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Bone Mineral Density Measured by Dual X-Ray Absorptiometry in Spanish Patients with Insulin-Dependent Diabetes Mellitus*

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Abstract. Previous studies suggest that low bone mass is a potential complication of insulin-dependent diabetes mellitus. Nevertheless, the factors that influence diabetic osteopenia are not well established. In order to evaluate the prevalence and magnitude of diabetic osteopenia and its association with clinical and metabolic variables, we studied 94 consecutive patients with insulin-dependent diabetes mellitus. Their age ranged from 20 to 56 years and duration of diabetes varied from 1 to 35 years. Bone mineral density (BMD) was measured by dual X-ray absorptiometry at lumbar spine and proximal femur and the values were expressed as z-score. The presence and extent of microvascular complications, degree of metabolic control, and other risk factors for osteoporosis were recorded and some biochemical markers of bone metabolism were assessed. Diabetic patients showed reduced BMD in all sites (lumbar spine: -0.89 ± 1.21; femoral neck: -0.99 ± 1.24; Ward triangle: -1.05 ± 1.24; $P < 0.0001$). Of the 94 patients 19.1% met diagnostic criteria for osteoporosis. BMD correlated with body mass index in all sites and with the duration of disease in Ward's triangle. Presence and extent of diabetic complications were associated with lower BMD, as was smoking. No correlation was found between BMD and biochemical markers. In conclusion, osteopenia is a common complication in patients with insulin-dependent diabetes mellitus. Microvascular complications are a critical point in the progression of diabetic osteopenia. Other risk factors for osteoporosis (nutritional status and smoking) must be taken into account.

Key words: Insulin-dependent diabetes mellitus — Bone mineral density — Dual X-ray absorptiometry — Bone turnover markers — Microvascular complications.

Although osteopenia is not generally regarded as one of the major complications of diabetes mellitus, there is some evidence that diabetic patients have lower bone mineral density (BMD) than normal subjects [1–4]. However, the relationship between insulin-dependent diabetes mellitus (IDDM) and reduced BMD is not well established. Several pathogenic possibilities have been proposed such as bone microangiopathy [5, 6], insulinopenia [7], impaired regulation of mineral metabolism [8, 9], alterations in local factors that regulate bone remodeling [10], and even an intrinsic disorder associated with IDDM [11]. However, the complete picture of the pathogenesis of diabetic bone disease is still unknown and it has become clear that no single mechanism can explain all the observed phenomena.

A significant reduction in BMD has been reported in clinical studies using single photon absorptiometry [12–14], but in the few studies carried out by dual X-ray absorptiometry (DXA) there are conflicting results [15–17]. Moreover, the presence, extent, and localization of diabetic osteopenia are not well established. Furthermore, the influence of sex, duration of disease, degree of metabolic control, insulinization level, nutritional status, risk factors for osteoporosis, as well as long-term microvascular complications is largely unknown.

The aim of the current study was to evaluate the BMD at lumbar spine (LS) and proximal femur by DXA in IDDM patients and to analyze its possible relationship with a set of clinical and metabolic variables.

Patients and Methods

We studied 94 consecutive outpatients (45 males, 49 females) with IDDM defined in accordance with the criteria of the World Health Organization (WHO) [18] who attended the diabetic clinic. Their age ranged from 20 to 56 years (mean ± SD, 30 ± 9 years). The mean body mass index was 23.9 ± 3.8 kg/m^2. The duration of disease varied from 1 to 35 years (12 ± 8 years) and the insulin dose from 23 to 78 UI/day (42 ± 9 UI/day). Metabolic control was assessed by glycosilated hemoglobin (HbA_{1C}) measurements (automated high performance technique, Kyoto Domchi kagaku, Japan). The normal range for HbA_{1C} in our laboratory was 3.9–6.0%. The mean HbA_{1C} for the last year (three to four determinations) was calculated for each patient and this value was used for statistical analysis (8.5 ± 1.8%, range 4.6–13.0%).

