Clinical Investigations

Bone Marker Alterations in Patients with Type 1 Gaucher Disease

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Abstract. Bone involvement is one of the most disabling aspects of type I Gaucher disease and its pathophysiology is still not well understood. As an invasive procedure, bone biopsies are not appropriate in a large population study. The development of sensitive bone resorption and formation tests have allowed the authors to study bone metabolism in a noninvasive manner in a group of type I Gaucher patients. Ten type I Gaucher adult patients with mild-to-severe bone disease were evaluated. Bone mineral density and markers of bone formation (total alkaline phosphatase and isoenzymes, carboxyterminal propeptide of type I procollagen, osteocalcin) and resorption (carboxyterminal telopeptide of type I collagen, urinary hydroxyproline, free-deoxypyridinoline and calcium) were measured in patients and in a control group, matched for sex and age. In Gaucher patients, carboxyterminal propeptide of type I procollagen (PICP), a bone formation index, was significantly lower compared with normal subjects (mean 101.17 ng/ml vs 140.75 ng/ml, P = 0.038), and analysis of bone resorption indexes showed a significant increase (mean 4.24 ng/ml vs 2.87 ng/ml, P = 0.012) of serum carboxyterminal telopeptide of type I collagen (ICTP). No significant differences were observed in osteocalcin, alkaline phosphatase, and urinary hydroxyproline. Bone mineral density revealed osteopenia in six patients, with a mean Z-score of −1.04. It was not possible to show a relationship between sex, splenectomy status, age, weight, spleen, and liver volume and bone density, expressed as a Z-score nor a correlation between Z score and severity of skeletal disease. Results have shown a predominance of the resorption phase in the bone metabolism of Gaucher patients. These markers could be useful in monitoring the effect of enzyme replacement therapy on Gaucher disease skeletal involvement.

Key words: Gaucher’s disease — Skeletal involvement — bone markers — Carboxyterminal propeptide of type I procollagen — collagen

Type 1 Gaucher disease (GD1) is one of the most common sphingolipidosis. It is caused by a deficiency of the lysosomal enzyme, acid beta-glucosidase, which leads to an accumulation of glucocerebrosides within the cells of the reticuloendothelial system [1]. Clinical signs include hepatosplenomegaly, pancytopenia, and osteolytic and osteopenic degeneration of the skeleton. Bone involvement is probably the most disabling aspect of GD1 and is the result of five specific processes: medullary expansion, failure of bone remodelling, diffuse or localized bone loss, osteosclerosis, and osteonecrosis and bone crisis [1–3]. The pathophysiology of skeletal involvement is still not well understood [3].

In a large study of GD1 skeletal manifestations, Stowens et al. [4] showed that in seven patients who underwent a bone biopsy there was a relative increase of bone resorption compared with bone formation. A histomorphometric analysis of bone tissue analysis could be useful to obtain information on bone metabolism in Gaucher disease, but this method is limited by the invasive nature of the procedure. In order to find new sensitive and noninvasive markers to study the bone metabolism of GD, we analyzed the concentration of serum and urinary markers for bone formation and resorption [5] as well as the correlation between the severity of skeletal involvement and bone mineral density (BMD) in a group of GD1 patients.

Material and Methods

Patients

Ten adult GD1 patients (5 females, 5 males) who attended our clinic for the first time were selected for the study. Their average age was 33.2 years (range, 25–40 years); mean age at diagnosis was 24.7 years. They were evaluated through laboratory and instrumental investigations before starting enzyme replacement therapy (ERT). No patient had previously received medications known to modify bone homeostasis (i.e., oral corticosteroids, fluoride, calcitonin, or bisphosphonates).

Organ Volume Assessments

Liver and spleen volumes were determined by CT scan as described elsewhere [6]. They were expressed in absolute value.
and as the fold increase over that predicted for normals, with the assumption that the normal weight of the liver is 2.5% of body weight and the normal weight of the spleen is 0.2%.

**Skeletal Evaluation**

According to Herman’s et al.’s [7] modified classification for staging bone involvement [8], patients were divided into 3 groups on the basis of severity of skeletal symptomatology: group 1 with mild involvement (Herman score 1–2), group 2 with moderate involvement (Herman score 3–4), and group 3 with severe involvement (Herman score 5).

**Bone Mineral Density**

BMD was measured at the lumbar spine (L1-L4) using dual energy X-ray absorptiometry (DEXA) (Hologic QDR 1000 scanner). T score (BMD standard deviation from the normal mean value of the bone mass peak in a young healthy population of the same sex) and Z score (the difference between the measured value and the normal mean value for age and sex, divided by the SD) were analyzed in all the subjects. In one patient, L2 was not analyzed because of partial collapse of the vertebral body, so the BMD is the result of the sum of L1-L3-L4. Z score was used to analyze the relationship between BMD and other patient characteristics.

**Laboratory Methods**

The following serum laboratory tests were performed after fasting overnight: calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) with bone and hepatic isoenzymes, carboxyterminal propeptide of type I procollagen (PICP), carboxyterminal telopeptide of type I collagen (ICTP), osteocalcin, intact parathyroid hormone (PTH). The total ALP was determined using an automatic Cohas Integra Roche analyzer. ALP isoenzymes were separated by electrophoresis in an agarose gel (HELENA, Beaumont, TX); PICP and ICTP were detected using a radioimmunoassay method (Orion Diagnostica) as was osteocalcin (Diagnostic Systems Laboratories); intact PTH was determined by radioimmunometric method (Diagnostic Systems Laboratories).

The urinary excretion of Ca, P, hydroxyproline, and free-deoxypyridinoline, normalized on creatinine excretion, was determined on the second morning void (2-hour fasting). Hydroxyproline was measured using high performance liquid chromatography (HPLC) by a fluorimetric detector. Free deoxypyridinoline was measured by competitive immunoassay using a monoclonal antibody method (Pyrilinks-D, Metra Biosystem).

**Controls**

In 10 healthy adult subjects matched for sex and age, the same biochemical markers were measured.

**Statistics**

Bone turnover indexes are presented as means (±SD); for statistical analysis, Student’s two-sided t-test was used; P < 0.05 was considered significant.

The influence of dichotomous variables (e.g., sex and splenectomy status) on bone density expressed as a Z-score was analyzed by one-way analysis of variance (ANOVA). Correlations were used to find the effect of continuous variables (e.g., age, weight, spleen, and liver volumes) on bone density. The effects that all the above-mentioned variables have on bone density were evaluated by multiple regression analysis. One-way ANOVA was used to evaluate the relationship between bone density Z-scores and severity of skeletal involvement (mild vs moderate vs severe). Statistical analyses were performed using SPSS 9.0 for Windows.

**Results**

The clinical features of the Gaucher population are reported in Table 1. Data concerning serum and urinary