Original Study

Use of a Gonadotropin-releasing Hormone Analog to Treat Idiopathic Central Precocious Puberty Is Not Associated with Changes in Bone Structure in Postmenarchal Adolescents

Renata Iannetta PhD, MD [1], Anderson S. Melo PhD, MD [1], Odilon Iannetta PhD, MD [1], Júlio S. Marchini PhD, MD [2], Francisco J. Paula PhD, MD [2], Carlos E. Martinelli PhD, MD [3], Ana Carolina J.S. Rosa e Silva PhD, MD [1], Rui A. Ferriani PhD, MD [1], Wellington P. Martins PhD, MD [1], Rosana M. Reis PhD, MD [1,*]

[1] *Department of Gynecology and Obstetrics, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil*
[2] *Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil*
[3] *Department of Pediatrics, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil*

A B S T R A C T

Study Objectives: To evaluate bone quantity and quality in postmenarchal adolescents treated for idiopathic central precocious puberty (CPP) in childhood with a gonadotropin-releasing hormone analog (GnRHa) and to determine the serum concentrations of bone remodeling markers.
Design and Participants: This cross-sectional study included 53 postmenarchal adolescent girls who were divided into 2 groups: 27 adolescents who were treated with GnRHa in childhood for idiopathic CPP (the CPP group) and 26 women who presented with physiological development of secondary sex traits (the control group). Interventions: None.
Main Outcome Measures: Weight, height, body mass index, age at menarche, time since menarche, body composition, bone mineral density (BMD), bone quality, and serum insulin, glucose, osteocalcin, and carboxyl-terminal telopeptide of type I collagen concentrations were compared in the 2 groups. BMD data were analyzed by using both dual-energy x-ray absorptiometry (DXA) and osteosonography, and body composition was measure with the use of DXA and electrical bioimpedance.
Results: BMD and bone quality did not differ significantly between the CPP and control groups when analyzed by using DXA or osteosonography. Serum osteocalcin concentration was significantly lower ($P = .02$) in the CPP than in the control group. Insulin was higher in the CPP group, and hyperinsulinemia was an independent predictor of bone quantity and quality assessed by using osteosonography. Body mass index and percent fat were determined by using DXA, and the duration of use of GnRHa treatment and the time since GnRHa discontinuation were not independent predictors of bone quantity and quality.
Conclusion: Postmenarchal adolescents treated with GnRHa for CPP in childhood did not show a reduction in bone quantity or quality.
Key Words: Precocious puberty, Bone mass, Bone collagen, Gonadotropin-releasing hormone analog, Osteocalcin

Introduction

Childhood and adolescence are periods of positive bone remodeling activity, and bone development during these periods has a crucial effect on peak bone mass as well as bone strength during later life.[1] The acquisition of bone mass during the first decades of life is influenced by myriad factors, including physiological (ie, age, sex, height, weight, sex, race, and pubertal status), genetic, and endocrine factors and life habits and physical activity levels.[2,3]

Among the endocrine factors, serum estrogen levels are fundamental for adequate skeletal maturation and mineralization during childhood/puberty and up to the third decade of life, which is considered the time of maximum acquisition of bone mass (peak bone mass).[4,5] Thus, it is important to identify the degree to which pubertal onset affects peak bone mass.

Central precocious puberty (CPP) is associated with disproportionately early bone maturation. In addition, the use of a gonadotropin-releasing hormone analog (GnRHa) to treat CPP[6] may be associated with a reduction in bone mass due to the promotion of hypoestrogenism, ultimately leading to impairment in bone quality and bone mass gain.[4,5] Despite these considerations, most studies have evaluated only variables related to bone mineral density (BMD), without dealing with possible precocious qualitative changes related to the loss of bone mass.[7–10]

The method most frequently used for the determination of BMD in girls with precocious puberty has been dual-energy x-ray absorptiometry (DXA), especially in girls treated with GnRHa.[7,9,11] However, this technique has limitations, such as the influence of bone size, and cannot be used to measure qualitative features of bone tissue.[2] Osteosonography is a complementary method that analyzes bone quality. In addition, osteosonography is a low-cost method that does not emit radiation and can be performed by using a small and easily transported device,[12] thus permitting the evaluation of bone tissue even at less well-equipped health care facilities.

The authors indicate no conflicts of interest.

* *Address for correspondence to:* Rosana M. Reis, PhD, MD, Avenida dos Bandeirantes 3900, Campus da USP, Ribeirão Preto–SP CEP, São Paulo, Brazil 14049-900; Phone: +55 16 3602 2926
E-mail address: romareis@fmrp.usp.br (R.M. Reis).

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Assessments of bone mass can be complemented by measuring serum markers of bone remodeling. Osteocalcin and bone alkaline phosphatase are frequently used markers of bone formation, whereas pyridolines and carboxyl- and amino-terminal telopeptide fragments of type 1 collagen (CTX) are markers of bone reabsorption.[1] To date, however, no studies have evaluated bone quality and quantity, as well as markers of bone remodeling, in the same sets of patients. Thus, the primary objective of the present study was to assess bone quantity and quality in postmenarchal adolescents who had been treated with GnRHa in childhood for idiopathic CPP. A secondary objective was to determine the serum concentrations of bone remodeling markers in these individuals.

Patients and Methods

Patients

This cross-sectional study involved 53 postmenarchal adolescent girls, aged 11-17 years: 27 had been treated with GnRHa in childhood for idiopathic CPP and 26 controls had presented with physiological development of secondary sex traits. CPP patients were selected at the outpatient clinic of childhood-pubertal gynecology of the Department of Gynecology and Obstetrics, Ribeirão Preto Medical School, University of São Paulo. Control subjects with physiological pubertal development were selected from the local state school network and included in the study in a consecutive manner (96 patients were eligible; 60 agreed to participate in the study but 34 failed to attend). The recruitment was performed between May and September 2013. Only patients who were born at term (37-42 weeks) with a birth weight appropriate for the gestational age were included in this study.

All patients were diagnosed with precocious puberty before the age of 8 years based on the onset and progression (Tanner pubertal stage M2 or M3 according to) of secondary sex traits during a 3- to 6-month evaluation period, along with responsiveness to an GnRHa test (luteinizing hormone concentration >3.9 IU/mL at 3 hours after receipt of GnRHa). These patients received intramuscular leuprolide acetate (3.75 mg per month for a minimum of 1 year and a maximum of 6 years [mean 2.5 years]). The criterion for the discontinuation of medication was the attainment of 11 years of chronological age or 12 years of bone age.[6] Of 145 patients diagnosed with CPP, 49 were eligible and 45 were recruited (4 did not have data about gestational age). Of these, 18 refused to participate in the study; therefore, 27 were included in the CPP group.

Exclusion criteria were CPP secondary to tumors, malformations, or infection, and/or trauma; radiological changes determined on skull computed tomography, nuclear magnetic resonance and pelvic ultrasonography; or diseases or the use of medications that might interfere with bone metabolism. The study was approved by the Ethics Committee of the University Hospital, Ribeirão Preto Medical School, University of São Paulo, and all subjects provided written informed consent to participate.

Methods

The patients were evaluated during a single visit and after a 12-hour fast. Anamnesis and physical examination data included age, weight, height, body mass index (BMI, defined as weight [kg]/height [m^2]), age at menarche, and time since menarche (Δt). After a 15-minute rest, 10 mL venous blood was collected from each subject and centrifuged at 2500 rpm ($1600 \times g$) at room temperature for 10 minutes. Serum samples were stored at $-70^{\circ}C$, so that all samples could be assessed for serum markers of bone remodeling at the same time.

Bone quality and quantity were determined by using DXA (Hologic 4.500 W) and osteosonography/osteosonometry (DBM Sonic BP; Igea, Capri, Italy). The variables analyzed by the use of DXA were BMD of the first to fourth lumbar vertebrae (BMDl), BMD of the total femur (BMDf), and volumetric bone density (BMDv):

$$\mathrm{BMDv}=\frac{\alpha}{\beta}$$

where α is mean BMD (g/cm^2) of the lumbar spine (L2-L4) and β is the square root of the mean area of the lumbar spine in cm^2 (L2-L4). Among the variables analyzed with the DBM Sonic BP were amplitude-dependent speed of sound (AD-SoS) for the evaluation of bone mass quantity and bone transmission time (BTT) for the analysis of bone quality.[13]

Serum concentrations of the bone remodeling markers, including osteocalcin and the CTX, were determined by using an ELISA (USCNK-Life Science Inc), with each sample assayed in duplicate. Fasting insulin serum level was determined through chemiluminescence by using a DPC Immulite 2000 apparatus (Diagnostic Products Corporation, Los Angeles, CA). Glucose levels were assessed by using the glucose oxidase method. Insulin resistance (IR) was determined according to the homeostasis model assessment–insulin resistance index (HOMA-IR)[14]:

$$\mathrm{HOMA-IR}=\frac{\text{fasting glucose (mg/dL)} \times 0.05551 \times \text{fasting insulin } (\mu\mathrm{U/mL})}{22.5}$$

Body composition was analyzed through the use of electrical bioimpedance (BIA) by using Biodynamics instrument Model 310e and of DXA. Fat mass was calculated as a percentage (%FM) as described previously.[15] The frequency of physical activity was similar in the CPP and control groups; this variable was therefore not included in the statistical analyzes.

Statistical Analysis

Normal distribution of the data was determined with the Kolmogorov–Smirnov test. Because all variables showed a normal distribution, *t* tests were used to compare bone evaluation data and body composition in the 2 groups. Results were expressed as mean (±standard deviation), and multiple linear regression was performed using BTT, BMDl, BMDf, and AD-Sos as response variables. The covariables