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Original Article

Bone Mineral Density in Sheehan's Syndrome; Prevalence of Low Bone Mass and Associated Factors

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Abstract

Hypopituitarism is a known cause of bone mineral loss. This study aimed to evaluate the frequency of osteopenia and osteoporosis in patients with Sheehan's syndrome (SS) and to determine the risk factors. This is a retrospective study of 60 cases of SS that have had a bone mineral density (BMD) measurement. Clinical, biological, and therapeutic data were collected. The parameters of osteodensitometry at the femoral neck and the lumbar spine of 60 patients with SS were compared with those of 60 age-, height-, and weight-matched control women. The mean age at BMD measurement was 49.4 ± 9.9 yr (range: 25–76 yr). The mean duration of SS was 19.3 ± 8.5 yr (range: 3–41 yr). All patients had corticotropin deficiency and were treated with hydrocortisone at a mean daily dose of 26.3 ± 4.1 mg. Fifty-seven patients (95%) had thyrotropin deficiency and were treated with thyroxine at a mean daily dose of 124.3 ± 47.4 µg. Thirty-five of the 49 patients, aged less than 50 yr at diagnosis and having gonadotropin deficiency (71.4%), had estrogen–progesterone substitution. Osteopenia was present in 25 patients (41.7%) and osteoporosis in 21 (35.0%). The BMD was significantly lower in the group with SS than in the control group ($p < 0.001$). The odds ratio of osteopenia–osteoporosis was 3.1 (95% confidence interval: 1.4–6.8) at the femoral neck and 3.7 (95% confidence interval: 1.7–7.8) at the lumbar spine. The lumbar spine was more frequently affected by low bone mineral mass ($p < 0.05$). The duration of the disease and the daily dose of hydrocortisone were independently and inversely associated with BMD at the femoral neck. The daily dose of thyroxine was independently and inversely associated with BMD at the lumbar spine. Estrogen–progesterone replacement therapy was not associated with BMD. Low bone mineral mass was very common in patients with SS. The lumbar spine was more frequently affected. The duration of the disease and the doses of hydrocortisone and thyroxine were involved in bone mineral loss.

Key Words: Hormone replacement therapy; hypopituitarism; osteoporosis; Sheehan's syndrome.

Introduction

Sheehan's syndrome (SS) is a pituitary failure caused by pituitary infarction, which is generally secondary to a postpartum hemorrhage *(1)*. Its prevalence is much higher in developing countries than in developed ones. It varied from 3.1% of women in India in 2005 to 5.1/100,000 in Iceland in 2009 *(2)*. Its prevalence is decreasing thanks to the improvement of obstetric care *(2)*. SS is still an important cause of hypopituitarism in Tunisia *(3)*.

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Ethical standards: The study protocol was approved by the authors' hospital ethics committee.
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Hypopituitarism is a known cause of osteoporosis that can be explained by somatotropic and gonadotropic failure *(4–6)* and by excessive doses of replacement therapy with hydrocortisone or thyroxine. As only a few studies investigated bone mineral density (BMD) in SS *(7–10)*, the present study aimed to evaluate the frequency of osteopenia and osteoporosis in patients with SS in comparison with a healthy control group and to determine the risk factors of low bone mineral mass.

Subjects and Methods

Subjects

This is a retrospective study concerning all the women with SS explored and treated at our tertiary referral hospital who have had a BMD measurement during follow-up. The diagnosis of SS was based on the presence of a hormonally confirmed pituitary failure and the patient's history of a profound bleeding delivery. Other causes of hypopituitarism were ruled out by clinical and imaging data. The 60 patients with SS were compared to 60 age-, height-, and weight-matched healthy control women. The controls were recruited as control volunteers for our previous studies *(11)* and gave their informed consent. Neoplastic, bone, chronic rheumatic, renal, digestive, and inflammatory diseases, and use of drugs likely to affect BMD (barbiturates, calcium, vitamin D, biphosphonates, etc.) were exclusion criteria. In addition, the control population had no personal history of pathological fracture and endocrine disease and did not receive glucocorticoid or hormonal therapy.

