemia were hypertension, hypercholesterolemia, hypothyroidism, uterine cancer with lung metastasis, renal and heart failure, myocarditis, ulcerative rectocolitis, and renal cancer.

The family history of diseases included: hypertension, cardiac arrhythmia, diabetes mellitus, hypothyroidism, kidney stones, prostate cancer, bladder cancer, and Duchenne muscular dystrophy. The frequency of antecedents to PMMA implantation and hypercalcemia were summarized in Table 1.

Table 1. Frequency of diseases, medications and symptoms.

	N	Positives	Relative frequency (%)
Chronic diseases	12	8	66.7
COVID-19*	15	8	53.3
AAS**	17	14	82.4
Vitamin D	16	14	87.5
Symptoms	16	7	43.8

\*= SARS-CoV-2 infection; \*\*= Anabolic Androgenic Steroids

The oral medications used were: hydrochlorothiazide, chlorthalidone, anlodipine, atorvastatin, rosuvastatin, levothyroxine, diclofenac sodium, desvenlafaxine, amitriptyline, mesalazine, budesonide, vedolizumab, triiodothyronine, melatonin, oxytocin, hydrolyzed collagen, isotretinoin, vitamin A, vitamin B (complex), vitamin C, vitamin E, vitamin K, coenzyme Q10, L-carnitine, organic silicon, iron, zinc, magnesium, vanadium, copper, chromium, molybdenum, manganese, selenium, biotin, folic acid, glutamine, D-ribose and tyrosine, polyvitamin and thermogenic.

The mean daily dose of vitamin D used 30 days before hypercalcemia was  $14585.54 \pm 13032.24$  IU/day, ranging from 0 to 46666.7 IU/day. Data on PMMA implantation were summarized in Table 2.

Table 2. PMMA implant.

	Mean	Minimum	Maximum	Standard Deviation
Total volume (mL)	620.75	300	1800	365.86
Implanted areas (no)	2.12	1	5	1.11
Interventions (no)	4	1	15	3.54
Months between implantation and hypercalcemia	11.8	2	52	12.57

Total calcium was corrected for albumin. Data on days of hospitalization and laboratory tests were presented in Table 3.

Table 3. Hospitalization and laboratory tests.

	Mean	Minimum	Maximum	Standard Deviation
Hospitalization (days)	5.88	0	17	5.38
Total calcium (mg/dL)	6.28	5.29	9.22	1.02
Ionic calcium (mg/dL)	12.01	10.2	15.20	1.42
Calcitriol (pg/mL)	107.04	40.00	169.00	41.2
Cholecalciferol (ng/dL)	55.99	14.91	101.00	27.01
Parathormone (pg/mL)	9.91	3.00	19.00	4.78
Creatinine (mg/dL)	1.83	0.87	3.75	0.72
Urea (mg/dL)	58.15	36.00	94.00	1.74
Sodium (mEq/L)	139.6	132.00	144.00	3.01
Potassium (mEq/L)	4.00	3.10	4.50	0.42
Phosphorus (mg/dL)	3.51	2.70	3.80	0.34

The absence of hypercalcemia symptoms correlated with older age of the patients ( $\rho = -0.59$ ;  $p < 0.05$ ; CI = -0.84 to -0.12;  $\rho^2 = 0.25$ ), with previous chronic diseases ( $\rho = -0.61$ ;  $p < 0.05$ ; CI = -0.89 to 0.01;  $\rho^2 = 0.37$ ) and higher total calcium values ( $\rho = -0.66$ ;  $p < 0.01$ ; CI = -0.84 to -0.22;  $\rho^2 = 0.44$ ). The magnitudes of the correlations indicate equal contribution of the variables for presence or absence of symptoms, with total calcium and previous chronic diseases ( $z = -0.20$ ;  $\rho = 0.42$ ), total calcium and age ( $z = 0.31$   $\rho = 0.38$ ), and

age and chronic diseases ( $z = 0.09$ ;  $p = 0.46$ ).

