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Biochemical changes: alert for mineral and bone disorders in children and adolescents with chronic kidney disease undergoing hemodialysis

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Abstract

Introduction: Mineral and bone disorder is a clinical condition characterized by biochemical alterations, bone abnormalities, and vascular calcification.

Objectives: To analyze the biochemical alterations involved in mineral and bone disorder in children and adolescents with chronic kidney disease (CKD) undergoing hemodialysis at a University Hospital in Maranhão.

Materials and Methods: Analytical longitudinal study conducted at the Nephrology Unit of the University Hospital of the Federal University of Maranhão. Data collection was performed through sociodemographic questionnaires, electronic medical records, and the biochemical examination information system of 16 pediatric patients undergoing hemodialysis treatment. Vitamin D was evaluated at one time point, and calcium, phosphorus, and PTH at two time points. Data were organized in a database using Microsoft Office Excel 2013 spreadsheet. Statistical analysis was performed using Stata® version 14.0. The STATA® version 14 program was used, the Wilcoxon test was applied, and a significance level of 5% was adopted.

Results: There was gender equality, with an age range between 3 and 17 years old, and predominantly brown and black skin color (81.2%). Congenital malformation (18.8%), CKD secondary to heart disease (25%), and of unknown cause (43.8%) were the most frequent etiologies. The most commonly used medications were calcitriol, sevelamer, and calcium carbonate. Biochemical findings revealed adequate vitamin D levels, variation in serum calcium levels (normocalcemia and hypocalcemia), hyperphosphatemia, and high PTH. There was a statistical difference in calcium levels between September and December ($P=0.006$).

Conclusion: After data analysis, it was possible to identify adequate serum levels of vitamin D and variations in calcium levels when comparing the collected months, showing statistical significance. Phosphorus and PTH were above the ideal parameters most of the time, which can be challenging for dietary and medication treatment.

Keywords: Dialysis, Mineral and bone disorders in chronic kidney disease, Secondary hyperparathyroidism, Pediatrics

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Introduction

Chronic kidney disease (CKD) is a heterogeneous clinical disorder characterized by progressive and irreversible kidney injury present for more than 3 months, based on anatomical, functional, or temporal components. Thus, any individual with a glomerular filtration rate (GFR) <60 mL/min/1.73m^2 or GFR >60 mL/min/1.73 m^2 associated with some evidence of kidney injury for a period of 3 months or longer is considered to have CKD (1).

In the pediatric population, congenital diseases are determinants for the development of kidney disease, mainly anomalies in kidney structures, polycystic kidney disease, and malformation of the urinary tract. Obtaining accurate data regarding the epidemiology of chronic kidney disease in childhood appears to be underestimated, as early stages are asymptomatic, leading to the diagnosis of the disease when emergency care is needed (2).

When diagnosed in childhood, CKD brings impairments beyond blood filtration and metabolite clearance. Some processes become compromised, including erythrocyte synthesis, maintaining blood pH balance, excretion of metabolic products, and biochemical imbalance that can interfere with growth and development (3).

If this biochemical imbalance is not controlled with dietary, medicinal, and dialytic therapy, it can lead to possible abnormalities in mineral and bone metabolism,

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Implication for health policy/practice/research/ medical education

Knowledge of laboratory alterations is an important tool for managing the mineral bone disorder since biochemical modifications are the first alterations to manifest in this disorder.

resulting in elevated phosphorus and reduced serum calcium, increased fibroblast growth factor 23 (FGF-23) expression, and PTH, leading to secondary hyperparathyroidism, which can lead to mineral and bone disorders (MBD) (4). MBD is a clinical condition characterized by biochemical alterations (related to calcium, phosphorus, PTH, and vitamin D), bone abnormalities (related to remodeling, mineralization, and bone volume), and vascular calcification, with possible consequences such as cardiovascular disease and fractures(5).

