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ORIGINAL PAPER

The use of quantitative ultrasound in a tertiary-level children hospital: role in the follow-up of chronically ill patients

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Abstract

Purpose To evaluate the use of QUS for the bone status assessment in children cared because of a chronic disease such as: inherited metabolic disorder, kidney disease and endocrine defect and considered by the attending physician as at specific risk.

Methods QUS outputs were calculated for each disorder and compared to: sex, age, Tanner stage, *Z*-score for height, weight and BMI (body mass index).

Results One-hundred-sixty-eight subjects aged between 3.5 and 18 years met the inclusion criteria. The overall bone quality indexes were under the normal range in all the groups considered. Impairment of bone quality parameters was more evident in the group of patients with inherited metabolic disorders, in which 65% of patients in charge were studied by QUS. Older age and sexual development were associated with less pronounced bone quality impairment, as measured by QUS, in the vast majority of conditions. Overall, the diseases for which the prediction of outcome was the strongest were: hyperphenylalaninemia, nephrotic syndrome and insulin dependent diabetes mellitus.

Conclusions QUS is capable to provide information on skeletal status in children. Initial evaluation by QUS may allow defining patients with chronic disorders who deserve further, more invasive diagnostic studies. Inherited metabolic disorders warrant specific attention and strict monitoring for their potential effect on bone.

Keywords Bone health · Growth · Pediatric chronic conditions · Puberty · Quantitative ultrasound

Abbreviations

BQI	Bone quality index
BUA	Broadband ultrasound attenuation
EC	Endocrine disease
IMD	Inherited metabolic disorders
QUS	Quantitative ultrasound
KD	Kidney disease
SOS	Speed of sound

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Introduction

Bone and mineral disorders not only cause a significant morbidity in the general population [1], but they also significantly affect the quality of life of people affected [2]. This is usually even more pronounced in subjects bearing skeletal abnormalities with early onset [3]. Children bone health results from many anthropological and physiological factors. Their potential impact on adulthood, have attracted many researchers [4, 5].

Furthermore, in children with chronic disorders, either inherited or early acquired, loss of bone health may have a much higher impact, not only on the quality of life, but sometimes even on the prognosis [6]. This lead to several studies addressing this issue in chronic kidney diseases [7],

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endocrine [8] and, more recently, inherited metabolic disorders [9].

The choice of the optimal method, either imaging or biochemical tests (although these last remain, so far, not-conclusive) is still debated. Dual X-ray absorptiometry (DXA), and Quantitative Computed Tomography (QCT) are the two current reference standards of BMD measurement [10]. However, these methods are costly, clinically based, radiation-associated, and require highly trained operators, thus limiting their friendly use for screening [11]. An additional method for assessing bone mineral content and thus the risk for osteoporosis, is quantitative ultrasound (QUS). In QUS, the attenuation and speed of propagation of a transmitted ultrasound wave describes the physical properties of the examined bone [12, 13]. Advantages of QUS are portability, no need for ionizing radiation, lower cost and higher time effectiveness. Its clinical applications for diagnosis of osteoporosis, fracture risk assessment, treatment initiation, monitoring of treatment and quality control has recently been addressed by the International Society of Clinical Densitometry (ISCD), 2007 Pediatric Position Development Conference [14]. In particular, calcaneal QUS is considered the standard parameter for QUS study of bone health status. The QUS technique in children and adolescents has been used to assess osteopenia and fracture rate in subjects with bone and mineral disorders [15], and steroid-sensitive nephrotic syndrome [16], to monitor uremic osteodistrophy and secondary hyperparathyroidism [17], and in patients with subclinical hypothyroidism [18].

There are a few studies on the simultaneous evaluation of QUS technique in the follow up of different chronic and rare pediatric diseases.

The aim of this study was to assess by QUS the bone status of children and adolescents with selected chronic and rare disorders and to identify those patients who deserved a tailored follow-up.

Methods

Study design

This was a retrospective cohort study, conducted at a single children hospital in the South of Italy. Between December 2016 and December 2019, QUS was made available in the hospital and proposed to the physician in charge for children with kidney disease (KD), inherited metabolic disorders (IMD), or endocrine disorders (ED). The attending physician was responsible for selecting patients considered at possible risk for bone alteration because of the underlying disorder. Patients were eligible for the study, provided they were aged ≤ 18 years, were clinically stable, and informed consent was provided by the patient (when older than 16 years), and by the parents or legal guardian. The study was approved by local institutional review board.