Older age of patients correlated with lower cholecalciferol levels ( $\rho = -0.50$ ;  $p < 0.05$ ;  $CI = -0.81$  to  $0.03$ ;  $\rho^2 = 0.25$ ). Patients with chronic diseases used lower total PMMA volume ( $\rho = -0.78$ ;  $p < 0.01$ ;  $CI = -0.94$  to  $-0.31$ ;  $\rho^2 = 0.61$ ). Patients with a history of COVID-19 had more PMMA interventions ( $\rho = 0.58$ ;  $p < 0.05$ ;  $CI = 0.08$  to  $0.85$ ;  $\rho^2 = 0.34$ ) and had lower creatinine ( $\rho = -0.57$ ;  $p < 0.05$ ;  $CI = -0.85$  to  $-0.04$ ;  $\rho^2 = 0.32$ ). They also showed a marginally positive correlation with calcitriol ( $\rho = 0.58$ ;  $p < 0.06$ ;  $CI = -0.05$  to  $0.9$ ;  $\rho^2 = 0.34$ ).

Longer hospital stay correlated with AAS use ( $\rho = 0.48$ ;  $p < 0.05$ ;  $CI = -0.02$  to  $0.32$ ;  $\rho^2 = 0.23$ ), greater number of regions implanted with PMMA ( $\rho = 0.62$ ;  $p < 0.01$ ;  $CI = 0.19$  to  $0.85$ ;  $\rho^2 = 0.38$ ) and greater number of interventions performed ( $\rho = 0.62$ ;  $p < 0.01$ ;  $CI = 0.16$  to  $0.86$ ;  $\rho^2 = 0.38$ ). However, none of the variables more strongly influenced the length of stay: use of AAS and number of PMMA regions ( $z = -0.44$ ;  $p = 0.33$ ), use of AAS and number of interventions performed ( $z = -0.53$  and  $p = 0.29$ ), or the number of PMMA regions and number of interventions performed ( $z = 0$ ).

Patients who used AAS also used a higher mean daily vitamin D dose ( $\rho = 0.49$ ;  $p < 0.05$ ;  $CI = -0.03$  to  $0.80$ ;  $\rho^2 = 0.24$ ) and applied PMMA to more body regions ( $\rho = 0.54$ ;  $p < 0.05$ ;  $CI = 0.07$  to  $0.82$ ;  $\rho^2 = 0.29$ ).

Injectable vitamin D use was confirmed in the positive correlation with vitamin D dose ( $\rho = 0.58$ ;  $p < 0.05$ ;  $CI = 0.10$  to  $0.84$ ;  $\rho^2 = 0.34$ ). Injectable vitamin D use correlated with greater number of body regions implanted with PMMA ( $\rho = 0.56$ ;  $p < 0.05$ ;  $CI = -0.02$  to  $0.80$ ;  $\rho^2 = 0.31$ ), longer time between implantation and diagnosis of hypercalcemia ( $\rho = 0.56$ ;  $p < 0.05$ ;  $CI = 0.02$  to  $0.85$ ;  $\rho^2 = 0.31$ ) and lower sodium values ( $\rho = -0.64$ ;  $p < 0.01$ ;  $CI = -0.88$  to  $-0.14$ ;  $\rho^2 = 0.41$ ).

