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Original Article

Bone Density in Patients With Berardinelli-Seip Congenital Lipodystrophy Is Higher in Trabecular Sites and in Type 2 Patients

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Abstract

Berardinelli-Seip congenital lipodystrophy (BSCL) is a rare autosomal recessive syndrome characterized by a difficulty storing lipid in adipocytes, low body fat, hypoleptinemia, and hyperinsulinemia. We report here laboratory, bone mineral density (BMD), and bone mineral content findings of 21 patients (24.1 ± 8.4 yr old, 14 females, 18 diabetics, 5.3% total body fat) with BSCL. The mean leptin was very low (0.91 ± 0.42 ng/mL), and the mean values of the *Z*-scores for all studied sites were positive, except for the 33% radius (*Z*-score −0.5 standard deviation [SD]). Twelve patients (57.1%) had a BMD *Z*-score higher than +2.5 SD in at least 1 site. There was no significant difference in the *Z*-scores between males and females. None of type 1 (*AGPAT2*) patients had *Z*-scores higher than +2.5 SD, and these patients had a smaller *Z*-score of BMD total body (0.26 SD vs 1.90 SD, $p = 0.022$) and of bone mineral content (1.59 SD vs 3.3 SD, $p = 0.032$) than type 2 (seipin) patients. Insulin, as well as $HOMA_{IR}$ (homeostasis model assessment), correlated positively with the BMD of all sites, except for the 33% radius. *Z*-Scores on this site (33% radius) were the smallest of all. More than half of our patients with BSCL have BMD *Z*-scores higher than +2.5 SD on at least 1 site, and this increase is more pronounced in the trabecular sites and in type 2 patients.

Key Words: Bone mass; density; insulin; leptin; lipodystrophy.

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Introduction

Berardinelli-Seip congenital lipodystrophy (BSCL) is a rare autosomal recessive syndrome characterized by a difficulty storing lipid in adipocytes, very low body fat, low leptin, and hyperinsulinemia *(1)*. BSCL was first described in 2 children in Brazil in 1954 by Waldemar Berardinelli *(2)*, and later by Martin Seip in Norway *(3)*. The clinical characteristics of BSCL include hepatosplenomegaly, fatty liver, altered carbohydrate metabolism, severe insulin resistance, hyperinsulinemia, acromegaloid habitus, and dyslipidemia *(1)*. There are currently 4 types described

in accordance to which gene is mutated: *AGPAT2* (type 1—OMIM #608594), *BSCL2* (type 2—OMIM #269700), CAV1 (type 3—OMIM #612526), and PTRF (type 4—OMIM #613327) *(4)*. Types 1 and 2 are responsible for almost 95% of total cases *(1)*.

Patients usually present with weight at the lower limit of normal and decreased total body fat, and some women have amenorrhea. Although these are risk factors for osteoporosis, their spine and hip bone mineral density (BMD) are often normal or even high *(5,6)*. Leptin and insulin have been shown to impact bone turnover and could affect peak bone mass *(7,8)*. Importantly, leptin-deficient mice (ob/ob) have high bone mass despite impaired reproductive status, highlighting the importance of leptin on bone metabolism *(9)*. Hyperinsulinemia may have an anabolic bone effect and type 2 diabetics, differently from type 1, have normal or even high bone mass, but more frequent peripheral fractures *(8)*.

We studied BSCL patients, evaluating their laboratory and densitometric abnormalities. We aimed to see if there are any BMD differences in bone sites (spine, femur, radius, and total body) or in BSCL types (types 1 and 2).

Materials and Methods

Study Population

In this cross-sectional noninterventional study, we enrolled 21 patients with BSCL treated a t the outpatient endocrine clinic of the Hospital Universitário Onofre Lopes, Natal, Rio Grande do Norte, Brazil. Inclusion criteria were age older than 5 yr, diagnosis of BSCL, and neither diseases nor use of drugs that interfere with BMD or bone metabolism. For the diagnosis of BSCL, we considered both clinical criteria (acromegaloid facies, prognathism, atrophic cheeks [loss of Bichat's fat ball], prominence of the umbilicus, muscle hypertrophy, phlebomegaly, and acanthosis nigricans) and laboratory criteria (hypertriglyceridemia, low leptinemia, and hyperinsulinemia). The low percentage of total body fat detected by dual-energy X-ray absorptiometry (DXA) or the presence of 1 of the 4 known mutations confirmed the syndrome.

Ethical Considerations

The research protocol was reviewed and approved by the Federal University of Rio Grande do Norte Ethical Committee (CAAE 14070213.3.0000.5537). Written informed consent was obtained from all participants or legal guardians.

Bone Densitometer Scan

BMD was measured at the lumbar spine (L1–L4), femoral neck, total hip, radius (total, ultradistal, and 33%), and total body less head (TBLH) using the same densitometer (GE Lunar DPX, GE Healthcare Clinical Systems, Brazil) and was analyzed by the same physician. The BMDs of patients under 20 yr of age were measured only in the lumbar spine (L1–L4) and TBLH, as recommended *(10)*. The BMD results were adjusted for age and sex and expressed by *Z*-score (BMD observed minus mean BMD for patients of the same age and sex, divided by the standard deviation [SD] of the reference population provided by the DXA manufacturer). The body composition (lean mass and body fat) and the bone mineral content (BMC) were obtained from a whole-body scan. We used an online calculator (https://bmdcs.nichd.nih.gov/zscore.htm) to measure TBLH BMC SD. We defined low and high bone densities as a BMD *Z*-score lower than −2.0 SD and higher than +2.5 SD, respectively *(11)*.

Laboratory Measurements

After an overnight fast, blood samples were collected and glycemia, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, creatinine, urea, alkaline phosphatase, calcium, phosphate, albumin, thyroid-stimulating hormone, insulin, parathyroid hormone, 25-OH-vitamin D, and leptin were determined. We used serum albumin to adjust the serum calcium. $HOMA_{IR}$ (homeostasis model assessment = fasting glycemia [mmol/L] × fasting insulin [μU/mL]/22.5) *(12)* was calculated for patients without insulin therapy, and a value higher than 2.7 was considered as indicative of insulin resistance *(13)*. Genetic analysis was performed in 18 patients. Deficiency and insufficiency of vitamin D were defined according to the criteria of the Endocrine Society (25-OH-vitamin D <20 and between 20 and 30 ng/mL, respectively) *(14)*.

Statistical Analysis

SPSS Statistics, version 22, was used to analyze the data (IBM Corp., Armonk, NY, USA). Parametric data were expressed as mean (SD), and nonparametric data were expressed as median (minimum-maximum). Proportions were presented as n (%). *t* Test was used to compare the mean values of parametric data, and the Mann-Whitney test was used for the nonparametric data. The Shapiro-Wilk test was used to analyze normality data distribution. To evaluate the correlation between 2 variables, Pearson (parametric variables) correlation coefficient was used. A p value <0.05 was considered statistically significant.

Results

Clinical Characteristics of Berardinelli-Seip Participants

Clinical and laboratory characteristics of the patients are presented in Table 1. The majority of patients had type 2 BSCL (mutation in the *BSCL2* gene) and 3 patients had type 1 (mutation in the *AGPAT2* gene). There was a predominance of female patients (n = 14, 66%), and the mean age was 24.1 ± 8.4 yr old. Of the 14 women, 11 had menarche at an average age of 15.5 ± 3.4 yr, and 3 had not yet menstruated (ages 5, 14, and 15 yr old). Of the 11 who had menarche, 4 patients had it at an age older than 16 yr, and