Methods

All patients were assessed for height and weight (in minimal clothing); height-for-age *z*-scores, weight-for-age *z*-scores, and body mass index-for-age *z*-scores (BMI *Z*-score) were calculated using World Health Organization standards [19].

Well-nourished patients were defined as BMI *Z*-score between 1 and − 1, obesity as BMI *Z*-score > 1.64 and short stature as height *Z*-score lower than − 2, using the WHO charts. Tanner stage was determined by physical examination and patients were categorized in five groups: Tanner 1–5 [20].

The QUS (SONOST 3000; OsteoSys Co., Ltd.) measurement score of the calcaneus region was used to calculate a bone mineral density (BMD) status according to the ISDC Pediatric Official Position (*Z*-score of − 2.0 or lower was defined as below the expected range for age, and a *Z*-score above − 2.0 was defined as within the expected range for age) [21]. The machine was calibrated daily according to the manufacturer's instructions; it provides curves reflecting the structural and mechanical properties of trabecular calcanear bone, no other bones can be examined with this machine. The outputs included the bone quality index (BQI), the broadband ultrasound attenuation (BUA, measured in dB/MHz), the speed of sound (SOS, measured in m/s) (Online Fig. 2, Video 1). BUA reflects bone density and structure by reduction analysis of ultrasound pulse intensity through the bone; SOS expresses speed of ultrasound wave through the bone and reflects bone mineral density. SOS is related to temperature, while BUA is inversely related to temperature. These correlation coefficients ($\alpha\,\beta$) are combined with BUA and SOS to obtain the BQI ($BQI = \alpha \times SOS + \beta \times BUA$) [22].

All QUS tests were performed by the same expert clinician (co-author A.T.).

Statistical analysis

Results were expressed as mean and standard deviation (SD) or median and range according to variable distribution; qualitative variables were expressed as percentages. QUS parameters were calculated for each chronic disorder and compared to growth and pubertal parameters: gender, age, Tanner stage, *Z*-score for height, weight and BMI.

All eligible patients had at least one QUS measurement, while some had a second or even a third measurement over the observation period. In this case, the first measurement was considered and included in the study.

The Kolmogorov–Smirnov test was utilized to assess the normality of parameter distribution to detect an association

between QUS outputs and patients' parameters, Pearson's correlation coefficient (Pearson's *r*) was used for parameters with normal distribution. Otherwise, for parameters with skewed distribution Spearman's correlation coefficient (Spearman's *r*) was evaluated. All data were analyzed by SPSS22.0 software (SPSS Inc., Chicago, IL, USA) and $p < 0.05$ was considered as statistically significant.

Results

In our intention, the study population comprised all patients followed at our children hospital for chronic and rare diseases, such as: inherited metabolic disorder (IMD); kidney disease (KD); endocrine disease (ED). They underwent QUS for screening of bone status. Figure 1 shows the flow-chart for enrollment of patients.

Over the 3-year observation time, of the 670 patients with chronic diseases, 271 (40%) underwent at least one QUS assessment; 168 were eligible and were included. Seventy-six patients had an inherited metabolic disorder (IMD), 72 a kidney disease (KD), and 20 an endocrine disease (ED) (Fig. 1).

The median age was 10.7 years (range, 3.5–18 years), 55% were female and 39% were prepubertal. Overall, the *Z*-score for weight, height and BMI was within the normal range for all patients, with a non-significant trend to lower height, weight and BMI SDS values for the kidney disease group, and higher weight SDS for the endocrine defect group (Table 1).

Two thirds of the patients (65%) had an inherited metabolic disorder, and 44 had Phenylketonuria (Table 2).