The pathophysiological process of mineral and bone disorder begins with the loss of renal function. Diminished functionality causes serum phosphorus levels to rise, and in an attempt to eliminate excess phosphorus, there is an increase in the expression of the hormone FGF-23, a phosphaturic hormone that is ineffective in CKD patients due to lack of diuresis. Additionally, renal alterations decrease the activation of vitamin D by inhibiting the expression of the 1-alpha-hydroxylase enzyme, the main protagonist in the process of calcium absorption in the body. Therefore, there is a reduction in calcium absorption with consequent hypocalcemia, followed by acute stimulation of the parathyroid gland, which becomes chronic, causing hyperplasia and hypertrophy of this gland, with a reduction in vitamin D, calcium, and Klotho receptors. This pathophysiological cascade is related to calcifications in the vessels and other tissues that impair the individual's health and directly influence growth (4).

Given the above, the balance of serum levels of phosphorus, calcium, vitamin D, and PTH in the pediatric population with CKD has taken a prominent place due to the difficulty in adhering to dietary and medicinal treatment adjunctive to hemodialysis treatment(6). Additionally, it is worth noting the scarcity of studies in the pediatric age group among patients with CKD on hemodialysis.

Objectives

The objective of this research is to analyze the biochemical alterations involved in mineral and bone disorder in children and adolescents with CKD on hemodialysis at a university hospital in Maranhão within a four-month treatment interval.

Materials and Methods

Study design

This research was designed as a longitudinal analytical study. The research was conducted at the Nephrology Unit of the Presidente Dutra University Hospital of the Federal University of Maranhão (HUPD-UFMA) between September and December 2023. All children and adolescents on hemodialysis treated at the Nephrology Unit of HUPD during the period from September to December 2023 participated in the study. This center provides comprehensive services and is recognized as a reference in the treatment of the pediatric population in the state of Maranhão. The inclusion criteria were: patients aged 2 to 18 years, on hemodialysis therapy for at least three months who agreed to participate in the study. The exclusion criteria were: patients who underwent kidney transplantation and those who were discharged during the study.

Three instruments were conducted for data collection. Initially, a questionnaire was applied to collect sociodemographic data developed by the researchers, aimed at characterizing the participants regarding age, sex (male and female), skin color (white, mixed race, and black), level of education (early childhood education (0 to 5 years old), early years (1st to 5th grade), and final years (6^{th} to 9^{th} grade), family income, and receipt of benefits (yes or no). In the same questionnaire, other information was collected about the clinical profile to characterize the participants regarding comorbidities (CKD of undetermined and secondary to heart disease, congenital malformation, glomerulopathies, and rare causes), medications used (calcitriol, sevelamer, and calcium carbonate), and duration of hemodialysis in months. The second instrument used was the electronic medical record (DIALSIST) used in the Nephrology Unit of HUPD at UFMA to complement sociodemographic information, and the information system (LABORATORY) used for collecting biochemical tests. The cut-off points for biochemical tests are presented in Table 1.

The data were organized in a database in a Microsoft Office Excel 2013 spreadsheet. For statistical analysis, Stata® version 14.0 was used. After categorizing the variables of interest, the data were described using relative and absolute frequencies for qualitative variables. For quantitative variables, the results were presented as mean ± standard deviation and medians with Q1 and Q3. To compare calcium, phosphorus, and PTH levels between the months of September and December, the Wilcoxon test was applied, and a significance level of 5% was adopted.

Results

In the sample (n = 16), an equal participation between male (50.0%) and female (50.0%) was observed. The age range of the participants varied from 3 to 17 years, with a mean age of 11.6 ± 2.4 years. The most frequent self-declared skin color was mixed race (43.8%). Regarding educational level, approximately 62.5% were between the 6th and 9th grades (final years of elementary school). The average family income was R$1471.00 ± 503.00, ranging from R$650.00 to R$2640.00. The majority of participants

Table 1. Reference values for laboratory tests

Parameters	Reference values		
Calcium	Hypocalcemia	Normocalcemia	Hypercalcemia
1-5 years	<9.4 mg/dL	9.4-10.8 mg/dL	>10.2 mg/dL
6-12 years	<9.4 mg/dL	9.4-10.3 mg/dL	>10.3 mg/dL
13-20 years	<8.8 mg/dL	8.8-10.2 mg/dL	>10.2 mg/dL
Phosphor	Hypophosphatemia	Normophosphatemia	Hyperphosphatemia
1-5 years	<4.5 mg/dL	4.5-6.5 mg/dL	>6.5 mg/dL
6-12 years	<3.6 mg/dL	3.6-5.8 mg/dL	>5.8 mg/dL
13-20 years	<2.3 mg/dL	2.3-4.5 mg/dL	>4.5 mg/dL
Vitamin D	Deficient: <20 ng/mL	Insufficient: >20 <30 ng/mL	Adequate: >30 ng/mL
PTH	Low: <100 pg/mL	Normal: 100-200 pg/mL	High: >300 pg/mL

PTH: parathormone; Reference: National Kidney Foundation, KDOQI Clinical Practice Guideline for Nutrition in Children with CKD: 2008 Update.

