0021-7557/11/87-05/450
Jornal de Pediatria

Impact of skeletal maturation on bone metabolism biomarkers and bone mineral density in healthy Brazilian male adolescents

Carla C. Silva,[1] Tamara B. L. Goldberg,[2] Hong S. Nga,[3] Cilmery S. Kurokawa,[4] Renata C. Capela,[4] Altamir S. Teixeira,[5] José C. Dalmas[6]

Abstract

Objective: To evaluate the behavior of biomarkers of bone formation and resorption in healthy male Brazilian adolescents according to their biological maturation.

Methods: Eighty-seven volunteers were divided into age groups according to bone age (BA): 10-12 years (n = 25), 13-15 years (n = 36), and 16-18 years (n = 26). Weight (kg), height (m), body mass index (kg/m^2), calcium intake from 3 days assessed by 24-h food recall (mg/day), pubertal event evaluation by Tanner criteria, and serum biomarker levels (osteocalcin [OC] [ng/mL], bone alkaline phosphatase [BAP] [U/L], and serum carboxyterminal telopeptide [S-CTx] [ng/mL]) were recorded and correlated to bone mineral density (BMD) (g/cm^2) measured by dual energy X ray absorptiometry of the lumbar spine, proximal femur, and whole body.

Results: Biomarkers showed similar behaviors, presenting higher median values in the 13-15 year group (BAP = 154.71 U/L, OC = 43.0 ng/mL, S-CTx = 2.09 ng/mL; $p < 0.01$) and when adolescents were in the pubertal stage G4. Median biomarker values decreased with advancing BA and sexual maturation. Biomarker values showed parallelism with peak height velocity, and, interestingly, bone formation biomarkers indicated significant negative correlation with BMD in the different evaluated locations, i.e., higher BMD values correlated with lower bone biomarker values.

Conclusions: This is the first study of healthy Brazilian adolescents with rigid and careful inclusion and exclusion criteria to assess the correlation of bone markers and BMD with biological maturation indicators. Our results can help understand bone turnover and monitor bone metabolism.

J Pediatr (Rio J). 2011;87(5):450-6: Bone biomarkers, adolescents, bone mineral density, bone age.

Introduction

Bone tissue extends throughout the body and is traditionally evaluated in static and point forms by imaging methods. Being radiopaque, its structure can be verified using qualitative techniques like simple X rays and more accurately using quantitative methods like bone densitometry by dual energy X ray absorptiometry (DXA) or quantitative tomography.[1] However, metabolic, physiological or pathological imbalances can affect radiopaque bone

1. Assistant professor, Department of Physical Education, Universidade Estadual do Norte do Paraná (UENP), Jacarezinho, PR, Brazil.
2. PhD. Associate professor, Adolescent Medicine Discipline, Department of Pediatrics, Graduate Program in Gynecology, Obstetrics, and Mastology, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu, SP, Brazil.
3. Resident physician, Faculdade de Medicina de Botucatu, UNESP, Botucatu, SP, Brazil. Ex-scholarship student, Programa Institucional de Bolsas de Iniciação Científica (PIBIC) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).
4. Investigators, Clinical and Experimental Pediatrics Research Center, Department of Pediatrics, Faculdade de Medicina de Botucatu, UNESP, Botucatu, SP, Brazil.
5. Assistant professor, Department of Tropical Diseases and Image Diagnosis, UNESP, Botucatu, SP, Brazil.
6. PhD. Associate professor, Department of Applied Mathematics, Universidade Estadual de Londrina (UEL), Londrina, PR, Brazil.

No conflicts of interest declared concerning the publication of this article.

Financial support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), process n. 04/07007-1 and 2007/07731-0.

Suggested citation: Silva CC, Goldberg TB, Hong SN, Kurokawa CS, Capela RC, Teixeira AS, et al. Impact of skeletal maturation on bone metabolism biomarkers and bone mineral density in healthy Brazilian male adolescents. J Pediatr (Rio J). 2011;87(5):450-6.