Patients with larger PMMA volumes had symptoms ( $\rho = 0.60$ ;  $p < 0.01$ ;  $CI = 0.14$  to  $0.85$ ;  $\rho^2 = 0.36$ ) and lower values in PTH ( $\rho = -0.55$ ;  $p < 0.05$ ;  $CI = -0.85$  to  $0.02$ ;  $\rho^2 = 0.30$ ). The greater number of regions implanted with PMMA correlated with the greater number of interventions to reach the final volume ( $\rho = 0.72$ ;  $p < 0.01$ ;  $CI = 0.34$  to  $0.90$ ;  $\rho^2 = 0.52$ ) and both correlated with more days of hospitalization ( $\rho = 0.62$ ;  $p < 0.01$ ;  $CI = 0.19$  to  $0.85$ ;  $\rho^2 = 0.38$ ) and ( $\rho = 0.62$ ;  $p < 0.01$ ;  $CI = 0.16$  to  $0.86$ ;  $\rho^2 = 0.38$ ) with equal magnitude of correlations ( $z = 0$ ). The lowest creatinine levels were found in patients with the highest number of interventions ( $\rho = -0.65$ ;  $p < 0.01$ ;  $CI = -0.88$  to  $-0.17$ ;  $\rho^2 = 0.42$ ).

Total calcium confirmed the elevation of ionic calcium ( $\rho = 0.66$ ;  $p < 0.01$ ;  $CI = 0.20$  to  $0.88$ ;  $\rho^2 = 0.43$ ). There was no correlation between calcium and calcitriol

levels with PMMA implant variables. PTH was lower in patients who had more days hospitalized ( $\rho = -0.57$ ;  $p < 0.05$ ;  $CI = -0.85$  to  $-0.03$ ;  $\rho^2 = 0.32$ ) and phosphorus had a negative correlation with PTH ( $\rho = -0.79$ ;  $p < 0.01$ ;  $CI = -0.96$  to  $-0.25$ ;  $\rho^2 = 0.62$ ).

Calcitriol elevation was associated with potassium elevation ( $\rho = 0.66$ ;  $p < 0.01$ ;  $CI = -0.04$  to  $0.92$ ;  $\rho^2 = 0.43$ ). Potassium values were lower in patients using vitamin D ( $\rho = -0.59$ ;  $p < 0.05$ ;  $CI = -0.70$  to  $-0.01$ ;  $\rho^2 = 0.35$ ) and in those using AAS ( $\rho = -0.59$ ;  $p < 0.05$ ;  $CI = -0.87$  to  $-0.01$ ;  $\rho^2 = 0.35$ ), with equal correlation coefficients ( $z = 0$ ). The therapeutic measures used were summarized in Table 4.

Table 4. Treatment frequencies.

	N	%
oral and intravenous hydration	17	100
dietary calcium and protein restriction	17	100
proscription of nonsteroidal antiinflammatory drugs	17	100
oral corticosteroid	16	94.1
diuretics	15	88.2
bisphosphonates	7	41.2
intramuscular corticosteroids	7	41.2
ketoconazole	6	35.3
immunosuppressants	4	23.5
immunobiologicals	3	17.6
colchicine	2	11.8
hemodialysis	0	0
plastic surgery	1	5.8

## Discussion

Between January 2022 and March 2023, 18 consecutive patients consulted with one of the authors and reported having intramuscular body PMMA implantation and subsequently developed hypercalcemia. One of the patients reported PMMA implantation in the buttocks for more than 10 years, with no data on the product or injector. On ultrasound examination, she presented an image of hyperechogenic particles in a snowstorm pattern with marked posterior acoustic shadowing with the same image in inguinal lymph nodes, confirming the presence of liquid silicon. The patient was excluded from the study and referred for treatment.

PMMA has been erroneously imputed as a risk factor for hypercalcemia in case reports of patients with previous chronic kidney disease, on nephrotoxic medications, in cases where there are no PMMA microspheres in the tissue, or in cases of massive silicon injections in the Positron Emission Tomography uptake area [6,9,10]. The literature does not separate PMMA cases from silicon and oil injections, so there is no specificity in understanding the unique repercussions of PMMA on calcium metabolism.



Patients with substances called biopolymers such as liquid silicon, synthol, mineral or vegetable oil, oily vitamins A, D and E for veterinary use or paraffin when included in the sample [9,10] lead to selection bias and nonexistent association between variables PMMA implantation and hypercalcemia.