(75.0%) received the continuous cash benefit . The average dialysis time for patients was 43 ± 43.9 months (Table 2).

Chronic kidney disease of undetermined cause, secondary to cardiopathy and congenital malformation (neurogenic bladder and crossed renal ectopia), are the most frequent causes of CKD among the participants. Other highlighted cases include rare causes (Caroli's disease) and glomerulopathies. Regarding medications, 50.0% of the participants were using calcitriol (vitamin D), 93.8% were on phosphorus chelator (sevelamer), and 18.6% were using calcium carbonate in their medication regimen (Table 3).

Table 2. Sociodemographic profile of pediatric patients (n=16), attended at the nephrology service of the University Hospital of the Federal University of Maranhão, São Luís/MA, 2023

Variables	Sociodemographic profile	
	Median [25-75%]	Mean ± SD
Age (years)	12.5 [3-17]	11.6 ± 2.4
Family income	1320 [650-2640]	1471 ± 503
Duration of hemodialysis in months	20 [9-82]	43 ±43.9
Gender	%	N
Female	50	8
Male	50	8
Skin color	%	N
White	18.8	3
Brown	43.7	7
Black	37.5	6
Level of education	%	N
Final years (6º-9º year)	62.5	10
Early years (1º-5º year)	18.7	3
Child education (0-5 year)	12.5	2
I didn't know how to answer	6,3	1
Receives continued benefit?	%	N
Yes	75	12
No	25	4

Regarding biochemical tests, it was observed that 62.5% of the participants had vitamin D within the appropriate values, with the average vitamin D level for patients being 32.12 ± 8.35 ng/mL and a median of 33.05 [18.2–47.4] ng/mL. As for the mineral calcium, there was only a decrease in serum calcium in December, remaining within the appropriate range during the initial three months (September, October, and November). Phosphorus levels were above the ideal value in all months. Between September and December, two measurements were taken for PTH. Elevated PTH (>300 pg/mL) was observed in 81.3% of participants in September and 62.5% in December, with an average of 1154 ± 1117 pg/mL and a median of 753 [109-3767] pg/mL in September, and an average of 622.6 ± 549 pg/mL and a median of 516 [82.89-2150] pg/mL in December. After comparing the biochemical data, it was possible to observe that during the study, only calcium showed significant changes ($P = 0.006$) between September and December. Phosphorus ($P = 0.148$) and

Table 3. Clinical profile of pediatric patients (n=16), attended at the nephrology service of the University Hospital of the Federal University of Maranhão, São Luís/MA, 2023

Variables	Clinical profile
Etiology	**% (N)**
CKD secondary to heart disease	25.0 (4)
Caroli's disease (rare cause)	6.2 (1)
CKD of undetermined cause	43.8 (7)
Glomerulopathies	6.2 (1)
Congenital malformation (neurogenic bladder and crossed renal ectopia)	18.8 (3)
What medications do they use related to mineral bone disorder ?	
Sevelamer	37.6 (6)
Sevelamer and calcitriol	43.8 (7)
Sevelamer, calcitriol and calcium carbonate	6.2 (1)
Sevelamer and calcium carbonate	6.2 (1)
Calcium carbonate	6.2 (1)

PTH ($P=0.156$) did not show significant changes within the collected time interval (Table 4).

Discussion

According to the sociodemographic profile of the present study, gender equality was observed among the participants, but according to Becherucci et al (7), the incidence and prevalence of CKD are higher in males due to a greater frequency of congenital anomalies of the urinary tract among them. The literature describes that skin color is another factor that specifically affects the epidemiology of CKD. Particularly in North America, the incidence of CKD is two to three times higher in African American children compared to Caucasian children, regardless of gender. In the present study, 43.7% of self-declared children were of mixed race and 37.5% were black (7).

The etiology of CKD in children and adolescents encompasses congenital, structural causes, and glomerulopathies. In the analysis of the present study, 43.8% of the participants were classified with etiology as CKD secondary to heart disease and congenital malformation (neurogenic bladder and crossed renal ectopia). In the studied population, 43.8% were classified as CKD of undetermined cause, something similar to the study developed by Becherucci et al (7), which reveals that epidemiological data may underestimate the real incidence and/or prevalence, considering that CKD is a clinically asymptomatic disease and that late presentation to health services hinders the investigation of etiology. In another study conducted by Zhong et al (8), which investigated the etiology of kidney disease in children, congenital malformation was reported in 48.3% of the participants.

According to Santos et al (9), CKD in pediatrics presents particularities that need to be highlighted. Children and adolescents, with progressive loss of renal parenchyma, undergo modifications in bone metabolism with possible modeling/remodeling that are more evident with the growing skeleton, manifesting as bone pain and deformities, ectopic calcifications, and low stature. These mentioned characteristics may be related to CKD-MBD, which is a condition characterized by a triad that includes biochemical abnormalities (related to abnormal levels of calcium, phosphorus, vitamin D, and PTH, FGF 23, and α-klotho), bone abnormalities (reduced mineralization),

Table 4. Biochemical tests of pediatric patients (n=16), treated at the nephrology service of the University Hospital of the Federal University of Maranhão, São Luís/MA, 2023

Variables	September	October	November	December
	% (N)	% (N)	% (N)	% (N)
Calcium				
Hypocalcemia	31.2 (5)	43.7 (7)	25.0 (4)	75.0 (12)
Normocalcemia	68.7 (11)	56.2 (9)	75.0 (12)	25.0 (4)
Median [Q1-Q3]	9.3 [8.4-9.8]	9.3 [7.2-9.9]	9.3 [6.5-10.5]	8.8 [7.1-9.8]
Mean ± SD, mg/dL	9.3 ±0.46	9.0±0.66	9.1±0.85	8.7±0.70
P value*		0.006		
Phosphorus				
Normophosphatemia	36.4 (4)	33.4 (3)	12.5 (1)	44.4 (4)
Hyperphosphatemia	63.6 (7)	66.6 (6)	87.5 (7)	55.6 (5)
Median [Q1-Q3]	6.3 [3.3-8.7]	5.85 [4.3-9.0]	6.3 [4.6-8.4]	5.6 [3.9-7.4]
Mean ± SD, mg/dL	6.2±1.51	6.2±1.30	6.2±1.26	5.65±1.2
P value*		0.148		
Vitamin D				
Deficient		6.3 (1)		
Insufficient		31.2 (5)		
Adequate		62.5 (10)		
Median [Q1-Q3]		33[18.2-47.4]		
Mean ± SD, mg/dL		32.1±8.35		
Parathormone				
Low PTH	18.7 (3)			25.0 (4)
Normal PTH	0			12.5 (2)
High PTH	81.3 (13)			62.5 (10)
Median [Q1-Q3]	753 [109-3767]			516 [82.8-2150]
Mean ± SD, mg/dL	1154±1117			622±549.5
P value*		0.156		

*Comparison between the means of biochemical exams in the months of September and December using the Wilcoxon test.

and extra-skeletal calcification (10).

From the analysis of this study, it was observed that vitamin D levels were within adequate values in a large part of the participants (62.5%). A suggested hypothesis refers to serum correction with the use of calcitriol in approximately 49.9% of the patients, considering that KDIGO (11) recommends that calcitriol or vitamin D analogs may be considered to maintain serum levels within the appropriate normal range for the child or adolescent's age.

In humans, vitamin D is primarily produced endogenously through skin exposure to sunlight, while a small percentage is absorbed in the gastrointestinal tract from some foods, such as fish, egg yolk, and mushrooms. Reduced kidney function results in no activation of vitamin D due to low synthesis of 1-alpha-hydroxylase, decreasing its serum levels (12).