Manuscript submitted Mar 18 2011, accepted for publication May 11 2011.

doi:10.2223/JPED.2125

structure, and are detected by these methods after a certain period. In this sense, the use of more dynamic methods tends to have a more significant contribution in detecting the earlier stages of bone mass reduction and consequently helps in understanding the mechanisms related to preventing this process.[1] In this context, literature has reported the use of bone metabolism biomarkers as a method for dynamically evaluating bone turnover.[2-5]

Infancy and adolescence are the exclusive periods of longitudinal physical growth, with high rates of bone matrix mineralization,[6,7] as 25% of bone mass is incorporated during the 2 years around maximum peak high velocity (PHV).[1] The development of the bone remodeling process is based on two antagonistic processes: bone formation and bone resorption. Together these two processes allow bone modeling and remodeling, which are completely interlinked, but during puberty the formation process is more important.[7-9] However, the use of bone metabolism biomarkers is still restricted during puberty, as it is difficult to delineate standard patterns, because results are influenced by intense bone growth and remodeling at this age and are also susceptible to the variations in biomarker function seen in puberty.[3,10] Gordon reported that image exams and bone biomarkers can be used together to monitor skeletal remodeling during infancy and adolescence.[2] Scientific literature suggests that bone biomarkers reduce after this phase of life, despite a continuing increase in body size and bone mineral density (BMD) which carries on for a few more years.[11]

All the interest surrounding accurate dynamic evaluation of bone tissue during puberty is based on the fact that this phase is a sensitive period for increasing bone reserves and minimizing losses in later life.[3] Bone mass is known to decline from the beginning of the 30s at between 1 and 2% in women and 0.3 and 1% in men. Male bone mass is higher than in females, as men have larger skeletons; moreover, their bone loss period starts later than in women by approximately a decade.[12] Studies have shown that one of the main factors in preventing non-communicable chronic diseases, such as osteoporosis and subsequent future fractures, is trying to reach optimal peak bone mass during adolescence or by the end of skeletal maturation.[13,14] Even though the recorded prevalence of osteoporosis in men is lower than in women, it is high in both genders, and data published in the United States reveal that 1-2 million men present osteoporosis and 8-13 million have osteopenia, and relate a 13.5% risk of fracture for those in their 50s and a 25.6% risk for those in their 60s.[15]

These issues have given rise to serious concerns in public health organizations, in the sense of giving stimulus to the prevention of bone mineral deposit loss and to the performance of bone mass screening, allowing early identification of individuals who still have a mild BMD problem.[16] Therefore, following bone mass incorporation by DXA analysis during infancy and adolescence, mainly in the second decade of life, when practically 95% of bone mass is incorporated, seems to be an adequate means of monitoring bone mineral deposits which present as a "reserve source" for bone health in adult and later life.

Facing the multiplicity of factors involved in interpreting results from the evaluation of bone biomarkers during puberty, there was a need to spread the knowledge on the subject and its applicability in clinical practice as one more tool for understanding bone metabolism. Based on these concepts, the objective of this study was to evaluate the behavior of some bone formation and resorption biomarkers according to skeletal growth and maturation in a sample of healthy male Brazilian adolescents, relating the biomarkers to BMD evaluated by DXA of the lumbar spine, proximal femur, and whole body.

Subjects and methods

Healthy white male volunteer adolescents between ages 10 and 18 years old took part in this cross-sectional study. They were students from the state of São Paulo, Brazil, and belonged to the high socio-economic class. Of the 497 students enrolled in the selected school, 87 adolescents who met all inclusion criteria were included in the study and participated in all evaluations. The project was approved by the Research Ethics Commission of Botucatu School of Medicine, Universidade Estadual Paulista (UNESP), protocols no. 261/2004-CEP and 52/2007-CEP. All participants received and returned written informed consent signed by both the adolescent and their parent or guardian.

The inclusion criteria required that adolescents' weights were between the 10th and 90th percentiles and that their heights were between the 10th and 97.5th percentiles for each age group,[17] and also that body mass index (BMI) was adequate for their age[18] and that they consumed dairy products daily.

Exclusion criteria included adolescents with a history of prematurity or low birth weight and those presenting any of the following conditions: diabetes mellitus, acute or chronic undernutrition, congenital or acquired bone diseases, gastrointestinal diseases associated with malabsorption, history of nephropathy, with or without chronic renal insufficiency, endocrinopathies, early or late puberty, chronic drug consumption, cystic fibrosis, celiac disease, and the use of drugs that negatively affect bone metabolism, such as anticonvulsants or antacids with aluminum.[19] Dietary exclusion criteria were: an exclusively vegetarian diet, high consumption of fiber, caffeine or soft drink and failure to consume dairy products daily.