The mean BQI *Z*-score felt close to the lower limit of the expected range for age for the three groups analyzed, without statistically significant differences among groups (data not shown). The lowest mean BQI *Z*-score levels were found in the inherited metabolic disorder group (-1.7 ± 0.8), although no statistically significant differences

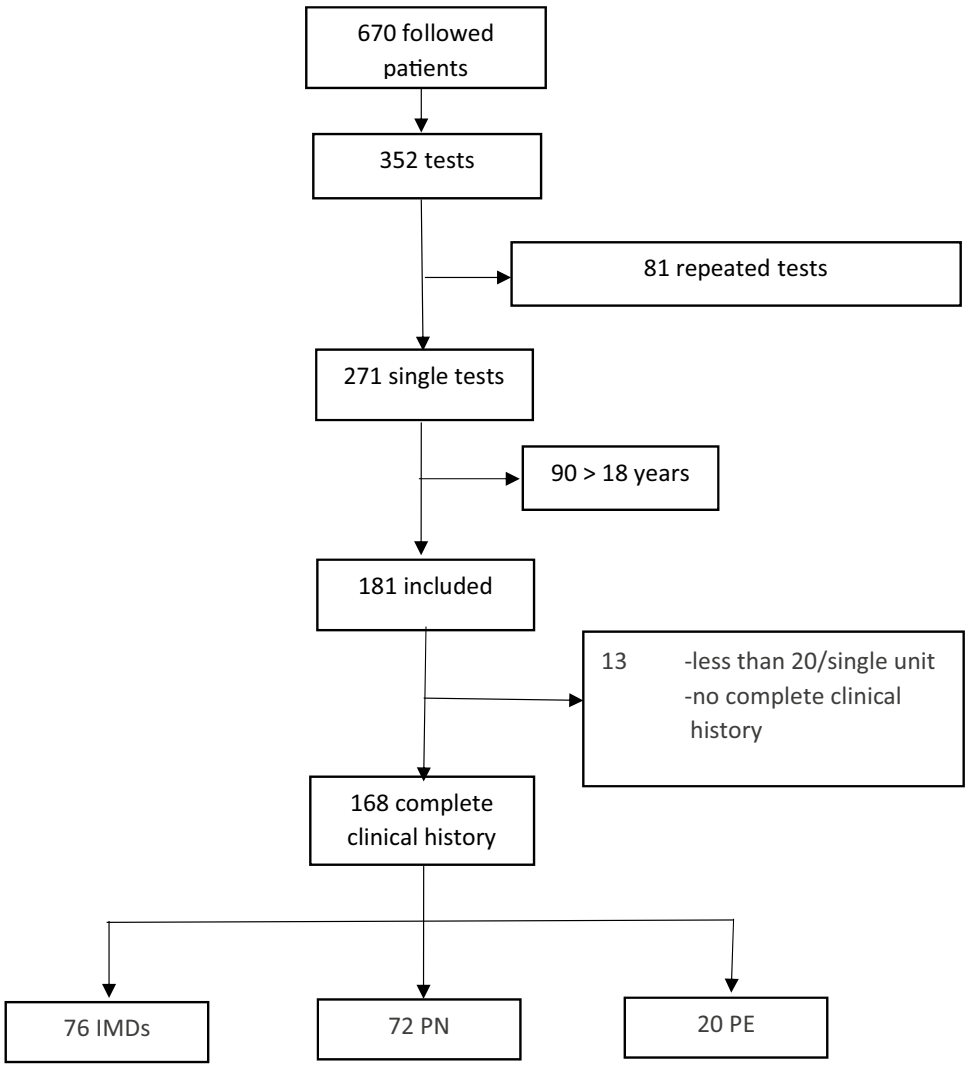

Fig. 1 Flow-chart of patients enrollment

Table 1 Characteristics of patients belonging to different groups of conditions

	Inherited metabolic disorders	Kidney disease	Endocrine disorders	All patients
Number of patients	76	72	20	168
Median age in years (range)	10.7 (3.5–16.8)	10.6 (3.7–16.9)	10.8 (6–18)	10.7 (3.5–18)
Gender F/M	40/36	38/34	15/5	93/75
Geographic origin	Caucasian	Caucasian	Caucasian	
Pubertal stage*	*n*	*n*	*n*	*n*
1	26	32	8	66
2	17	17	4	38
3	12	10	3	25
4	9	5	4	18
5	12	8	1	21
Height *Z*-score	−0.4 ± 1.2	−0.9 ± 1.6	−0.4 ± 1.6	−0.5 ± 1.5
Weight *Z*-score	−0.17 ± 1	−0.5 ± 1.5	0.7 ± 1.7	−0.2 ± 1.4
BMI *Z*-score	0 ± 1	−0.7 ± 4	1.1 ± 1.5	0.4 ± 2.9