According to the FDA (Food and Drug Administration) a systematic review (SR) and a randomized clinical trial (RCT) investigated hypercalcemia and granulomatous disease in patients with PMMA fillings [11]. SR [10] investigated cases with different implanted materials not providing specific analysis of which material led to hypercalcemia. RCT found no difference in complications between PMMA fillers and saline injections [12].

In United States, Canada [13], Europe and China [14] products containing 20% PMMA microspheres are expensive [15]. This cost combined with the need for larger volumes to perform the intramuscular implantation technique is reflected in the absence of international publications that deal exclusively with PMMA, even in case reports. On the other hand, the literature on the use of injectable silicon with the same aesthetic objectives is vast. Thus, without support from the international literature, the works published in Brazil assume greater importance in the study of intramuscular PMMA.

### Injectable Body Implants

Body injections of oils have been related to hypercalcemia since the 1960s [16]. The oils produce low inflammatory response, they divide into microdroplets moving through the intercellular space by the action of gravity. Macrophages phagocytize the droplets and transport them to the nearest lymph node chain, leading to recognition by lymphocytes in adaptive immunity. The microdroplets can access circulatory pathways producing oily micro and macroembolizations in skin, lungs, brain and kidneys [17], with tragic clinical consequences such as necrosis, embolism and death. The misdiagnosis between PMMA, a solid product that produces a localized attachment response, and injectable silicon, an oil that displaces and poses serious risks to the individual's health, leads to inadequate treatment and follow-up of each entity. Still, it promotes misinformation among the population, even stimulating the action of criminals who inject clandestine products based on the confusion between the materials. This situation is a public health problem in Brazil [18].

In the investigation of patients with hypercalcemia of extrarenal origin, it is common to perform (PET-Scan) in search of areas of increased tracer uptake. However, it does not provide the diagnosis of the material in the

tissue [19]. Areas implanted with oils or particulate products will present regardless of hypercalcemia, hypermetabolic response, and localized neoangiogenesis. Biopsy of the area of hypercaptation confirms the diagnosis of the material in the tissue. In the case of PMMA microspheres will be present because it is unabsorbable. The clear, birefringent, homogeneous, 40micra microspheres are surrounded by regular foreign body histiocytic reaction with no suppurative activity, no lymphocytic reaction, presenting collagen fibers deposited between the microspheres and in the capsule of the microsphere grouping [20]. The oils will present with numerous round or oval vacuoles, empty due to oil loss in histological processing, low foreign body histiocyte reaction, foamy histiocytes, lymphocytes present, and mild local fibrosis or necrosis [21].

Ultrasound [22] is considered the gold standard imaging exam for the recognition of aesthetic injectables, but MRI [23] also provides specific images of the implanted material, both noninvasive.

### PMMA

PMMA used in Brazil for aesthetic treatments is an injectable product from the collagen biostimulators class, which has inert and nonabsorbable 40micra microspheres suspended in a rapidly absorbed aqueous gel vehicle [24]. When the microspheres are injected into the host, they behave like microprostheses. Circulating monocytes invade the injected area and differentiate into macrophages that adhere to the microspheres, initiating the natural foreign body recognition immune response. Unable to phagocytize the microparticles, some macrophages fuse into foreign body giant cells and differentiate pluripotent cells into fibroblasts. The process evolves with neovascularization and isolation of the microspheres by the collagen envelope synthesized by the fibroblasts. The collagen undergoes remodeling, the number of foreign body giant cells and macrophages reduces within 6 months, and the reaction will remain stable for the following years [20,21].

The foreign body reaction is essential for the fixation of particulate materials in the tissue and subsequent neocollagenesis. This reaction is the same for aesthetic particulate absorbable collagen biostimulators such as calcium hydroxyapatite, poly-L-lactic acid and polycaprolactone [25]. Hyaluronic acid and all solid microparticulate materials may undergo late pathological hyperimmune adaptive reaction mediated by macrophages and/or lymphocytes, with numerous foreign body giant cells and intense local metabolic activity known as LIR (Late Inflammatory Response) [26].