A unicentric, randomized, double-blind, placebo-controlled study developed by Etemadi et al (13) evaluated the supplementation of 50 000 IU of cholecalciferol in 86 adults for 12 weeks. The results were favorable to the use, as there was an increase in α-klotho levels. Klotho is a protein found in some tissues participating in tissue signaling of FGF-23 and the enzyme 1-alpha-hydroxylase, modulating the conversion of calcidiol (25D) into calcitriol (1,25D).

Regarding calcium, serum values were within the normal range in the first three months in most participants; however, it was observed that 75.0% of patients presented hypocalcemia in the last month of collection. These findings reflect the significant statistical difference found between the months of September and December ($P=0.006$). These changes may be attributed to some aspects. The low family income observed among the research participants may be associated with this variation in calcium, since the patients do not receive vitamin D and calcium carbonate, as they do not fit into specialized components, having to buy these medications. Physiopathological aspects may have contributed, since vitamin D may have varied in the following months, which may have influenced the intestinal absorption of calcium; however, it was not possible to analyze the subsequent exams because the protocols establish that they must be performed quarterly. Another aspect to consider is the iatrogenic effect of the calcium chelator, used by almost the entire sample.

Diet should be considered as a method to correct hypocalcemia, but other aspects need to be considered, such as adequate dialysis and the judicious use of medication therapy. According to the clinical protocol and therapeutic guidelines for bone mineral disorder(14), intake of calcium-rich foods should be encouraged, but the daily amount needs to be accounted for, including dialysis bath (dialysate) and medications used. According to the dietary reference intakes (DRIs), recommended dietary allowance (RDA) for calcium varies between 700 and 1,300 mg/day, depending on age group, similar to information provided in renal disease guidelines.

Hypocalcemia is a classic characteristic of bone mineral disorder in chronic kidney disease (CKD-MBD), as, physiopathologically, there is a reduction in 1-alpha-hydroxylase, the enzyme responsible for activating 25(OH) into 1,25(OH). This reduced activation results in little movement of calcitriol to intestinal cells, reducing gastrointestinal calcium uptake. The absorption of this mineral is not entirely affected because there are two absorption pathways: transcellular, which occurs through intestinal cells, and paracellular, which occurs between intestinal cells. Transcellular calcium transport to the enterocyte and its exit is dependent on the action of 1,25-dihydroxyvitamin D3 (15).

In the present analysis, it was observed that between September and December, there was a predominance of hyperphosphatemia compared to normophosphatemia, without significant statistical difference ($P=0.148$). The literature describes that methods for preventing and/or correcting hyperphosphatemia essentially include the use of medication therapy, dialysis regimens, and modification of dietary habits.

In this study, about 93.6% of the sample used a phosphate binder without calcium in the chemical composition (sevelamer); however, medication therapy alone may not have been sufficient to adjust serum phosphorus levels, requiring guidance from a nutritionist on certain strategies and food sources. Phannajit et al (16) showed that in stage 5 CKD patients on dialysis with hyperphosphatemia, the use of sevelamer compared to calcium-based binders (calcium carbonate) was a protective factor against vascular calcification in dialysis patients. Regarding nutritional treatment, KDIGO (11) recommends limiting phosphate intake in the diet, associated or not with other treatments. According to DRIs, through RDA, the recommendation for phosphorus varies between 460 to 1,250 mg/day, depending on age group, similar to information described in the Brazilian Guidelines for treatment and evaluation of CKD-MBDs.

In the last years, phosphate overload has become more relevant in CKD due to its association with extraosseous calcification and mortality, primarily cardiovascular(17). Phosphate is absorbed throughout the small intestine. In the first portion (duodenum), absorption occurs via active transport. In this case, phosphate transport occurs through sodium ion cotransport. The ratio of sodium-dependent phosphate transport is increased by 1,25-dihydroxyvitamin D3. Phosphate transport in the jejunum and ileum occurs via passive mechanisms (15).

This mineral is found in a wide variety of foods in organic and inorganic forms. Organic phosphate is naturally found in foods that are protein sources, whether of plant or animal origin. However, the absorption of phosphate from animal-derived foods is more efficient in the gastrointestinal tract (GIT) than that from plant-derived foods, being around 70% and 40%, respectively

(18). Inorganic phosphate, which can be absorbed by the GIT up to 100%, is found in chemical additives used in processed and ultra-processed foods (19).