*By Tanner

Table 2 Study population by disease groups and main results of QUS study

	Proportion of patients investigated*	SOS (mean ± SD)	BUA (mean ± SD)	BQI (mean ± SD)	BQI *Z*-score (mean ± SD)
Inherited metabolic disorders					
Organic acidemia	4/10 (40%)	1501.6 ± 14.2	64.9 ± 17.3	62.8 ± 17	−1.8 ± 1.1
Urea cycle disorders	6/16 (37%)	1510.1 ± 16.2	60.6 ± 1	67.1 ± 1	−1.6 ± 0.9
Hereditary carbohydrates defects	9/14 (64%)	1446.1 ± 15.5	66.6 ± 13.3	59.5 ± 14.7	−2 ± 0.8
Hyperphenilalaninemia	6/22 (27%)	1507.3 ± 15.4	77.9 ± 15.1	72.2 ± 16	−1.1 ± 0.7
Osteogenesis imperfecta	7/7 (100%)	1481.8 ± 13.5	48.1 ± 11.9	44.7 ± 15.4	−2.6 ± 0.9
Phenylketonuria	44/47 (93%)	1504.2 ± 17.6	67.8 ± 15.5	65.8 ± 17.3	−1.5 ± 0.9
Total	76/116 (65%)	1491.8 ± 15.4	63.2 ± 12.3	61 ± 13.5	−1.7 ± 0.8
Kidney diseases					
Chronic glomerulopathy	6/82 (7%)	1504.24 ± 11.7	69.97 ± 13.2	66.74 ± 13.3	−1.49 ± 0.5
Idiopathic hypercalciuria	14/78 (18%)	1491.02 ± 13.2	55.18 ± 22.5	51.16 ± 13.7	−2.18 ± 0.7
Chronic renal insufficiency	12/61 (20%)	1502.83 ± 15.8	64 ± 10.8	63.28 ± 13.9	−1.9 ± 1
Hereditary rickets	6/7 (86%)	1511.19 ± 9	74.29 ± 14.2	73.52 ± 10.4	−1.02 ± 1
Nephrotic syndrome	15/69 (22%)	1495.97 ± 16.5	55.74 ± 11.8	56.22 ± 13.1	−1.96 ± 0.5
Inherited tubulopathies	19/31 (61%)	1495.90 ± 13.4	56.76 ± 17.3	55.32 ± 14.4	−1.94 ± 0.6
Total	72/328 (22%)	1500.19 ± 7.3	62.65 ± 8.1	61.04 ± 8.3	−1.63 ± 0.5
Endocrine disorders					
Insulin dependent diabetes mellitus	5/42 (12%)	1503.77 ± 20.2	69.49 ± 18.6	66.21 ± 21.6	−1.57 ± 0.9
Obesity (	8/167 (5%)	1507.03 ± 23.5	61.15 ± 17.3	65.13 ± 16.5	−1.27 ± 1.1
Turner syndrome	7/17 (41%)	1501.06 ± 8.7	65.74 ± 13.9	62.71 ± 9.6	−2.01 ± 0.8
Total	20/226 (9%)	1503.95 ± 2.9	65.46 ± 4.1	64.68 ± 1.8	−1.61 ± 0.4

*Number of patients investigated/total number of patients in charge with that diagnosis

were found comparing the BQI *Z*-score of the three groups: IMD vs KD BQI *Z*-score *p*-value: 0.30, IMD vs ED BQI *Z*-score *p*-value: 0.33, KD vs ED BQI *Z*-score *p*-value: 0.47. For four subgroups, QUS parameters felt under or were equal to the lower limit of the expected range for age (BQI *Z*-score < − 2): patients with hereditary carbohydrate defects (BQI *Z*-score: − 2 ± 0.85) had a particular reduction of SOS values; patients affected by osteogenesis imperfecta (BQI *Z*-score − 2.6 ± 0.9) with a particular reduction of BUA parameters; patients with idiopathic hypercalciuria (BQI *Z*-score: − 2.18 ± 0.71) had a reduction of both SOS and BUA; patients with Turner Syndrome (BQI *Z*-score

− 2.01 ± 0.83) had a reduction particularly of SOS values (Table 2).