The LIR, also called pathological granuloma or angry bumps, presents with pain, edema, heat, and erythema in all areas implanted with the same material. Macrophage immune memory and lymphocyte-mediated trigger mechanisms such as infection, trauma, surgery, drugs, adjuvants and type 4 hypersensitivity response have already been associated as triggers of LIR [27,28]. However, in PMMA body implants, the incidence is very rare: 80% of new cases (1/10,000 patient-years) will occur within 6 months to 2 years from implantation [29].

The body technique of PMMA differs from the technique of other biostimulators because it uses a greater number of particles and the muscle plane for injection. It would be logical to expect that a larger number of particles would cause greater macrophage recruitment, greater inflammatory activity, and greater extrarenal production of calcitriol. Yet two observations contradict this deduction: muscle tissue has less immunological activity when compared to subcutaneous tissue, and in over 20 years of using the intramuscular technique, hypercalcemia has not presented itself as a complication of the treatment [7,8].

Few patients, even with large volumes of PMMA, evolve with hypercalcemia. Thus, understanding that foreign body reaction is desired and equivalent among collagen biostimulators and that it will stabilize in up to 6 months [27] and that late inflammatory events on particulate products are very rare [26-29], it is assumed that hypercalcemia is one of the manifestations of the hyperimmune spectrum of LIR to any particulate product. Therefore, to understand whether PMMA implantation can lead to hypercalcemia, it is necessary to evaluate the immunological triggers of LIR together with the characteristics of the population undergoing medical aesthetic treatments and the specific technique of use of body PMMA.

### Hypercalcemia

The most accepted explanation for hypercalcemia related to particulate products is the activation of macrophages from the implant. When activated, they start to express the CYP27B1 gene that encodes the enzyme 25-hydroxyvitamin D 1 $\alpha$ -hydroxylase. This enzyme converts the prohormone calcidiol (25-hydroxyvitamin D) into calcitriol (1,25-dihydroxyvitamin D), the active form of vitamin D [30].

Calcitriol increases the reabsorption of calcium and phosphorus in the intestine and kidneys. In bone, the bone remodeling response is dose-dependent, at low levels the activity is osteogenic, at high levels the activity is osteoclastic, making more calcium available in the blood.

For some time the hypercalcemia determined by the extrarenal production of calcitriol in sarcoidosis has served as a basis for understanding the events related to hypercalcemia in LIR. Care must be taken in extrapolating the interpretation of hypercalcemia from sarcoidosis to what occurs in PMMA implantation. Sarcoidosis is a multisystem granulomatous disease of immunological and infectious nature linked to predispose genetic, ethnic, and environmental polymorphisms [31]. The PMMA implant presents its histology related to the innate foreign body reaction, which may be pathological in LIR, but is completely different from the epithelioid granuloma reacting to the adaptive T-lymphocyte immunity of sarcoidosis. The microspheres that stimulated localized neoangiogenesis and neocollagenesis form a fixed tissue, unable to move or migrate into circulatory pathways, and do not represent systemic disease. Thus, of local presentation, the PMMA implant does not conjugate the characteristics of sarcoidosis except for hypercalcemia itself.

Hypercalcemia is defined as an increase in serum total calcium above 10.5 mg/dL and ionic calcium above 5.1 mg/dL [32]. Increased calcium produces negative feedback on PTH secretion by the parathyroid glands and increased calcitonin secretion by the thyroid. Both lead to increased renal excretion of calcium. Blood levels up to 12 mg/dL do not require immediate treatment, levels between 12 and 14 mg/dL can be tolerated chronically but acutely require therapeutic measures. Levels higher than 14mg/dL need urgent medical intervention [32]. Renal damage may be transient or permanent depending on the severity and duration of hypercalcemia. Hypercalciuria and nephrolithiasis may, if the damage is sustained, lead to interstitial fibrosis and nephrocalcinosis [6] through calcium phosphate deposition and result in chronic renal failure.

