Evaluation of Bone Metabolism and Bone Mass in Patients with Type-2 Diabetes Mellitus

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The objectives of this study were to determine whether type-2 diabetes was associated with a higher bone mineral density (BMD) in men and women and to evaluate the differences in mineral metabolism between diabetic and normal subjects by using biochemical bone turnover markers.

In this study, 52 patients (37 females/15 males) aged 41–64 with type-2 diabetes mellitus and 48 nondiabetic control subjects (34 females/14 males) were evaluated. In men, BMD was significantly higher in diabetics at the forearm ($p < 0.05$), whereas in women tended to be higher at the hip ($p=0.002$). Serum osteocalcin ($p<0.0001$), bone alkaline phosphatase (BAP) ($p<0.05$) and carboxyterminal telopeptide (CTx) ($p < 0.05$) were higher in the control group than in diabetics. In men, serum osteocalcin ($p<0.05$) and CTx ($p<0.005$) and, in women, serum osteocalcin ($p<0.0001$) and BAP ($p<0.05$) were lower in diabetic subjects.

In conclusion, our findings suggest that although bone formation is decreased in type-2 diabetes, diabetic patients are not susceptible to bone resorption. This low bone turnover can slow the rate of bone loss and cause a higher bone density than expected for their age.

Key words: type-2 diabetes mellitus ■ bone mineral density ■ bone turnover ■ osteocalcin ■ fracture risk

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INTRODUCTION

There have been conflicting reports about the skeletal involvement in patients with diabetes mellitus. Many authors described various alterations of bone mineralization in diabetic subjects by using both radiographic and photonic techniques.[1] This controversy is largely related to the complex pathophysiology of diabetes mellitus characterized by hyperglycemia and concomitant metabolic conditions due to impaired insulin secretion or diminished tissue response to insulin. The endocrine and metabolic alterations in diabetes mellitus can trigger disorders of calcium homeostasis, skeletal metabolism and bone mass. Additionally, there is disagreement upon the possible influences of gender and metabolic control and duration of diabetes on bone tissue.[2]

The prevalence of osteopenia in type-1 diabetes has been reported to be 50–55% in previous studies.[3] A reduced bone mass and an increased fracture risk have been shown to occur in type-1 diabetes mellitus.[4,5] The demineralization process involves especially trabecular bone, and the reduction in bone mass is more significant in the first five years after the onset of the disease.[6] On the contrary, in type-2 diabetes, several but not all cross-sectional studies have found normal[6,7] or elevated[8-11] bone mass, and these results are surprising given the increased fracture risk associated with type-2 diabetes.[12-14]

The objectives of this study were: 1) to determine whether type-2 diabetes was associated with a higher bone mineral density (BMD) in men and women, and 2) to evaluate the differences in mineral metabolism between diabetic and normal subjects by using biochemical bone turnover markers.

SUBJECTS, MATERIALS AND METHODS

Subjects

Fifty-eight patients attending our general internal medicine outpatient clinic (41 females/17 males) with type-2 diabetes mellitus were enrolled in a consecutive way. Diabetes was defined as self-report of diabetes previously diagnosed by a physician, use of hypoglycemic medications or fasting glucose ≥126 mg/dl (≥7.0 mmol/l) and a casual plasma glucose ≥200 mg/dl (≥11.1 mmol/l) in accordance with the American Diabetes Association criteria.[15] The exclusion criteria were insulin treatment and diseases (i.e., hyperthyroidism, Cushing's syndrome, primary hyperparathyroidism, renal failure, malabsorption), and/or medications that

might affect bone and mineral metabolism. After the exclusion of two patients with hyperthyroidism and four patients with primary hyperparathyroidism, 52 patients (37 females/15 males) aged 41–64 years (mean ± SD, 53.92 ± 6.0 years) were studied. The diabetes duration and hypoglycemic medications of patients, menstrual and menopausal state, duration and management of other disorders unrelated to diabetes were all recorded. The duration of diabetes varied from 0–240 months (57.47 ± 59.35 months). The treatment of the patients consisted of diet in 11 patients, oral hypoglycemic agent(s) in six patients, diet plus oral hypoglycemic agent(s) in 28 patients, and seven patients were newly diagnosed. Twenty-six female patients were postmenopausal and were not taking any hormone replacement therapy.