Correlations between QUS parameters, growth and pubertal variables

Linear regression analysis with growth and pubertal parameters revealed a strong correlation of hyperphenylalaninemia (*r*: 0.88/0.88, *p*: 0.01/0.02) and Phenylketonuria (PKU) (*r*: 0.52/0.54, *p*: 0.0001/0.0001) with age and pubertal stage, for all the three QUS outputs. For patients with carbohydrate disorders, QUS parameters correlated strongly with height (Table 3). Weaker or no correlation was found with height, weight and BMI *Z*-score for other IMDs.

In the subgroup of kidney diseases, in most of the conditions bone status correlated with age and sexual development for all QUS outputs, with particular strength for age and inherited renal tubulopathies (*r*: 0.72 *p*: 0.0001) and sexual development and nephrotic syndrome (*r*: 0.95 *p*: 0.0001).

For hereditary rickets, among whom two patients were males affected by X-linked hereditary rickets, gender was the most powerful predictive factor for QUS parameters (*r*: 0.7 *p*: 0.0001). Weight and height had little correlation with changes in bone quality with the exception of nephrotic syndrome, particularly for BQI and BQI *Z*-score.

Also for endocrine disorders, age and pubertal stage showed the strongest correlation with outputs, this finding was particularly true for IDDM (*r*: 0.9/0.90 *p*: 0.03/0.0001) and Turner syndrome (*r*: 0.78/0.75 *p*: 0.0001/0.0001).

Discussion

Recently, the approach to the diagnosis and monitoring of osteoporosis in children has moved away from a BMD-centric focus to a more functional approach [23], including an evaluation of bone quality indexes related to child age, pubertal development, diet, and physical activity [24]. Indeed, ultrasonography has become, in the last years an easy-to-use and effective mean to speed-up diagnosis in children in many specialist contexts [25–27].

In this study, we reviewed the use of QUS in children with selected groups of chronic disorders in our tertiary-level Children Hospital. Studies in which different pediatric chronic conditions are simultaneously assessed and compared for bone status parameters, are scarce.

The first result is that all three subgroups of patients showed evidence of BQI *Z*-score at the lower limit of the expected range for age. This is consistent with the inclusion criteria, since only patients with suspected bone health impairment were included in the study. Although this difference did not reach statistical significance, the group of patients with inherited metabolic disorder had a higher level of impairment of bone quality parameters. In this group, the compliance for QUS study was of two thirds. This finding is in keeping with a recent cross-sectional, observational study of the spectrum of microarchitectural bone disease in inborn errors of metabolism: report by Sidhu et al. [9] showing impaired cortical and trabecular bone in comparison to a reference population.

Table 3 Correlations of QUS parameters with growth and pubertal variables adjusted for age

	Age	Gender	Tanner stage	Height SDS	Weight SDS	BMI SDS
SOS	**HPE**/PKU		**HPE**/PKU	HPE/HCD	HPE	
	CG/**IRT**	**HR**	CG/IRT			
	IDDM/obesity/TS	obesity	**IDDM**/obesity/TS			
BUA	**HPE/PKU**		**HPE/PKU**	UCDs	HCD	HCD
	CG/IH/ **HR**	**HR /NS**	CG	**HR**		
			IDDM		**TS**	**TS**
BQI	**HPE**		UCD/**HPE**/PKU/OI	**HCD**/HPE/OI	OI	
	CG/IH/NS/HR/**IRT**	HR	CG/IH/**NS**/CKD/IRT	**HR**		**NS**
		IDDM, obesity	**IDDM**	Obesity, TS		
BQI *Z*-score	**HPE**, OI	OI	**HPE**, OI	**HCD**, HPE, OI	OI	
		CKD, **HR**	**NS**		NS	NS
	IDDM, obesity, **TS**	IDDM, obesity	IDDM, obesity, **TS**			

Bold $0.9 < r < 0.7$; not in bold $0.69 < r < 0.5$

HPE hyperphenylalaninemia, *PKU* phenylketonuria, *HCD* hereditary carbohydrate disorders, *UCDs* urea cycle disorders, *OI* osteogenesis imperfecta, *IRT* inherited renal tubulopathy, *IH* idiopathic hypercalciuria, *NS* nephrotic syndrome, *HR* hereditary rickets, *CG* chronic glomerulopathy, *CKD* chronic kidney disease, *TS* turner syndrome, *IDDM* insulin dependent diabetes mellitus

The most frequently predictive parameters of bone quality were age and sexual development, with the increase of which almost all the parameters of QUS improved.