### Incidence

The 17 cases presented in the study were diagnosed with hypercalcemia between 2017 and 2022 (Graph 1), representing 0.0002% of the 676,550 adult hospitalizations for renal failure in Brazil in the same period [33]. Although there is no data on the number of patients undergoing PMMA body implantation between 2017 and 2022, a publication on the subject [8] mentions that 36 physicians with an average of 12 years of experience using the product performed 12,285 body implants without reporting hypercalcemia among the complications. Thus, the cases of hypercalcemia investigated would represent 0.001% of patients who have had body treatments with PMMA, according to the 2018 publication.

## Chronic Diseases and COVID-19

The patients reported previous diseases that compromise renal function alone, such as renal and heart failure, renal cancer, and ulcerative rectocolitis. The younger ones had symptoms at diagnosis of hypercalcemia ( $\rho = -0.59$ ;  $p < 0.05$ ;  $IC = -0.84$  to  $-0.12$ ;  $\rho^2 = 0.25$ ), lower total calcium levels ( $\rho = -0.66$ ;  $p < 0.01$ ;  $IC = -0.84$  to  $-0.22$ ;  $\rho^2 = 0.44$ ) and had no previous chronic diseases ( $\rho = -0.61$ ;  $p < 0.05$ ;  $IC = -0.89$  to  $0.01$ ;  $\rho^2 = 0.37$ ). It is concluded that symptomatic patients seek care more quickly for the acute increase in calcium, which is not at the highest levels; and that patients with chronic diseases and more age may tolerate or confuse symptoms of hypercalcemia with those of their previous diseases, or have chronic increases in calcium, leading to higher serum calcium levels in the diagnosis of hypercalcemia.

It was observed that 53.3% (Table 1) of patients who had COVID-19 before had increased calcitriol in marginally positive correlation ( $\rho = 0.58$ ;  $p < 0.06$ ;  $CI: -0.05$  to  $0.87$ ;  $\rho^2 = 0.34$ ). Despite the marginal significance of the correlation, COVID-19 explains 34% of the increase in calcitriol, confirming its association with hypercalcemia.

Information on vaccination, silicon prosthesis implantation, and tanning habits were not described in the medical records preventing investigation of autoimmune events that can lead to renal failure in ASIA syndrome (Autoimmune Syndrome Induced by Adjuvants) and of increased peripheral vitamin D conversion [34].

## Implant

The mean volume of PMMA in the implants was 620.75mL (Table 2). In a cohort of 1681 patients with gluteal PMMA implantation, the mean volume injected in the first session in 24 patients with complications was  $408.42 \pm 196.20$ mL, while 1657 patients who received  $326.64 \pm 176.26$ mL had no complications [7]. This finding confirms the increase in implant volumes after 2018.

In patients who had larger implant volumes, PTH levels were lower ( $\rho = -0.55$ ;  $p < 0.05$ ;  $CI = -0.85$  to  $0.02$ ;  $\rho^2 = 0.30$ ). It is noteworthy that the maximum PTH value was 19.00pg/mL, demonstrating that suppression of this hormone is a characteristic of the entity regardless of the volume used. With suppressed PTH, the length of hospital stay was longer ( $\rho = -0.57$ ;  $p < 0.05$ ;  $CI = -0.85$  to  $-0.03$ ;  $\rho^2 = 0.32$ ), mean of 5.88 days (Table 3), suggesting chronification of the condition.

## Medications

Although COVID-19 infection is associated with kidney damage [35], the pandemic has led to more than 100% increase in vitamin D sales by 2020 [36]. With this, hypervitaminosis and intoxication from vitamin D use [37] have become important variables in the study of hypercalcemia. 87.5% of the patients in this study used a mean vitamin D dose of 14585.54 IUI/day in the month preceding hypercalcemia (Table 2). Vitamin D doses above 4000 IU/day for prolonged periods, due to its deposition in fat, result in cholecalciferol concentrations of up to 150ng/mL [38]. Thus, acute use of high doses or chronic use of lower doses of vitamin D are related to hypercalcemia.