Data collection began at school, where, in the first instance, adolescents were randomly selected, and those not presenting any dysfunction or condition listed in the exclusion criteria were invited to have their weight and

height measured. Students fitting the abovementioned criteria were then questioned about smoking and alcohol consumption. Secondary sexual characters were evaluated and the results compared to the Tanner criteria.[20] To evaluate skeletal maturation, bone age (BA) was obtained by the Greulich-Pyle method.[21] Dietary characterization was obtained next using a 3-day dietary record.

Blood samples were collected later by a single trained biomedical assistant. Biological samples consisted of 5 mL of blood in a dry tube, to obtain serum and later bone biomarker levels. Volunteers fasted for a minimum of 8 hours and sample collection was performed between 7 a.m. and 9 a. m. Soon after collection, the serum was stored and maintained at the Pediatrics Department Experimental Research Laboratory at -70 °C until used for measuring bone formation biomarkers bone alkaline phosphatase (BAP), expressed in U/L, and osteocalcin (OC), expressed in ng/mL, and the resorption marker serum carboxyterminal telopeptide (S-CTx), expressed in ng/mL. BAP was measured by quantitative immunoassay using anti-BAP monoclonal antibody (Metra BAP, Metra™ Biosystems), with intra and inter-assay coefficients of variation of 5 and 6%, respectively. OC was measured by the competitive Metra™ OC immunoassay kit (Metra™ Biosystems), with intra and inter-assay coefficients of variation of 8 and 7.6%, respectively. S-CTx was quantified by electrochemiluminescence assay using the commercial ß-Cross Laps/serum kit (Roche) and the Elecsys 1010 analyzer (Roche), with an inter-assay coefficient of variation of 5%.

We opted to form groups based on BA, according to the following limits: group 1: 10 complete years to 12 years, 11 months and 29 days (n = 25); group 2: 13 complete years to 15 years, 11 months and 29 days (n = 36); and group 3: 16 complete years to 18 years, 11 months and 29 days (n = 26). In this sense, the choice of biomarker analysis in relation to skeletal growth evaluated by BA in detriment of pubertal stages resulted from both demonstrating a high Spearman linear correlation coefficient value (R = 0.93) with $p < 0.01$.

Evaluation was performed using DXA, with Hologic QDR 2000 equipment. Adequate evaluation of bone mass was achieved using a pediatric software, and BMD results are expressed in g/cm^2. Measurements were taken from the L1-L4 lumbar spine, total proximal femur (femoral neck, trochanter, intertrochanter, and Ward's area), and whole body.

Data were analyzed in Statistica software, version 6. Assessment of descriptive statistical values (mean ± standard deviation) included analysis of variance and the Scheffé test. Kruskal-Wallis analysis of variance was performed for comparisons between BA groups and bone biomarkers, as the Shapiro-Wilk test verified that variable totality did not indicate normal distribution of these data. Spearman's coefficients of correlation between bone biomarkers and BMD results in the evaluated locations were calculated. Minimum statistical difference was considered at 5%.

Results

General sample characterization of the 87 adolescents is shown in Table 1, which presents anthropometric indicators (body weight, height, and BMI), mean calcium intake, and bone mineralization indicators (BMD in the L1-L4 lumbar spine, proximal femur, and whole body) of age groups established by BA.

Results show that values increase with age and present significant differences when mean values are compared by analysis of variance and differences identified by the Scheffé test. There are significant increases in body weight, height, and BMI with advancing age, typical events coherent to the natural process of intense physical growth experienced during puberty. BMD also shows significantly increasing behavior with advancing skeletal maturation in all locations evaluated. Calcium ingestion evaluated from a 3-day dietary record is similar between age groups. This finding agrees with study inclusion criteria, which insist on a daily intake of dairy products.

Figure 1 below shows median values of BAP, OC and S-CTx bone biomarkers according to BA groups. Kruskal-Wallis analysis of variance for all biomarkers showed p values to be significant and < 0.01. Although non-parametric statistical analysis did not identify differences between IOs, it is possible to see that the 13-15 year group has higher medians than the other IOs for all bone biomarkers, i.e., for both formation (BAP and OC) and resorption (S-CTx) markers. It is important to highlight that the later age group (16-18 years) has substantially lower medians than the younger groups.

