Increased bone density and decreased bone turnover, but no evident alteration of fracture susceptibility in elderly women with diabetes mellitus.

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Abstract

Bone density, bone turnover and fracture susceptibility was evaluated in 1132 randomly recruited women, all 75 years old. Seventy-four of the women had diabetes while 1 058 women had not. Areal bone mineral density (aBMD) of the hip and lumbar spine was investigated by Dual Energy X-ray Absorptiometry (DXA), and bone mass of the calcaneus by ultrasound. Urinary deoxypyridinoline/creatinine (U-DPD/Crea), serum C-terminal cross linked telopeptide of type 1 collagen (S-CTX) were assessed as markers of bone resorption and serum bone specific alkaline phosphatase (S-bone ALP) and serum Osteocalcin (S-OC) as markers of bone formation. Also, serum 25(OH) vitamin D and serum parathyroid hormone (S-PTH) were assessed. Fracture susceptibility was evaluated retrospectively and prospectively for up to 6.5 years.

In diabetic women the aBMD of the femoral neck was 11 percent higher ($p<0.001$) and BMD of the lumbar spine was 8% higher ($p=0.002$) than in non-diabetic women. There was no difference in bone mass by ultrasound of the calcaneus. Women with diabetes had higher BMD of the femoral neck ($p<0.001$) and lumbar spine ($p=0.03$) also after correction for differences in body weight. In diabetic women U-DPD/Crea, S-CTX, and S-OC were decreased when compared to non-diabetic women ($p=0.001$ or less). After correction for covariance of body weight and plasma creatinine, S-CTX ($p<0.001$) and S-OC ($p<0.001$) were still lower in the diabetic women. Diabetic patients had hypovitaminosis D ($p=0.008$) a difference explained by differences in time spent outdoors and body weight. S-PTH did not differ between the groups. Women with diabetes had no more lifetime fractures (52%) than women without diabetic disease (57%), ($p=0.31$).

This study shows that elderly women with diabetes and without severe renal insufficiency have high bone mass and low bone turnover. The high bone mass and low bone turnover is not likely to have a strong influence on fracture susceptibility.

Introduction

Despite previous efforts, it remains an unsettled question whether diabetic patients in general have a bone deficit or bone gain, a disturbance of bone turnover and/or a change in fracture susceptibility.

Areal bone mineral density (aBMD) in young individuals with type I diabetes appear to be decreased in most (1-4), but not all studies (5, 6). In older patients with type I diabetes or insulin dependent diabetes a decreased bone density has been reported (7-9). