Bone mineral density and risk of fractures in aging, obese post-menopausal women with type 2 diabetes. The GIUMO Study

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ABSTRACT. Background and aims: Type 2 diabetes mellitus (DM) has a high prevalence in aging obese postmenopausal women. It is not clear whether or not diabetes produces an increase in bone mineral density or an increase in fracture rates. Objective: The main objective of this study was to investigate whether type 2 DM produces a higher prevalence of vertebral, hip and non-vertebral fractures in obese postmenopausal Caucasian women. A secondary objective was to study the influence of DM in quantitative ultrasound measurements of the heel (QUS) and bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA), in both lumbar spine (L2-L4) and proximal femur. Method: This study was a prospective cohort of 111 patients with type 2 DM and 91 control individuals (CTR) over age 65 and obese, recruited from 16 centers in Spain. Main Outcome Measures: Lateral dorsal and lumbar X-rays were performed to assess vertebral fractures. Hip and non-vertebral fractures were noted from medical records, written reports or X-ray studies. QUS measurements were made of the calcaneus and BMD measurements of the lumbar spine (L2-L4) and proximal femur. Results: Patients had higher BMD in the lumbar spine (L2-L4) than controls (0.979 g/cm² vs 0.927 g/cm², p=0.035), but we found no statistically significant differences in the proximal femur. QUS measurements showed similar values in both groups: BUA (69.3 dB/MHz vs 66.7 dB/MHz, p=0.291), SOS (1537 m/sg vs 1532 m/sg, p=0.249) andQUI (87.5 vs 83.7, p=0.153). No statistically significant differences were found in any case. There was no association between vertebral, hip and non-vertebral fractures and DM. The crude odds ratio, without adjusting was 1.045 (CI 95% 0.531 ; 2.059), and the adjusted odds ratio was 0.927 (CI 95% 0.461 ; 1.863). Conclusions: In obese postmenopausal Caucasian women, type 2 DM produces an increase in BMD of the lumbar spine without changes in BMD of the proximal femur or in QUS measurements of the heel. The prevalence of vertebral, hip and non-vertebral fractures did not increase in type 2 DM. (Aging Clin Exp Res 2009; 21: 27-32) ©2009, Editrice Kurtis

INTRODUCTION

Low bone mineral density is often mentioned as a complication of DM. Most studies indicate that it is a complication for patients with insulin-dependent DM, especially those with poor metabolic control (1). However, conflicting findings have been reported in patients with non-insulin-dependent DM. Some authors report elevated (2-6), some report decreased (7-9), and others unaltered (10-12) BMD. However, less is known of the risk of fractures in diabetic patients. Some studies have found no association (13, 14), whereas other larger prospective studies have found strong associations between DM and the risk of fracture (15-18). For instance, the Study of Osteoporotic Fractures, a large prospective study of older women, found that DM was associated with increased risk of foot (16) and proximal humerus fracture (17), but not of hip fracture (15). However, two prospective Norwegian studies found associations between DM and risk of hip fracture (18, 19). Recently, in elderly nursing home patients with type 2 DM, it has been reported that, despite higher

*For the list of members, see Appendix.

Key words: Bone mineral density, diabetes mellitus, fractures, obesity, osteopenia, osteoporosis, postmenopausal women, quantitative ultrasound.

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bone mass and lower bone turnover, hip fracture risk is comparable with that of women without DM (20). Conversely, there are few studies that have estimated BMD by QUS and the risk of fractures in DM.

The objectives of this study were to determine (1) whether diabetic post-menopausal Caucasian women had a higher risk of fragility fractures and (2) whether type 2 DM was associated with a higher BMD as estimated by QUS of the heel and by DXA of the lumbar spine and proximal femur.

MATERIALS AND METHODS

Patients

Patients included women aged more than 65 years old who were suffering from obesity and type 2 DM. The control group (CTR) was composed of women of similar age and weight who did not suffer from DM. They were usually friends or neighbors of the patients and came along with them to the study. Exclusion criteria were known current malignancies or completed treatment for any type of malignancy during the past year, hypercalcemia (>2.6 mmol/L), advanced kidney and/or liver dysfunction (defined as serum creatinine levels above 1.9 mg/dL and liver transaminases >3.5 times higher than the upper limit of normal), bilateral hip replacements, history of total gastrectomy, decompensated heart failure (NYHA class 4), chronic alcoholism, known osteomalacia, untreated thyroid disease, or chronic steroid treatment with more than 5 mg prednisolone equivalent/day.

All participants were informed about the aims of the study and gave their written consent. The study was performed following the Good Clinical Practice guidelines (http://www.wma.net/e/policy/b3.htm) and was carried out in accordance with the ethical principles laid down in the revision of the Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm). The study protocol was approved by the Ethics Committee of the Hospital University Insular, Canary Islands.

Physical examination

A complete physical examination of all patients was performed. Height and weight were measured to obtain the body mass index (BMI; calculated as weight [kg]/height [m]) of each subject. Height was measured without shoes, and weight with light clothing was estimated on a balance scale. Post-menopausal women were defined as those who had had their last menstrual period at least 1 year before, in accordance with the clinical definition of the World Health Organization (21).

Handling and processing of blood samples and laboratory analysis

Fasting blood samples were drawn and specimens allowed to clot at room temperature for 15 min. They were then immediately centrifuged and measured by an automatic autoanalyzer.

Measurements

QUS

All subjects had QUS measurement of the calcaneus, performed on a Sahara clinical sonometer (Hologic, Bedford, MA). The system consists of two unfocused transducers mounted coaxially on a monitor calliper. One transducer acts as the transmitter and the other as a receiver. The transducers are acoustically coupled to the heel using soft rubber pads and an oil-based coupling gel. The Sahara device measures both broadband ultrasound attenuation (BUA) and speed of sound (SOS) at a fixed region of interest in the mid-calcaneus. BUA and SOS results are combined to provide the quantitative ultrasound index (QUI) with the formula:

\[ \text{QUI} = 0.41 \times (\text{BUA} + \text{SOS}) - 571 \]

DXA

BMD was measured by DXA (Hologic QDR-1000, Bedford, MA) at the lumbar spine (L2-L4) and proximal femur of all patients. The precision of the techniques and reference values for the Spanish population have been published elsewhere (22, 23).

X-rays and fractures

Lateral dorsal and lumbar X-rays were performed for all study participants. Diagnosis of vertebral fractures was established with the criteria of Genant (24) on a Morpho-Express device (25). Non-vertebral fractures were noted from written reports from radiologists, emergency reports, and X-rays provided by the patients, and after examining their medical records. In both patients and controls, fractures were recorded only if properly documented and due to a minor trauma, as long as a record existed for each patient (with the exception of childhood fractures, which were excluded).

When height and weight were measured, participants wore indoor clothing and no shoes. Body mass index (weight in kg/height in m²) was calculated as a measure of obesity.

Statistical methods

For diabetic patients and controls, categorical variables were summarized in percentages and numerical ones either in means and standard deviations or in medians and percentiles 5 and 95, according to the hypothesis of normality. Proportions were compared with the chi-square test and, when not possible, with Fisher’s exact test. Means were compared with Student’s t-test and medians by means of Wilcoxon’s test for independent samples. For the markers DXA and ultrasound measurements the age-fitted means fitted by age were obtained and compared by the corresponding F-test. A contrast of hypothesis was considered to be statistically significant when the corresponding p-value was lower.