Lastly, Spearman's coefficients of correlation between bone biomarkers and BMDs from the lumbar spine, proximal femur, and whole body were studied. Analysis of Table 2 shows that formation bone biomarkers (BAP and OC) demonstrated significant correlations, but the bone resorption biomarker (S-CTx) demonstrated very low correlation scores, indicating that S-CTx was not associated with bone mass acquisition in the evaluated adolescents. An interesting aspect is that bone formation biomarkers indicate negative values; in other words, lower values for formation biomarkers correlate to higher bone densities in the respective locations (Table 2).

Discussion

Studies relating adolescence and bone health have gained important recognition in the international research scene, as comprehension of the mechanisms involved in bone mineralization, especially those which occur in puberty, can be a response to the development of quality

Table 1 - Mean values and standard deviations of anthropometric indicators, calcium intake, and bone mineralization indicators regarding BA groups (n = 87)

Variables	BA (years)		
	BA 1 (10-12) (n = 25)	BA 2 (13-15) (n = 36)	BA 3 (16-18) (n = 26)
Weight (kg)	38.4±7.9*	52.1±8.2*	62.9±8.6*
Height (m)	1.48±0.08*	1.64±0.08*	1.74±0.06*
BMI (kg/m^2)	17.3±2.09*	19.1±1.88*	20.6±2.51*
Calcium intake (mg/day)	802.1±202.0	747.1±255.0	911.0±264.2
BMD - L1-L4 (g/cm^2)	0.63±0.08*	0.78±0.15*	0.94±0.10*
BMD - femur (g/cm^2)	0.78±0.04*	0.90±0.13*	1.03±0.11*
BMD - whole body (g/cm^2)	0.84±0.03*	0.92±0.09*	1.06±0.07*

BA = bone age; BMD = bone mineral density; BMI = body mass index.
Scheffé test to find the differences between the BAs ($p < 0.01$)
* BA 1 < BA 2 < BA 3.

bone mass, which could result in active adult years during aging as well, through the empowerment of a dignified life, from the point of view of autonomy, independence, and physical capacity.[8,22]

Various researchers have highlighted the importance of understanding BMD in children and adolescents, showing that BMD values increase with age,[2,7,8,14] but this growth does not have a linear distribution, as it is greater during adolescence. The same observations have been described in our environment by Silva et al. when they demonstrated that the critical period for bone mass increase in healthy male adolescents was between the ages of 13 and 15 years old and in sexual development stage G4.[23,24] In this sense, literature has reported that the adolescence period is marked by a significant bone formation rate, as bones are characterized by presenting a metabolically active tissue, which undergoes a continuous process of effective remodeling.

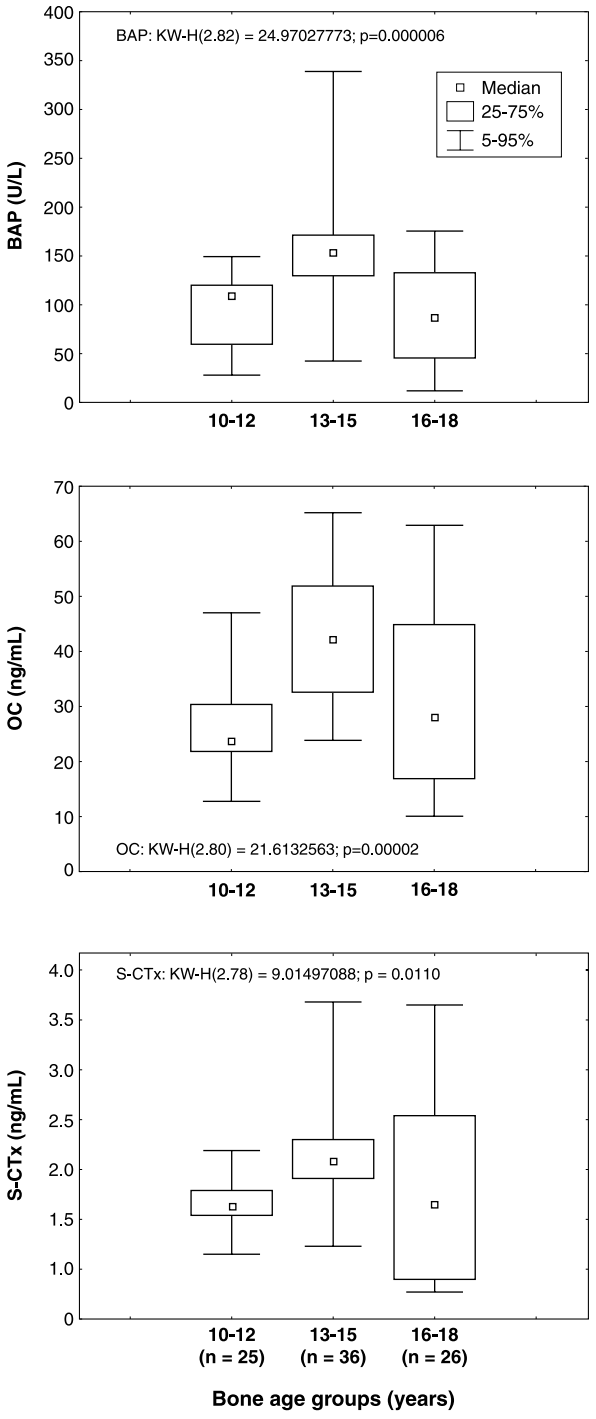
The results of this study shown in Table 1 are similar to those reported in specialized literature. In our sample of male adolescents, there is a substantial significant increase in bone mass in the evaluated regions with advancing skeletal age, particularly from 14 years of age onwards, with the highest mean values between 16 and 18 years.[7,10,23] The box plot graphs show median biomarker values of skeletal age groups, from 10 to 18 years old. Statistical treatment by Kruskal-Wallis analysis of variance indicated values of $p < 0.01$ for bone formation biomarkers (BAP and OC) and for the bone resorption biomarker (S-CTx). The graphs show that median values for the 13-15 year old group were substantially higher and then dropped in the 16-18 year old group. Lower biomarker concentrations were seen at the end of puberty, a behavior already highlighted by other authors, who reported values in 18 year olds similar to those observed in adults.[12]