We evaluated a total of 56 nondiabetic men and women (42 females/14 males) of similar age, sex and body mass index (BMI), who attended for periodic health examination to the check-up center of our hospital. Two subjects with hyperthyroidism, and six subjects with primary hyperparathyroidism were excluded. This left 48 otherwise healthy, nondiabetic control subjects of men and women (34 females/14 males) matched by age, sex and BMI. Twenty-two of 34 female patients were postmenopausal and were not taking any hormone replacement therapy. The measurements of the control group were carried out in parallel to those in diabetic patients.

The study protocol was approved by the local ethics committee–institutional board and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki as revised in 2000.

Anthropometric and Biochemical Measurements

During the clinic visit, a medical history was obtained by a standard questionnaire. Weight was measured with a calibrated balance-beam scale with participants without shoes, and height was measured using a stadiometer. BMI—weight divided by square height (kg/m^2)—was calculated as a measure of obesity.

After an overnight fast (eight hours), blood was drawn to measure the levels of calcium, phosphorus, total alkaline phosphatase (ALP), glucose, creatinine, bone alkaline phosphatase (BAP), intact parathyroid hormone (PTH), type-1 collagen carboxyterminal telopeptide (CTx), osteocalcin (OC), type-1 collagen propeptide C (TICP). Twenty-four-hour urine samples were analyzed for urinary calcium and creatinine measurements (U-Ca and U-Cr) and spot urine samples for deoxypyridinoline measurements (DPD).

The serum levels of glucose, calcium, phosphorus, creatinine and ALP were determined by automated techniques (Roche Modular System); BAP, osteocalcin, CTx and TICP by microenzyme-linked immunosorbent assay (micro-ELISA, Tecan); intact PTH, TSH and urinary deoxypyridinoline by electrochemiluminescence immunoassay (ECLIA, Immulate 2000).

Renal function of diabetic patients was evaluated with measurements of 24-hour albuminuria by RIA (30–300 mg/24 hour was considered as microalbuminuria and >300 mg/24 hour as macroalbuminuria).

Bone Mineral Density

BMD was measured by dual-energy x-ray absorptiometry technique (DXA Hologic QDR-4500A; Hologic, Bedford, MA). DXA is the preferred technique for the evaluation of BMD because of its low radiation dose, accuracy and rapid performance.[16] BMD was measured at lumbar L1–L4 anteroposterior, femoral (neck, trochanter, intertrochanteric region, total) and forearm [one-third, mid and ultradistal (UD)] levels. Bone mass is expressed as BMD resulting from BMC (bone mineral content in grams)/area ratio (g/cm^2), T score [standard deviation (SD) from the mean value obtained in 30-year-old normal subjects] and Z score (SD from the mean value obtained in subjects of the same age and sex). The scanner was recalibrated daily using the manufacturer's software and phantom. The T scores that were -1 SD or greater were considered normal, between -1 and -2.5 SD osteopenia and less than -2.5 SD osteoporosis. BMD examinations were done in 50 diabetic and 43 control subjects at lumbar, 48 diabetic and 43 control subjects at femoral, 45 diabetic and 33 control subjects at forearm levels.

Table 1. Characteristics of study participants

	Men			Women		
Characteristic	**Nondiabetic**	**Diabetic**	**p**	**Nondiabetic**	**Diabetic**	**P**
n	14	15		34	37	
Age (years)	52.57 ± 7.39	53.67 ± 5.83	NS	52.09 ± 5.52	54.14 ± 6.61	NS
Height (cm)	164.57 ± 5.96	170.53 ± 7.85	0.03	156.24 ± 6.62	154.73 ± 5.24	NS
Weight (kg)	76.85 ± 11.51	77.66 ± 11.66	NS	73.03 ± 13.82	75.87 ± 10.85	NS
BMI (kg/m^2)	28.53 ± 4.67	26.74± 3.51	NS	29.82± 5.58	31.70 ± 4.19	NS
Menopause status (%)	–	–		66.7%	72.2%	NS
Menopause duration	–	–		38.03 ± 44.14	41.14 ± 51.63	NS

NS: not significant; BMI: body mass index

Statistical Analysis

All statistical analyses were performed with SPSS statistical software package (version 10.0, SPSS; Chicago, IL). Numerical data are expressed as mean ± SD and as a percentage in the qualitative variable. Statistical analyses were conducted separately and in combination for men and women. The distribution of variables was analyzed with the Kolmogorov-Smirnov test. To test for the difference between quantitative variables in diabetic patients and control subjects, independent sample Student's t test is used for variables that are normally distributed. Nonnormally distributed numerical data were analyzed with Mann-Whitney U test. Differences between categorical variables were analyzed by Chi square with continuity correction or Fischer's exact test where appropriate. Analysis of covariance was used to assess differences in mean BMD, osteocalcin and BAP adjusted for menopause status among female subjects. For all comparisons, P values of <0.05 were considered as statistically significant.

