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Normal bone density and trabecular bone score, but high serum sclerostin in congenital generalized lipodystrophy

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ABSTRACT

Context: Berardinelli–Seip Congenital Lipodystrophy (BSCL) is a rare autosomal recessive syndrome characterized by a difficulty in storing lipids in adipocytes, low body fat mass, hypoleptinemia, and hyperinsulinemia. Sclerostin is a product of *SOST* gene that blocks the Wnt/β-catenin pathway, decreasing bone formation and enhancing adipogenesis. There are no data about sclerostin in people with BSCL.
Objective: We aimed to evaluate serum sclerostin, bone mineral density (BMD), and L1–L4 Trabecular Bone Score (TBS) in BSCL patients, generating new knowledge about potential mechanisms involved in the bone alterations of these patients.
Design, setting, and patients: In this cross-sectional study, we included 11 diabetic patients with BSCL (age 24.7 ± 8.1 years; 6 females). Sclerostin, leptin, L1–L4 TBS, BMD were measured. Potential pathophysiological mechanisms have been suggested.
Results: Mean serum sclerostin was elevated (44.7 ± 13.4 pmol/L) and was higher in men than women (55.3 ± 9.0 vs. 35.1 ± 8.4 pmol/L, p = 0.004). Median of serum leptin was low [0.9 ng/mL (0.5–1.9)]. Seven out of 11 patients had normal BMD, while four patients had high bone mass (defined as Z-score > +2.5SD). Patients on insulin had lower sclerostin (37.3 ± 9.2 vs. 52.6 ± 13.4 pmol/L, p = 0.05). The mean TBS was 1.402 ± 0.106, and it was higher than 1.300 in nine patients.
Conclusions: Patients with lipoatrophic diabetes (BSCL) have high serum concentrations of sclerostin, normal or high BMD, and reasonable trabecular bone mass measured by TBS. This is the first report of high sclerostin and good bone microarchitecture (TBS) in BSCL patients.

1. Introduction

Congenital generalized lipodystrophy is a rare autosomal recessive disease first described in Brazil by Waldemar Berardinelli [1], and five years later by Martin Seip in Norway [2], named later as Berardinelli–Seip Congenital Lipodystrophy (BSCL). Patients with this syndrome lack the capacity to store lipids in adipocytes, causing severe insulin resistance diabetes, hepatomegaly, hypertriglyceridemia, and pancreatitis.

There are currently four types of BSCL described [3–6], and Types 1 and 2 are the most prevalent, accounting for 95% of cases [7]. In the Brazilian BSCL cohort, from the state of Rio Grande do Norte, there are very high prevalence rates of Type 2 as described previously [8] due to consanguineous marriages.

We have previously shown that patients with BSCL have normal or even elevated BMD [9]. Hyperinsulinemia, hypoleptinemia, muscular hypertrophy are some potential mechanisms involved [10]. Sclerostin is a product of *SOST* gene, generated almost exclusively by osteocytes. It binds to the LRP5 or LRP6 receptor, preventing the action of the Wnt/β-catenin pathway, and decreasing bone formation. Recent reports suggest that sclerostin may also enhance adipogenesis through

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inhibition of the Wnt/β-catenin signaling system [11]. It is often reported to be high in type 2 diabetes (T2D) but not in Type 1 [12]. There are no data on serum sclerostin of Berardinelli–Seip Congenital Lipodystrophy (BSCL) patients. Once these patients have diabetes with severe insulin resistance and very low body fat, sclerostin should be altered in some way.

In the last years, the acknowledgment about sclerostin is increasing, and it is no longer considered with only a bone function. The aim of our paper was to generate new data of sclerostin in a group of patients with diabetes (BSCL) and, differently of type 2 diabetes, with normal bone density and low adipogenesis. These data help to understand better the several functions of sclerostin.

2. Materials and methods

2.1. Study population

In this descriptive cross-sectional non-interventional study, we enrolled 11 patients with BSCL treated at the outpatient endocrine clinic of the Hospital Universitário Onofre Lopes, Natal, RN, Brazil (Table 1). Inclusion criteria were a diagnosis of BSCL without other diseases or use of drugs that interfere with BMD or bone metabolism (except diabetes and its treatments). Clinical (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, hypoleptinemia, hyperinsulinemia) were considered for BSCL diagnosis. The presence of mutations in genes AGPAT2 or BSCL2 confirmed the syndrome.