Tuchman et al. found a strong correlation between bone biomarkers and PHV, observing parallelism between high marker levels and increased growth velocity.[25] Moreover, despite BMD is still progressing upwards with age until reaching peak bone mass, we see that growth velocity

Table 2 - Coefficients of correlation between bone biomarkers and bone mineralization indicators in the lumbar spine (L1-L4), proximal femur, and whole body (n = 87)

	S-CTx (ng/mL)	OC (ng/mL)	BAP (U/L)
BMD - spine (g/cm^2)	-0.22 (p = 0.28)	-0.13 (p = 0.51)	-0.37 (p = 0.04)*
BMD - femur (g/cm^2)	-0.02 (p = 0.93)	-0.45 (p = 0.02)*	-0.57 (p = 0.00)*
BMD - whole body (g/cm^2)	-0.02 (p = 0.91)	-0.47 (p = 0.00)*	-0.69 (p = 0.00)*

BAP = bone alkaline phosphatase; BMD = bone mineral density; OC = osteocalcin, S-CTx = serum carboxyterminal telopeptide.
* Significant correlations.



BAP = bone alkaline phosphatase; KW-H = Kruskal-Wallis analysis; OC = osteocalcin; S-CTx = serum carboxyterminal telopeptide.

Figure 1 - Median of BAP, OC and S-CTx according to bone age group (n = 87)

reduces as adolescents near their final height, which agrees with bone marker behavior, thus reinforcing the relationship between these events. From this perspective, van Coeverden et al. evaluated the magnitude of the relationship between bone turnover as assessed by bone biomarker levels and PHV by measuring the levels of sexual steroids, insulin-like growth factor 1 (IGF-1), and insulin-like growth factor binding protein 3 (IGF-BP-3).[7] The authors performed a semi-longitudinal study with 155 boys and 141 girls between 8.2 and 15.7 years old. Their results showed that rapid height growth was concomitant with bone mineralization but not with bone turnover. At the end of puberty, they observed a decline in estradiol rates, which inhibited chondrocyte proliferation. As a consequence, the authors verified a decline in growth velocity and bone biomarkers levels. Bone mass, however, showed a later increase, which were probably influenced by sexual steroids, IGF-1, and IGF-BP-3.[7]

Data found in our study (Table 2) revealed significant negative correlations between OC, BAP and S-CTx biomarkers and BMD in the lumbar spine, proximal femur, and whole body among all adolescents. These results differ from those presented for males by van Coeverden et al., who did not find significant differences in bone marker values among youngsters in pubertal stages G4 and G5; this was probably due to their sample containing individuals with an upper limit of 15.7 years of age, and because those found in stage G5 presented a mean age of 13.8±0.9 years. Moreover, their results correlated with bone mass content, not with data related to BMD, observing significant correlation, but not negative as in our study, probably influenced by the age cutoff, which did not take into account the complete age band encompassing adolescence, omitting to show the lower bone marker values found at the end of this phase of life, as seen in our study.