In particular, our patients with Phenylalanine metabolism impairment, 44 with PKU and 6 with hyperphenylalaninemia, had low bone mineral mass, by BQI *Z*-score close to − 2, in keeping with previous studies [28–30]. This defect is shared by patients with hyperphenylalaninemia, who were protected by a free diet regimen. Yet, interestingly we observed a strongest correlation of QUS parameters with age and pubertal development, suggesting an improvement of bone status with increasing age and after puberty, which is not yet clearly reported in patients with this metabolic disorder, at the best of our knowledge.

Patients with Hereditary carbohydrates defects, especially galactosemia, in our series showed low BQI *Z*-score (− 2 ± 0.8). This finding is already reported in a meta-analysis based on data from children and adults by van Erven et al. [31], where, in spite of a less severe reported mean BMD-*Z* score, up to 25% of galactosemia patients were considered to be at risk of a BMD *Z* score < − 2. Osteogenesis imperfecta, an hereditary connective tissue disorder, showed the lowest BQI *Z*-score levels (− 2.6 ± 0.9), confirming to be a very severe bone disease with a particular propensity to bone fragility, as already reported in previous studies [32].

Among patients with endocrine disorders, those with Turner syndrome showed the lowest QUS parameters; this is fully expected since osteoporosis is a known feature of these patients, due to intrinsic bone defect exacerbated by hormonal factors [33]. Indeed, estrogen replacement therapy is essential for maintaining bone health in TS as well as in other disorders of sexual development [34]. Patients with insulin dependent diabetes mellitus showed the known improvement of bone parameters over the years, toward the pubertal spurt [35, 36].

Our data in obese patients suggest a trend toward the osteopenia with improving values after puberty. Many studies indicate that the positive effects of body weight on bone mineral density cannot counteract the detrimental effects of obesity on bone quality. However, obese patients may have a not uniform behavior [37], and the exact mechanism underlying their bone deterioration remains unclear [38]. Much is known about bone status of children with kidney disease. Altered bone health induced by chronic inflammation and/or use of glucocorticoids, results in significant morbidity: short stature, bone pain and deformities, fractures, functional complications [7, 39].

In particular, children with Idiopathic hypercalciuria showed the lowest BQI values, which progressively improved with age, possibly due to increment of body mass and reduction in bone resorption, up to almost normalizing in adulthood [40]. Hereditary rickets in our series was associated to a mildly decreased BQI, possibly effect of treatment; regression analysis confirmed significant differences between genders, consistent with the presence of males with the X-linked form in this subgroup.

This study has some limitations. We offered to our colleagues the opportunity to screen by QUS their patients with chronic diseases. We did not include a control group with healthy subjects. Although the total number of patients investigated is relatively high, when the analysis breaks down the population into subgroups, numbers of patients end up in being relatively small. Thus, although the distribution of the results appears quite coherent with available evidences, our findings deserve confirmation on other comparable or even larger patient groups. Furthermore, by study design, we decided not to correlate QUS outputs to laboratory parameters; this because we wanted to explore the use of QUS for screening of patients deserving additional, tailored studies. We were supported, in this design, by the recent study by multiple regression analysis of various laboratory variables, none of which was found to be an independent predictor of BQI [6]. Attempt to correlate calcium intake with bone stiffness was also not successful [24].

Conclusions

Our data suggests that bone impairment is common in children and adolescents with different types of chronic illnesses. This impairment tends to decrease with age, in almost all conditions. QUS confirms as a feasible and affordable method to provide useful information on skeletal status in chronically ill children. Patients with inherited metabolic disorders deserve specific attention and strict monitoring for the potential effect of the underlying disease on bone.

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Author contributions AT performed QUS and wrote the manuscript, MFF, MG and VC made contributions to study sample and interpretation of data; GB made statistical analysis and interpreted data; MA and SP revised critically the manuscript. All authors approved the final version of the manuscript.

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Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article.

Code availability N/A.

Declarations

Conflict of interest No financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Ethics approval Ethic approval was obtained from the local ethic commettee.

Consent to participate Written informed consent was obtained from the participants of the study/their parents.

Consent for publication Permission for publication was included in the informed consent form.

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