2.2. Serum measurements

Blood samples were collected after an overnight fasting. Serum sclerostin was measured by ELISA (Biomedica, Vienna, Austria, reference range 12–29 pmol/L). We used serum albumin to adjust the serum calcium. $HOMA_{IR}$ (homeostasis model assessment) was calculated (fasting glycemia [mmol/L] × fasting insulin [μU/mL]/22.5) [13] and a value higher than 2.7 was considered as indicative of insulin resistance [14]. Osteocalcin, C-telopeptide (CTx), and leptin, due to availability, were only measured in seven 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) [15].

2.3. Bone density and TBS measurement

BMD was measured in the lumbar spine (LS), femoral neck (FN), total hip (TH) radius ultra distal (UD), radius 33% (R33), and total body less head (TBLH) using the same densitometer (GE Lunar) and was analyzed by one of the authors (JGL). Patients under 20 years of age had the BMD measured only in the LS and TBLH as recommended [16]. We defined low and high bone density as a BMD Z-score lower than −2.0SD and higher than +2.5SD, respectively [17]. L1–L4 Trabecular Bone Score (TBS, TBS insight v3.0, Medimaps SASU, Merignac, France) was measured by one of the authors (RW) blinded to the clinical and laboratory characteristics of participants. It was used to estimate bone microarchitecture [18].

2.4. Statistical analysis

Parametric data are expressed as mean (standard deviation), and non-parametric data are expressed as median (minimum - maximum). Proportions are presented as n (%). The Shapiro-Wilk test was used to analyze normality data distribution. T-Test was used to compare mean of parametric data, and the Mann-Whitney test was used for non-parametric data. A p-value < 0.05 was considered statistically significant.

2.5. 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.

3. Results

3.1. Clinical characteristics of Berardinelli–Seip participants

Eight patients had BSCL Type 2 (mutation in *BSCL2* gene), and three patients had Type 1 (*AGPAT2* gene mutation). These patients are part of a cohort previously published [8]. The mean age was 24.7 ± 8.1 years old, and there were six females. Five patients had menarche at an average age of 14.4 ± 2.3 years, and one had not yet menstruated (15 years old). There was no history of alcohol intake or smoking. The mean BMI of patients was 20.6 ± 3.6 kg/m^2, and the total body fat measured by DXA scan was 5.5 ± 0.9%. Muscle hypertrophy detected on physical examination was present in nine patients (81.8%). All patients had diabetes. The mean age of diabetes onset was 15.8 ± 5.5 years old, and the diabetes duration was 11.1 ± 7.2 years. They were on one or more treatments, including insulin (6/11; 54.5%), metformin (4/11; 36.4%), and DPP-4 inhibitor (one patient).

3.2. Laboratory findings

The glycemic control was poor, and the kidney function was normal (Table 2). Hypertriglyceridemia was present in ten patients (90.9%), and

Table 1
Clinical, laboratorial and densitometric results of each BSCL patient.

Patient #	Gene mutated	Age (years)	Gender	BMI (kg/m^2)	Treatment	HbA1c (%)	Leptin (ng/mL)	Sclerostin (pmol/L)	L1–L4 BMD (Z-score)	Total body BMD (Z-score)	TBS
1	BSCL2	27	Female	19.3	Insulin	9.3	1.1	31.89	0.09	0.20	1.286
2	BSCL2	28.9	Male	22.6	Metformin	7.4	0.5	62.76	1.00	1.40	1.514
3	BSCL2	41	Female	22.4	Insulin	7.9	0.5	41.67	1.08	1.00	1.423
4	BSCL2	26.6	Male	23.8	Insulin, metformin	8.4	0.5	45.67	3.31	2.90	1.591
5	BSCL2	33.2	Male	27.2	Diet	7.9	NA	57.26	5.59	5.60	1.478
6	AGPAT2	15.4	Female	16.2	Insulin, metformin	12.4	NA	30.73	1.15	−0.20	1.377
7	AGPAT2	12.5	Male	18.6	Diet	6.5	NA	45.98	1.04	1.00	1.448
8	AGPAT2	19.1	Female	15.2	Insulin	12.4	NA	48.57	1.12	0.00	1.310
9	BSCL2	22.1	Male	23.4	Metformin	9.3	1.1	64.66	1.58	−0.30	1.440
10	BSCL2	25.7	Female	19.9	Insulin, linagliptin	8.9	0.8	25.46	0.86	1.60	1.331
11	BSCL2	20	Female	18.2	Diet	12.3	1.9	32.31	0.65	1.20	1.234

NA = not available. BMI = body mass index. Normal values: leptin 3.7–11.1 (female) and 2.0–5.6 ng/mL (male); sclerostin 12–29 pmol/L.