The results of our study, which is the first study in Brazil on white healthy male adolescents using strict inclusion/exclusion criteria, are similar to those published by Yilmaz et al. who showed a reduction in biomarker concentrations at the end of puberty only in female adolescents, while BMD had still increased, revealing a negative correlation between bone turnover and BMD.[26] In males, these authors did not observe a negative correlation between BMD and formation markers. However, they only evaluated boys between 10 and 15 years old, with which they probably lost sensitivity of the test and could not analyze the process of bone mass evolution, because bone formation and turnover markers reduce in the years after their upper age limit, as observed in our study when the adolescents had BAs compatible with 16, 17, and 18 years of age.

With respect to the relationship between formation and resorption bone biomarkers and secondary sexual characters, our data reveal that the biomarkers had higher medians when the adolescents evaluated reached pubertal stage G4 (BAP 148.51 U/L, OC 43.58 ng/mL, S-CTX 2.10 ng/mL), the moment coinciding with maximum PHV, and when they have BAs between 13 and 15 years (BAP = 154.71 U/L, OC = 43.0 ng/mL, S-CTx = 2.09 ng/mL; $p < 0.01$). The lowest medians for the studied markers were seen in stage G5 (BAP 62.21 U/L, OC 20.45 ng/mL, S-CTX 1.21 ng/mL).

A statistically significant association between these markers and secondary sexual characters was observed, from the study of correlation coefficients (data not shown).

Other researchers have compared bone formation biomarkers and bone resorption in children (n = 86), with a mean age of 10 years, and adults (n = 30), with a mean age of 28 years, from both sexes. Results showed high BAP and cross-linked N-telopeptide (NTx), a bone resorption marker, in the children's group (BAP = 170.1±131.4 ng/mL and NTx = 89.8±38.9 ng/mL) compared to adults (BAP = 20.2±7.5 ng/mL and NTx = 15.3±2.5 ng/mL; $p < 0.01$). The authors declared that their results were consistent with specialized literature, which highlights a substantial increase in bone metabolic activity in children and adolescents during physical growth. Their results also indicated that, after the long growth period, BAP and NTx values showed considerable decline.[9]

The clinical importance of bone metabolism biomarkers is due to their rapid production during bone remodeling compared to evaluations resulting from BMD by traditional methods. Scientific literature has given biomarkers specific importance, especially concerning osteoporosis, which is considered one of the main causes of fractures by fragility. Bone markers are proven dynamic effective tools in evaluating patients with osteoporosis and following the effects of drugs used in their treatment, but it is strongly recommended that bone markers are not used for diagnosing this disease, for which DXA is recommended. In prospective studies on post-menopause women, increased resorption markers have correlated with double the risk of fractures. However, it is important to stress that marker responses relate to the skeleton as a whole and not just to specific locations, as results obtained do not reveal a risk of a probable fracture in a specific location.[27]

Hence, tests for biochemical markers of bone remodeling provide important information for understanding the dynamics of bone metabolism and can be repeated at much shorter intervals. However, the large individual variability in biomarker concentrations and their liberation in different anabolic and catabolic processes prevent their isolated use in diagnoses.[4] Therefore, despite their importance, bone biomarkers are still used in a restricted way in clinical practice and are considered complementary to bone densitometry,[28] in situations other than evaluation and follow-up of osteoporosis. The data presented in this study confirm that bone mass evaluation must be performed using bone biomarkers as a complement of BMD evaluation. The study and follow-up of markers favor a qualitative evaluation of bone formation and resorption, resulting from the high anabolism found during puberty. However, biomarker analysis must be complemented by studying bone densitometry, the translation of time and pattern of formation and resorption rates.[29,30] The resultant combination of evaluating various bone formation and resorption biomarkers is useful in understanding and investigating bone turnover in both healthy and unhealthy children and adolescents, as well as in monitoring the resultant effects of treating diseases which affect bone metabolism.

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Correspondence:
Tamara Beres Lederer Goldberg
Departamento de Pediatria,
Disciplina de Medicina do Adolescente, UNESP
CEP 18607-918 - Botucatu, SP - Brazil
Tel.: +55 (14) 3811.6274 / 3811.6083
Email: tamara@fmb.unesp.br