Older patients showed lower cholecalciferol levels ( $\rho = -0.50$ ;  $p < 0.05$ ;  $CI = -0.81$  to  $0.03$ ;  $\rho^2 = 0.25$ ), which confirms the literature on reduced vitamin D in aging. However, the obtained mean vitamin D of 55.99ng/dL (Table 3) is higher than the recommended value of 30 ng/mL mentioned as ideal for bone benefit in endocrinology [38], evidencing the systematic use of vitamin D by the study patients.

Patients who used doses of 600,000 IU of intramuscular vitamin D in the month preceding hypercalcemia were those with the longest elapsed time between the last PMMA implant and diagnosis of hypercalcemia ( $\rho = 0.56$ ;  $p < 0.05$ ;  $CI = 0.02$  to  $0.85$ ;  $\rho^2 = 0.31$ ). The mean time elapsed was 11.8 months (Table 2). It is inferred that the use of high doses of vitamin D is a predisposing factor for the activation of macrophages in the stabilized implant and appearance of the LIR. Or the intramuscular route of high-dose vitamin D may be the sole reason for hypercalcemia, independent of the PMMA implant. The design of this study does not allow us to evaluate which of the possibilities confirms the finding.

Other relevant data presented in this study is that patients who seek medical aesthetic body treatments often use over-the-counter medications with the intention of improving their aesthetic complaints. About 5 to 15% of these patients have body dysmorphic disorder and use illicit drugs and AAS [39]. AAS can be used orally, intramuscularly, or in sustained-release subcutaneous implants. The concomitant use of AAS and vitamin D overload leads to hypercalcemia with nephrocalcinosis, nephrolithiasis, and prerenal injury in addition to interstitial glomerular damage by direct toxicity of AAS [40], regardless of PMMA implantation.

When hypercalcemia was diagnosed, 14 patients (82.3% of the sample) were using AAS (Table 2). The available data make it possible to state that patients using AAS also used a higher mean daily dose of vitamin D ( $\rho = 0.49$ ;  $p < 0.05$ ;  $CI = -0.03$  to  $0.80$ ;  $\rho^2 = 0.24$ ) and

requested implants in more body regions ( $p= 0.54$ ;  $p<0.05$ ; CI= 0.07 to 0.82;  $p2= 0.29$ ). This finding shows conformity with the literature on medication abuse and body dysmorphic disorder in patients with aesthetic complaints.

The longer length of hospitalization (Table 3) was associated with AAS use ( $p= 0.48$ ;  $p<0.05$ ; CI= -0.02 to 0.32;  $p2= 0.23$ ), number of implanted regions ( $p= 0.62$ ;  $p<0.01$ ; CI= 0.19 to 0.85;  $p2= 0.38$ ) and number of interventions performed with PMMA ( $p= 0.62$ ;  $p<0.01$ ; CI= 0.16 to 0.86;  $p2= 0.38$ ). Therefore, there is a need to investigate the use of AAS in addition to vitamin D among patients who are candidates for PMMA body implants.

**Laboratory Tests**

High calcitriol levels can lead to renal dysfunction with loss of control of hydroelectrolyte balance, dehydration and metabolic acidosis, with increased plasma exposure to potassium, justifying its serum increase ( $p= 0.66$ ;  $p<0.01$ ; CI= -0.04 to 0.92;  $p2= 0.43$ ). Bicarbonate levels in blood gas could substantiate this finding.

PTH may serve as a marker of chronic disease or of greater difficulty in controlling serum calcium levels (Table 3) since it was shown to be lower among patients who had more days hospitalized ( $p= -0.57$ ;  $p<0.05$ ; CI= -0.85 to -0.03;  $p2= 0.32$ ).