Methods

The following data were collected:

- clinical data: age, parity, age at delivery, age at diagnosis of SS, impaired axes, received treatment (dose and duration), history of bone fracture, smoking, weight, and height;
- biological data: serum calcium, phosphorus, and free thyroxine (FT4) at follow-up; and
- results of osteodensitometry.

The average daily doses of hydrocortisone and thyroxine were calculated for each patient as duration-weighted. The BMD was measured in all patients by dual-energy X-ray absorptiometry (Lunar Prodigy, GE Healthcare, London, UK) at 2 sites: the lumbar spine L1–L4 and the femoral neck. All measurements were made with the same instrument and the same software between 2005 and 2010. *T*- and *Z*-scores were determined according to the Italian specific reference database that was used for geographic and sociocultural considerations.

In women aged 50 yr or more, BMD was considered normal if the *T*-score was equal to or higher than –1.0 standard deviation (SD). Osteopenia was defined as a *T*-score between –1.0 SD and –2.5 SD. Osteoporosis was defined as a *T*-score equal to or less than –2.5 SD. *Z*-score was used in those aged less than 50 yr.

Statistical Analysis

Our patients' BMD data were compared with those of the control population; then, the clinical, biological, and therapeutic data were studied in the group of patients with SS to determine the risk factors of low bone mineral mass. These data were analyzed using the SPSS 11.5 program (SPSS Inc., Chicago, IL). All results were expressed as averages ± SD for quantitative variables and frequencies and percentages for qualitative variables. Student's *t* test was used to compare averages between independent groups (normality of data has been verified using the Kolmogorov and Smirnov test, and equality of variances has been verified using Levene's test). Pearson's chi-square and Fisher's exact tests were used to compare proportions between independent groups. McNemar's test was used to compare proportions of bone mineral loss between the spine site and the femoral one. Ninety-five percent confidence interval (CI) and OR were calculated using Cornfield's method. The linear correlation between two continuous variables was studied by Pearson's correlation coefficient. Multivariate regression used multiple linear regression backward method. A p value less than 0.05 was considered as significant.

Results

The mean age at BMD measurement was 49.4 ± 9.9 yr (range: 25–76). The mean duration of SS was 19.3 ± 8.5 yr (range: 3–41 yr). The diagnosis delay, that is, the time that elapsed between the obstetric event and the diagnosis, was 8.1 ± 7.3 yr (range: 1–31). The mean parity was 3.5 ± 2.5 (range: 1–11). The serum calcium and phosphorus levels were normal in all patients (94.1 ± 4.3 mg/L and 34.4 ± 9.3 mg/L, respectively).

All patients had corticotropin deficiency and were treated with hydrocortisone. The daily dose of hydrocortisone was usually 30 mg until 2000–2005 and was then reduced to 20 mg. The mean dose was 26.3 ± 4.1 mg/d. Fifty-seven patients (95%) had thyrotropin deficiency and were treated with thyroxine. The mean daily dose was 124.3 ± 47.4 µg. The mean FT4 level during follow-up was 10.0 ± 3.1 ng/L (range: 0.4–17.1, normal: 7.1–19.4 ng/L). An overdose of thyroxine was noted in one case and an underdose in 3 cases (5%). Fifty-seven patients (95%) had gonadotropin deficiency. Thirty-five of the 49 patients, aged less than 50 yr with gonadotropin deficiency (71.4%), had estrogen–progesterone substitution. Different types of estrogen have been used: oral conjugated equine estrogen or percutaneous 17 beta-estradiol gel. The mean duration of estrogen–progesterone replacement therapy was 7.3 yr (range: 1–20). Somatotropin deficiency was diagnosed in the 7 cases that had growth hormone (GH) measurement under insulin stimulation test. None of the patients received a GH replacement therapy. Diabetes insipidus was present in 1 patient and this patient was treated with desmopressin. None