In the present analysis, no significance was found within the collected time interval ($P=0.156$). There was a predominance of high PTH, accounting for about 81% in September and 62.5% in December. According to the 2020 census of the Brazilian Society of Nephrology, approximately 93% are on hemodialysis. Of these, 18% had PTH levels above 600 pg/mL, similar to the results obtained in this study. Although its value for predicting the diagnosis of hyperparathyroidism secondary to CKD is controversial, PTH levels above 300 pg/mL have been adopted by the latest guidelines for patients with CKD on renal replacement therapy (11).

In patients with CKD-MBD, hypocalcemia and hyperphosphatemia lead to an acute increase in PTH secretion by the parathyroid glands, which, in turn, leads to increased release of calcium from the bones. Prolonged parathyroid stimulation can lead to proliferation of its cells, resulting in diffuse hyperplasia with progression to nodular hyperplasia (20).

For the treatment of hyperparathyroidism secondary to CKD in pediatric patients, KDIGO (11) suggests the use of calcitriol or vitamin D analogs to maintain serum calcium levels within the appropriate normal range for age. In this study, about 49.9% of patients used calcitriol as a tool to maintain calcium levels and control PTH. According to a double-blind, randomized study, including 98 patients (49 in each group), conducted with children ≥9 years old with stage 3-5 CKD on dialysis, where one group received supplementation with 1000 IU and the other group 4000 IU of vitamin D3. At 6 months, plasma levels of 25(OH) D were ≥30 ng/mL in 33.3% and 74.4% in the 1000 IU and 4000 IU doses, respectively. It was concluded that in children with CKD, it is unlikely that 1000 IU of vitamin D3 daily will achieve or maintain plasma 25(OH) sufficiency. In children with stage 3-5 CKD, a daily dose of 4000 IU of vitamin D3 was effective in achieving or maintaining vitamin D sufficiency(21). However, supplementation with higher doses of vitamin D may be more effective.

Similar to KDIGO (11), the clinical protocol and therapeutic guidelines (16) suggest the use of calcitriol in children with stage 2 to 5 CKD on dialysis with serum PTH levels above the upper limit of normal. However, some studies conducted in other countries analyze the use of other medications involved in PTH regulation. According to Al-Ahmad et al (22), cinacalcet is used by approximately 79% of pediatric nephrologists practicing in the Kingdom of Saudi Arabia and the Gulf Cooperation Council countries in children older than 5 years and 42% in children aged 5 years or younger aiming at PTH control in CKD.

Conclusion

The data analysis revealed that, contrary to the expectations based on the literature, serum vitamin D levels remained appropriate in a large portion of the participants, suggesting possible effective interventions with the use of vitamin D supplementation. Calcium was the only mineral that showed a significant reduction after data analysis.

PTH and serum phosphorus did not show significant changes but remained elevated during the collection period. These serum values are challenging in treatment because they can directly contribute to the risk of vascular calcification, fractures, and growth retardation.

Therefore, knowledge of laboratory alterations is an important tool for managing the mineral bone disorder since biochemical modifications are the first alterations to manifest in this disorder.

Limitations and positive points of the article

The study presented some limitations due to the small number of participants and the duration of data collection. However, the nephrology unit at HUPD-UFMA, in the hemodialysis modality, stands as the only specialized center in pediatric hemodialysis, and all children and adolescents treated by the State of Maranhão at HUPD-UFMA during the study period participated in the study.

Author's contribution

Conceptualization: Bruno Ramos da Silva and Nayra Anielly Cabral Cantanhede.

Methodology: Bruno Ramos da Silva and Nayra Anielly Cabral Cantanhede.

Data curation: Bruno Ramos da Silva, Beatriz Castro Sousa, Indyara Dolores Santos Dias, Juliana Moreira da Silva Cruvel, Vanessa Farias Louseiro.

Formal analysis: Bruno Ramos da Silva and Nayra Anielly Cabral Cantanhede.

Writing-original draft: Bruno Ramos da Silva and Nayra Anielly Cabral Cantanhede.

Writing-review and editing: Bruno Ramos da Silva and Nayra Anielly Cabral Cantanhede.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and approved by the Research Ethics Committee (CEP) of HUUFMA via the Plataforma Brasil under protocol number 6.247.861. Accordingly, written informed consent taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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