**Treatment**

The treatments instituted for the patients (Table 4) confirmed the updated literature on the management of hypercalcemia [32]. It is worth noting that at the end of this study, no patients had started renal replacement therapy and no deaths were recorded.

Patients who seek aesthetic body treatments have low compliance with the chronic use of corticosteroids. The adverse effects directly interfere with the patients' body images, and they abandon the treatment. If hypercalcemia recurs with the risk of permanent renal damage, plastic surgery should be considered. The surgical goal is the nonmutilating reduction of part of the implanted areas to reduce the tissue probably activated in the LIR, as indicated for one patient in the study (Table 4).

**Final Considerations**

This study indicated a correlation between the variables studied, but does not intend to evaluate the cause and effect between them. Studies with a larger sample size may clarify these relationships. Case-control studies may elucidate the frequency of hypercalcemia among patients with PMMA body implants, and histological studies may prove the histological and pathological granulomatous activation of LIR. Recommendations based on the results of this study and the updated literature are presented in Table 5.

Table 5. Technical recommendations, clinical investigation, laboratory tests, and imaging tests for the use of PMMA body implants.

RECOMMENDATIONS			
Technical procedures, clinical investigation, laboratory tests, and image exams for the use of *PMMA in body implants			
<ul style="list-style-type: none"> <li>✓ Recognize patients who have body implants of materials such as liquid silicon and hydrogel, avoid any injection into these areas, and refer them to specific therapy according to the material presented.</li> <li>✓ Support the injector physician in the use of safe techniques and volumes in treatments with PMMA.</li> <li>✓ Promptly recognize hypercalcemia from **LIR before permanent renal damage occurs.</li> <li>✓ Ensure the attending physician has qualified information about PMMA treatment in medical records, lab tests and imaging.</li> <li>✓ Create a database on the medical procedure of PMMA microspheres implantation for further studies.</li> </ul>			
DATA	LABORATORY	IMAGE	PROCEDURE
Medical history of preexisting diseases, descriptive data on previously performed body injectable procedures, COVID-19 and vaccination data, general and body prosthesis surgeries, tanning habits, medications and supplements in use, and complete physical examination	Complete blood count, platelets, fasting glucose, C-reactive protein, erythrocyte sedimentation rate, antinucleus factor, rheumatoid factor, total calcium, ionic calcium, albumin, calcitriol, cholecalciferol, parathormone, creatinine, urea, sodium, potassium, phosphorus, total estrogen and testosterone, common urine test. They must be performed before and at 3, 6, 12, and 24 months after the PMMA body implant	Doppler ultrasound or nuclear magnetic resonance imaging when investigating the presence of previous injectable implants, and before and up to 45 days after PMMA implantation for confirmation of treated areas and volume used	Detailed description of volume, devices, lot, validity, and brand of PMMA product used, techniques performed, number of interventions, and injected body areas. Use up to 300mL of PMMA implant per patient or, at the discretion of the injector physician, a larger volume, provided that laboratory follow-up is instituted frequently, or until new studies indicate safety in the use of larger volume.

\*PMMA= Polymethylmethacrylate; \*\*LIR= Late Inflammatory Response



## Conclusion

The results of this study indicate that hypercalcemia in patients with exclusive PMMA microsphere body implants is a rare manifestation of LIR and presents in of preexisting renal disease, COVID-19 infection, vitamin D use, and AAS use. Based on the data and available scientific literature, recommendations for patient investigation, implant volume limit, and patient follow-up after the procedure were made.

## Acknowledgement

Not applicable.

## Ethical Approval

This study was approved by the National Research Ethics Committee (CONEP) under number 5.158.889 and is in accordance with the 1975 Declaration of Helsinki, revised in 2013.

## Informed consent

Not applicable.

## Funding

Not applicable.

## Data sharing statement

No additional data are available.

## Conflict of interest

The authors declare no conflict of interest.

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