RESULTS

A total of 100 subjects (71 female/29 male) aged 41–64 years participated in this cross-sectional study. The mean age of diabetic subjects was 54.00 ± 6.34 years, and of nondiabetic controls 52.23 ± 6.04 years. No significant difference was present between the diabetic subjects and controls regarding age and BMI in men and women. The mean fasting blood glucose levels (FBG) of diabetic subjects were 179.80 ± 69.04 mg/dl, and the duration of diabetes was 57.47 ± 59.35 months. Twenty-six diabetic and 22 nondiabetic women were in the postmenopausal state. The mean duration of menopause in diabetic women was 41.14 ± 51.63 months, and in control subjects 38.03 ± 44.14 months. Characteristics of the subjects and controls are given in Table 1.

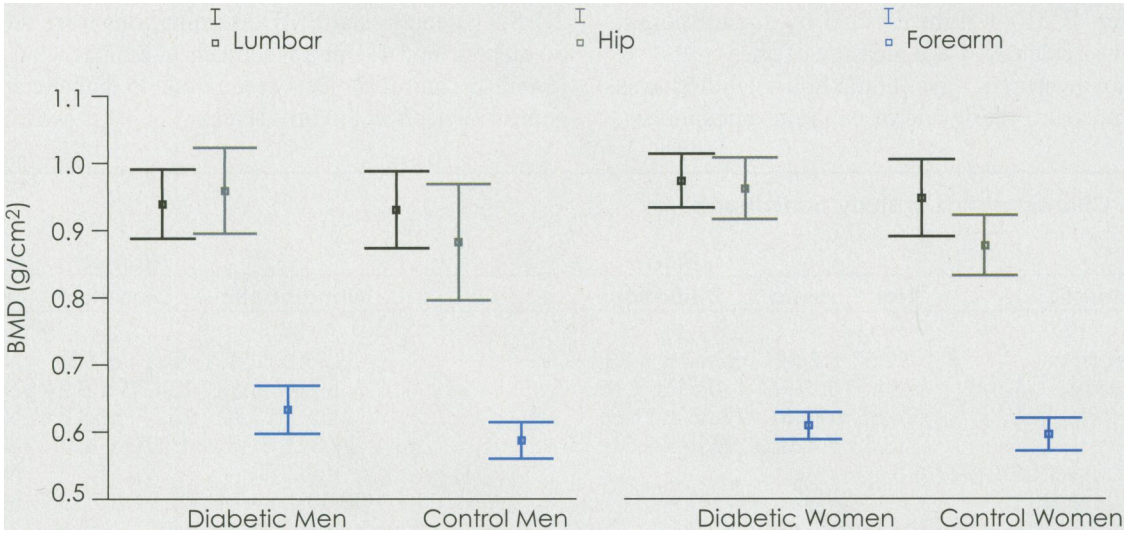
Thirty-four patients with diabetes were on oral hypoglycemic agents: four patients acarbose, 15 patients sulfonylurea (gliclazide, glimepiride, glipizide), nine patients metformin; one patient was on combination therapy with nateglinide and metformin, two patients with sulfonylurea and metformin, two patients with acarbose and sulfonylurea and one patient with acarbose and metformin. Among diabetic patients, no significant difference in BMD was found considering the modes of therapy (i.e., diet, oral hypoglycemic agent, none) (data not shown).

In the diabetic population (n=52), body weight ($p<0.01$) of all body habitus parameters yielded the highest correlation coefficients with BMD at the hip, and in the control group at the hip ($p<0.01$) and forearm levels ($p<0.05$). In diabetics, age correlated negatively and significantly with BMD at the hip ($p=0.01$).