The presence of chronic complications of diabetes was evaluated. Ophthalmologic exploration was performed using funduscopy and retinal fluorescein angiography and then the patients were placed into three groups: no retinopathy, background/preproliferative retinopathy, and proliferative retinopathy. Diabetic nephropathy was assessed by repeated determinations of 24-hour urine microalbuminuria, measured by immunoturbidimetry, and then the patients were divided into three groups: no nephropathy (UALB <30 mg/day), microalbuminuric/preclinical nephropathy (UALB between 30–300 mg/day) and overt nephropathy (UALB >300 mg/day). Patients with creatinine levels greater than

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220 μmol/liter were excluded. The presence of peripheral or autonomic neuropathy were analyzed by clinical history and physical examination.

All women were premenopausal and eumenorrheic at the time of the study. Furthermore, none of the diabetic patients suffered from any other medical condition or were taking any medication thought likely to interfere with their bone metabolism. Alcohol consumption was not excessive (<40 g/day) and all had an appropriate degree of both physical activity and daily calcium intake.

The BMD was assessed by dual X-ray absorptiometry (Hologic QDR1000, Hologic Inc., Waltham, MA, USA). Measurements were made of the usual L2–L4 area at the LS, femoral neck (FN), and Ward's triangle (WT). The values were expressed as z-score (number of SD adjusted by age and sex) in comparison with a reference healthy Spanish population (1221 males and 1331 females) [19]. The precision of measurement with repositioning was <2% for both spine and proximal femur BMD. Osteoporosis was defined as a value for BMD 2.5 SD or more below the young adult mean at spine or proximal femur according to recent WHO criteria [20].

Fasting morning blood samples were drawn for determinations of serum concentrations of calcium, phosphorus, creatinine, alkaline phosphatase, and tartrate-resistant acid phosphatase using an autoanalyzer (Hitachi 704 autoanalyzer, Tokyo, Japan). Intact parathyroid hormone (PTH-I) (IRMA, Incstar, Stilwater, MN, USA) and osteocalcin (BGP) (RIA, Incstar, Stillwater, MN, USA) were determined using commercial kits.

The results were expressed as mean ± standard deviation (SD) except when indicated. One sample *t*-test was used to assess the difference between the mean BMD z-score at each site and zero. The significance of the difference between groups was determined with analysis of variance. A linear correlation test was used to determine the relationship between BMD values and other variables. A probability of $P < 0.05$ was taken to indicate significant differences.

Results

The BMD values expressed as z-score were lower in diabetic patients when compared to reference standards in all sites (LS: −0.89 ± 1.21; FN: −0.99 ± 1.24; TW: −1.05 ± 1.24; $P < 0.0001$). The percentages of the BMD decrease in different sites were LS 9.1%, FN 12.0%, and WT 16.3%. No significant differences were found when comparing BMD values between the measurement sites. Eighteen diabetic patients (19.1%) were considered to be osteoporotic; 9 men and 9 women. Male patients showed a lower BMD than female at the lumbar spine (−1.17 ± 1.04 versus −0.64 ± 1.30; $P < 0.05$) but no difference was found in the FN or the WT. A weak negative correlation was found between the duration of diabetes and the BMD (z-score) in the Ward's triangle ($r = -0.315$; $P < 0.002$). No correlation was found between mean HbA_{1C} levels and the BMD in any region. The body mass index had a direct correlation with the BMD in LS ($r = 0.354$, $P < 0.001$), FN ($r = 0.377$, $P < 0.001$), and WT ($r = 0.229$, $P < 0.026$). The insulin dose (U/day) did not correlate with the BMD measurements.

Thirty-six (38%) diabetic patients had some degree of chronic diabetic complications; 31 presented retinopathy, 19 had nephropathy, and 9 had neuropathy. According to predefined criteria, we calculated the mean z-score values in subgroups of patients with retinopathy and nephropathy. Overall, patients with more advanced complications showed lower BMD. These results are presented in Figures 1 and 2. Patients with autonomic or peripheral neuropathy also showed lower BMD values. Diabetic patients who smoked (41/94) had a lower BMD than nonsmokers in FN (−1.29 ± 1.02 versus 0.76 ± 1.23; $P < 0.04$) and TW (−1.35 ± 1.15 versus −0.81 ± 1.16; $P < 0.03$).

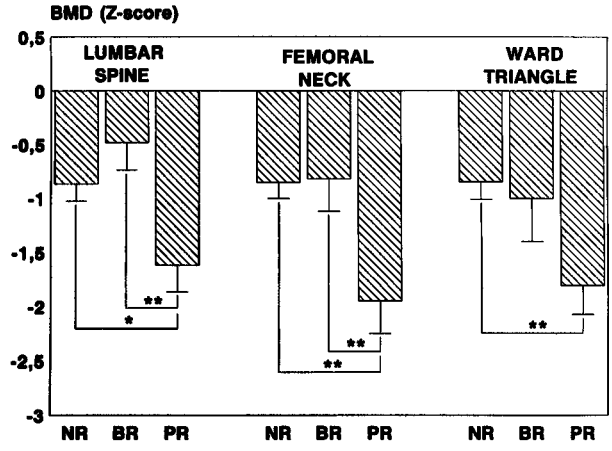

Fig. 1. Bone mineral density values (z-score) in insulin-dependent diabetic patients without retinopathy (NR), with background/preproliferative retinopathy (BR), and with proliferative retinopathy (PR). Data are shown as mean ± SEM. $*P < 0.05$; $**P < 0.01$.

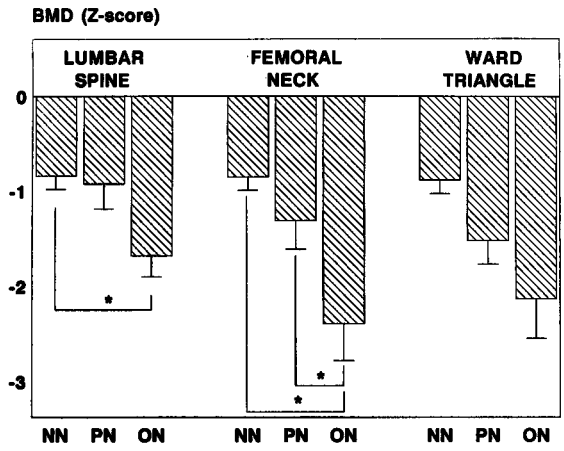

Fig. 2. Bone mineral density values (z-score) in insulin-dependent diabetic patients without nephropathy (NN), with microalbuminuria/preclinical nephropathy (PN), and with overt nephropathy (ON). Data are shown as mean ± SEM. $*P < 0.01$.

Mean values of serum calcium, phosphorus, alkaline phosphatase, tartrate-resistant acid phosphatase, BGP, and PTH-I were all found to be in normal range according to our laboratory (Table 1) and no correlations were found between biochemical markers and BMD measurements.

Discussion

Our results highlight the magnitude of diabetic osteopenia, thanks to the significant advance that the DXA offers in the assessment of BMD [21]. Hence, approximately 20% of the study population met diagnostic criteria of osteoporosis according to the new definition established by WHO [20], and both types of bone (cortical and trabecular) were similarly affected. Our findings contrast with previous reports [15, 16, 22] which showed minor changes in BMD. Such controversial data could be explained because of differences in the clinical profile of our patients: longer duration of diabetes, lower body weight, prevalence of risk factors for

Table 1. Biochemical markers of bone metabolism

	Mean ± SD	Range	Normal values
Calcium	2.37 ± 0.10	2.02–2.62	2.13–2.63 mmol/liter
Phosphorus	1.26 ± 0.19	0.84–1.81	0.81–1.61 mmol/liter
Alkaline phosphatase	165 ± 49	57–296	100–280 UI/liter
T-R acid phosphatase	6.16 ± 2.84	2.80–13.70	4.0–7.6 UI/liter
Osteocalcin	1.9 ± 0.3	0.1–5.4	1.8–6.6 μg/liter
PTH-I	19 ± 16	8–53	10–55 ng/liter

T-R: tartrate-resistant acid phosphatase; PTH-I: parathyroid hormone, intact molecule

osteoporosis, and more advanced long-term complications of insulin-dependent diabetes mellitus. Furthermore, we found a lower spinal BMD in male patients and this finding had been scarcely reported.

The duration of disease seems to have an obvious influence on the BMD, as reported previously [16, 17], although a significant negative correlation was only found in the Ward's triangle in our study. The body mass index correlated with the BMD in all measurement sites. This is a common finding that agrees with the protective effect of body weight on the BMD. In fact, an increased BMD has been described in obese noninsulin-dependent patients [23–25]. Hence, the insulin-dependent diabetic population is not an exception, and therefore, this relationship addressed the importance of nutritional status in diabetic osteopenia.

We were unable to demonstrate any relationship between the degree of metabolic control and BMD. However, hyperglycemia has been implicated in the occurrence of other complications of diabetes and some studies suggest that hyperglycemia could also affect the osteoblastic function [26]. Probably, a more long-term evaluation of metabolic control would have allowed us to find this relationship, as addressed by Olmos et al. [16] and therefore clarify the precise role of metabolic control on BMD. Moreover, the insulinization level does not seem to give any additional information regarding the risk for osteopenia.

The presence and extent of microangiopathic complications were sharply associated with reduced BMD. Thus, patients with proliferative retinopathy and overt nephropathy showed a more significant osteopenia. Also, patients with neuropathy showed similar findings. The effect of microangiopathy on bone metabolism is not clear [27]. However, our data suggest that the development of microvascular complications is a critical point in the progression of diabetic osteopenia.

The effect of other risk factors for osteoporosis must be taken into account. In this sense, the negative influence of smoking on BMD in our diabetic population may be of major relevance. The deleterious effect of smoking seen in healthy young adults [28] can be exaggerated in diabetic patients.

Although in previous reports [29] the low turnover of bone remodeling in diabetic patients has been addressed, and in histomorphometrical studies [30] diabetic osteopenia has been considered as a slow remodeling disorder, no correlation between the BMD and the biochemical markers could be found in our study. It seems clear that it is not possible to identify diabetic patients at high risk for osteopenia on the basis of information provided by a single measurement of these parameters.

In summary, our results suggest that diabetic osteopenia is truly a prevalent complication of insulin-dependent diabetes mellitus. Duration of disease, nutritional status, presence and extent of microvascular complications, and the association with other risk factors for osteoporosis are the main circumstances implicated. In the future, with longer survival of insulin-dependent diabetic patients it will be necessary to investigate if these disturbances are associated with a high prevalence of fragility fractures, which are the endpoint of osteoporotic disease.

References

1. Selby PL (1988) Osteopenia and diabetes. Diabetic Med 5: 423–428
2. Bouillon R (1991) Diabetic bone disease. Calcif Tissue Int 49:155–160
3. Compston JE, Smith EM, Matthews C, Schofield P (1994) Whole body composition and regional bone mass in women with insulin-dependent diabetes mellitus. Clin Endocrinol 41: 289–293
4. Seino Y, Ishida H (1995) Diabetic osteopenia: pathophysiology and clinical aspects. Diabetes Metab Rev 11:21–35
5. Burkhardt R, Moser W, Bartl R, Mahl G (1981) Is diabetic osteoporosis due to microangiopathy? Lancet i:844
6. Mathiassen B, Nielsen S, Johansen JS, Hartwell D, Ditzel J, Rodbro P, Christiansen C (1990) Long-term bone loss in insulin-dependent diabetes patients with microvascular complications. J Diabetic Complications 4:145–149
7. Craig R, Rowe D, Kream B (1984) Regulation of bone collagen synthesis and procollagen mRNA levels by insulin. Calcif Tissue Int 36:557–561
8. Muñoz-Torres M, Díaz Pérez de Madrid J, Escobar Jiménez F, Ortego N, González A, García-Calvente C (1991) Alterations of mineral metabolism in type 1 (insulin-dependent) diabetic patients (abstract) Diabetologia 34(suppl 2):A164
9. Verrotti A, Chiarelli F, Capani F, Morgese G (1992) Calcium metabolism in type I diabetes mellitus. Diabetes Nutr Metab 5:231–236
10. Brownlee M (1990) Collagen changes in diabetes: basic aspects and clinical implications. In: Belfiore F, Molinatti GM, Reaven GM (eds) Tissue-specific metabolic alterations in diabetes. Karger Gmbh, Bassel, pp 54–60
11. Levin ME, Boisseau VC, Avioli LV (1976) Effects of diabetes mellitus on bone mass in juvenile and adult onset diabetes. N Engl J Med 294:241–245
12. Santiago JV, McAlister WH, Ratzan SK, Bussman Y, Haymond G, Shackelford G, Weldon VV (1977) Decreased cortical thickness and osteopenia in children with diabetes mellitus. J Clin Endocrinol Metab 45:845–848
13. Hui SL, Epstein S, Johnston C (1985) Bone mass in type I diabetes. J Clin Endocrinol Metab 60:74–80
14. McNair P (1988) Bone mineral metabolism in human type I (insulin-dependent) diabetes mellitus. Dan Med Bull 35:109–121

15. Gallacher SJ, Fenner JAK, Fisher BN, Gallacher SJ, Fenner JAK, Fisher BN, Kuin JD, Fraser WD, Logue FC, Cowan RA, Boyle IT, MacCuish AC (1993) An evaluation of bone density and turnover in premenopausal women with type 1 diabetes mellitus. Diabetic Med 10:129–133
16. Olmos JM, Perez-Castrillon JL, García MT, Garrido JC, Amado JA, González-Macías J (1994) Bone densitometry and biochemical bone remodeling markers in type 1 diabetes mellitus. Bone Miner 26:1–8
17. Kayath MJ, Dib SA, Vieira JGH (1994) Prevalence and magnitude of osteopenia associated with insulin-dependent diabetes mellitus. J Diabetic Complications 8:97–104
18. World Health Organization Study Group (1985) Diabetes Mellitus. World Health Organization Technical Reports Series No. 727, Geneva
19. Díaz Curiel M, Castro N (1992) Bone mineral density in the Spanish population measured by dual X-ray absorptiometry (DEXA) (abstract) Bone Miner 17(suppl 1):133
20. World Health Organization Study Group (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organization Technical Reports Series No. 843, Geneva
21. Hansen MA, Hassager C, Overgaard K, Marslew U, Riis B, Christiansen C (1990) Dual energy X-ray absorptiometry: a precise method of measuring bone mineral density in the lumbar spine. J Nucl Med 31:1156–1162
22. Ponder SW, McCormick DP, Fawcet HD, Tran AD, Ogelsby GW, Brouhard BH, Travis LB (1992) Bone mineral density of the lumbar vertebrae in children and adolescents with insulin-dependent diabetes mellitus. J Pediatr 120:541–545
23. Wagasuki M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T (1993) Bone mineral density measured by dual energy X-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. Bone 14:29–33
24. Rishaug U, Birkeland KI, Falch JA, Vaaler S (1995) Bone mass in non-insulin-dependent diabetes mellitus. Scand J Clin Lab Invest 55:257–262
25. van Daele PLA, Stolk RP, Burger H, Algra D, Grobbee DE, Hofman A, Birkenhager JC, Pols HAP (1995) Bone density in non-insulin-dependent diabetes mellitus. Ann Intern Med 122: 409–414
26. Verhaeghe J, Van Herck E, Visser WJ, Suiker AMH, Thomasset M, Einhorn TA, Faierman E, Bouillon R (1990) Bone and mineral metabolism in BB rats with long-term diabetes: decreased turn-over and osteoporosis. Diabetes 39:477–482
27. Mathiassen B, Nielsen S, Ditsel J, Rodbro P (1990) Long-term bone loss in insulin-dependent diabetes mellitus. J Intern Med 227:325–327
28. Ortego-Centeno N, Muñoz-Torres M, Hernandez-Quero J, Jurado-Duce A, de la Higuera Torres-Puchol J (1994) Bone mineral density, sex steroids, and mineral metabolism in premenopausal smokers. Calcif Tissue Int 55:403–407
29. Pietschmann P, Shernthener G, Woloszcuk W (1988) Serum osteocalcin levels in diabetes mellitus: analysis of the type of diabetes and microvascular complications. Diabetologia 31: 892–895
30. Goodman WG, Hori MT (1984) Diminished bone formation in experimental diabetes. Relationship to osteoid maturation and mineralization. Diabetes 33:825–831