Table 2 and Figure 1 summarize associations between diabetes and BMD at the hip, lumbar spine and forearm in men and women separately. In men, BMD was significantly higher in diabetics at the forearm ($p<0.05$)—but not different at the lumbar spine and the femoral neck—than that of control subjects. However, in women, BMD was significantly higher in diabetics at the hip ($p<0.01$), but there was no association between diabetes and BMD at lumbar or forearm levels. The association between diabetes and BMD at the hip remained statistically significant after further adjustments for menopause status ($p<0.05$).

Measurements of bone turnover markers for both groups according to their diabetic status are summa-

Figure 1. BMD (gr/cm²) at lumbar, femoral and forearm levels according to diabetes status in men and women



rized in Table 3. No significant differences were found in measurements of serum calcium, phosphorus, ALP, intact PTH, TICP, urinary DPD and 24-hour urine calcium and phosphorus between diabetic and nondiabetic subjects. In the controls, serum osteocalcin ($p<0.0001$), BAP ($p<0.05$) and CTx ($p<0.05$) were significantly higher than the diabetics. When the turnover markers of men and women were evaluated separately, in men levels of serum osteocalcin ($p<0.05$), and CTx ($p<0.005$) were significantly higher in controls, whereas in BAP level, there was no significant difference between the two groups. In women, no significant difference was found in the CTx level between the two groups, but there were significant differences in the levels of BAP ($p<0.05$) and serum osteocalcin ($p<0.0001$). These differences persisted after further adjustments for menopause status (Figure 2).

DISCUSSION

The effect of diabetes on BMD is still not clear. In type-1 diabetes, there is an increase in bone turnover and reduction in BMD, probably due to inflammatory processes and growth factor deficiencies.[17,18] Although there have been conflicting studies on the relationship between type-2 diabetes and BMD, most of the studies carried out on type-2 diabetics revealed a normal or high-normal bone mass at both appendicular and axial skeletal sites.[8,10,12] Several previous studies demonstrated increased BMD in women with type-2 diabetes but not in men.[11,19] The Rotterdam Study, however, which examined the association between diabetes and BMD in elderly people, displayed that diabetes was associated with a 3% increase in hip and spine BMD both in men and women.[8] The outcomes of our study support this overall conclusion. Our study provides evidence for an association between noninsulin-dependent diabetes and elevated bone density both in men and women. In the present study, we found an increase in BMD values among diabetic women at all examined levels. It was significant only at the femoral level, but the degenerative changes of the spine due to osteoarthritis might be obscuring spinal density. An increase in BMD values at all examined levels with significance only at the forearm level was also present in diabetic men. These results suggest that examining BMDs at different sites may reveal different results, especially in type-2 diabetic patients. Therefore, it seems insufficient to measure the BMD of type-2 diabetic patients at a single site.

Inconsistencies also exist in the available reports on biochemical markers of bone metabolism in diabetes.[6,19-22] Consensus has thus not yet been reached on how to interpret the effect of diabetes on bone metabolism. In the present study, among all the parameters that have been looked for, significant changes were confined to serum osteocalcin, BAP and CTx in diabetic patients compared to the control group. When we compared measurements of men and women separately, we found significant reduction in serum osteocalcin and CTx levels of diabetic men, and in osteocalcin and BAP levels of diabetic women, even after further adjustments for BMI and menopause status.

The higher BMD values both in women and men with type-2 diabetes may be caused by the anabolic effect of insulin on bone tissue.[23] Early in the course of type-2 diabetes, there is a period of insulin resistance leading to hyperinsulinemia. The serum insulin levels

Table 2. Bone mineral density (g/cm^2) at lumbar, femoral and forearm levels according to diabetes status in men and women (mean ± SD)

	Men					Women				
Characteristic	n	Nondiabetic	n	Diabetic	p	n	Nondiabetic	n	Diabetic	P
Lumbar										
L1	13	0.858 ± 0.104	14	0.928 ± 0.121	NS	30	0.815 ± 0.145	36	0.864 ± 0.148	NS
L2	13	0.932 ± 0.089	14	0.982 ± 0.135	NS	30	0.914 ± 0.150	36	0.940 ± 0.163	NS
L3	13	0.922 ± 0.088	14	0.987 ± 0.118	NS	30	0.969 ± 0.169	36	0.976 ± 0.150	NS
L4	13	0.966 ± 0.119	14	0.992 ± 0.119	NS	30	0.977 ± 0.160	36	1.028 ± 0.162	NS
Total	13	0.923 ± 0.092	14	0.974 ± 0.118	NS	30	0.925 ± 0.149	36	0.959 ± 0.145	NS
Femoral										
Neck	13	0.725 ± 0.098	13	0.772 ± 0.095	NS	30	0.715 ± 0.124	35	0.781 ± 0.136	0.050
Troch	13	0.641 ± 0.080	13	0.691 ± 0.083	NS	30	0.622 ± 0.091	35	0.675 ± 0.129	NS
Inter	13	1.051 ± 0.168	13	1.151 ± 0.116	NS	30	1.011 ± 0.140	35	1.141 ± 0.181	0.002
Total	13	0.881 ± 0.123	13	0.956 ± 0.098	NS	30	0.852 ± 0.116	35	0.941 ± 0.147	0.010
Forearm										
One-third	11	0.715 ± 0.050	13	0.751 ± 0.059	NS	22	0.610 ± 0.079	32	0.620 ± 0.079	NS
Mid	11	0.600 ± 0.040	13	0.655 ± 0.055	0.012	22	0.531 ± 0.060	32	0,547 ± 0.063	NS
UD	11	0.448 ± 0.048	13	0.499 ± 0.060	0.037	22	0.396 ± 0.061	32	0.415 ± 0.061	NS
Total	11	0.588 ± 0.040	13	0.637 ± 0.055	0.024	22	0.512 ± 0,064	32	0.528 ± 0.062	NS

NS: not significant

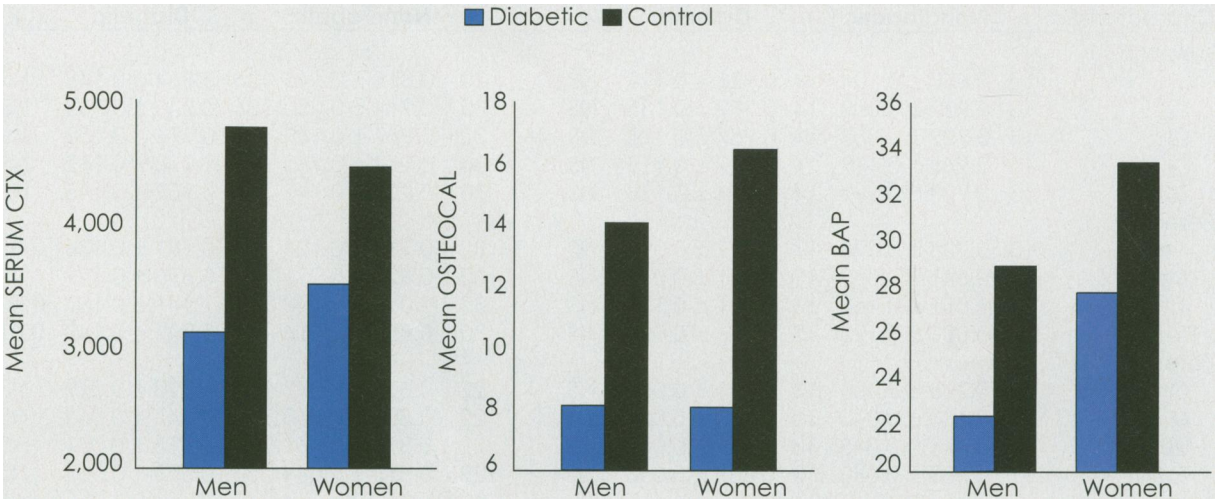
were found to be correlated with BMD in several epidemiologic studies.[24] Insulin may act either directly on bone or by binding to the receptor of insulin-like growth factor. IGF-I and IGF-II are potent bone-stimulating growth factors and have been shown to decrease collagen degradation and increase collagen synthesis in cultures.[25] Hyperinsulinemia also has negative effect on sex hormone-binding globulin, resulting in higher free estrogen and testosterone levels, which might attenuate bone resorption and subsequent higher BMD.[26,27] However, most of the reports on bone turnover in diabetes indicate that serum osteocalcin is significantly decreased irrespective of age and type of diabetes, which is interpreted to represent decreased bone formation.[28-33] In diabetic animal models, decrease in bone growth and formation, and reduction in osteoblast surface and number were observed in bone histomorphometry,[28] and similar findings have been reported in humans with diabetes.[18,34,35] On the other hand, BAP was reported to be elevated in type-2 diabetes in some other studies.[35-37] The reports on bone resorption in diabetic patients are also limited with conflicting results.[6,31,38-40] In experimental diabetes, bone histomorphometry indicates that bone resorption may also be depressed.[28] Both in type-1 and type-2 diabetes, low levels of circulating PTH have been observed and correlated to the severity and duration of the disease;[41-43] in our subjects, circulating PTH levels were comparable to nondiabetic control values. Depending on our findings, we suggest that in type-2 diabetes, bone formation is decreased. Additionally, diabetic patients are not susceptible to bone resorption either. This low bone turnover can slow bone loss

Table 3. Levels of the main bone turnover markers in diabetic patients and in the control group (mean ± SD)

	Normal Range	Diabetic Subjects			Control Subjects			P Value
		Number	Mean	SD	Number	Mean	SD	
Calcium (mg/dl)	8.6–10.2	52	9.77	0.35	48	9.71	0.41	NS
Phosphorus (mg/dl)	2.3–4.7	52	3.87	0.55	48	3.67	0.51	NS
Creatinine (mg/dl)	0.6–1.2	52	0.80	0.22	48	0.84	0.21	NS
ALP (U/L)	91–258	52	107.98	68.96	48	93.38	32.95	NS
BAP (U/L)	11–43.5	50	26.27	9.58	45	32.02	12.92	0.01
Intact PTH (pg/ml)	12–65	50	48.35	19.04	45	49.87	16.46	NS
OC (ng/ml)	3.7–10.0	48	8.11	5.72	47	15.78	8.24	0.00
TICP (ng/ml)	76–163	49	94.94	55.23	47	89.39	37.95	NS
CTx (pg/ml)	1,200–5,400	50	3,407	2,409	46	4,572	2,221	0.01
U-Ca (mg per 24 hours)	100–300	41	210	135	42	190	145	NS
U-Cr (mg per 24 hours)	600–2,000	42	1,072	406	40	1,181	624	NS
DPD (nM DPD/mM Cr)	3.0–7.4	45	9.55	6.90	43	9.10	7.51	NS

NS: not significant; ALP: alkaline phosphatase, BAP: bone alkaline phosphatase, PTH: parathyroid hormone, OC: osteocalcin, TICP: type-1 collagen propeptide C, CTx: type-1 collagen carboxyterminal telopeptide, U-Ca: urine calcium, U-Cr: urine creatinine, DPD: deoxypyridinoline

Figure 2. Comparisons of bone turnover markers in diabetic and nondiabetic men and women



rate and cause a higher bone density than expected for their age.

Nevertheless, data from the literature suggest that type-2 diabetes mellitus may increase fracture risk independent of the measured BMD values, which are normal or high normal. Although data from the Rotterdam Study showed an increased BMD at the spine in men and women with type-2 diabetes and fewer fractures,[8] the Study of Osteoporotic Fractures in women aged >65 years with type-2 diabetes found an increased risk of hip and proximal humerus fractures despite a higher BMD. There was also a trend toward increased risk of vertebral, forearm, ankle and foot fractures.[12] The more recent studies carried out on vast cohorts demonstrated a higher rate of fractures in both type-1 and type-2 diabetic patients. According to these studies, the relative risk for femoral fractures in type-2 diabetic patients was 1.5–2.66.[4,10,12] In animal studies, experimental models of diabetes have suggested an altered bone structure and decreased bone strength that may help to explain the paradox of an incremented risk of fractures in type-2 diabetic elderly in the presence of normal or elevated BMD.[28,44] In addition, diabetic elderly have an increased risk of falls related to poor vision, neuropathy, hypoglycemia, foot ulcers, amputations and weaken muscular performance.[45,46]

This study included a relatively small number of cases—especially men—and it is possible that failure to detect relations between diabetes and BMD in men may be attributable to low power. Although we could assess the severity of diabetes using duration or type of treatment as an indicator, better measures of glycemic control, such as hemoglobin$_{A1C}$ levels, were not available. Thus, the relationships between osteocalcin and BAP levels to duration and metabolic control of diabetes were not evaluated.

In conclusion, our findings suggest that, although bone formation is decreased in type-2 diabetes, diabetic patients do not have increased bone resorption. This low bone turnover can slow bone loss rate and cause higher bone density than expected for their age. However, the reduction in bone turnover rate may also increase skeletal fragility by inducing the accumulation of microdamage and give rise to fractures.

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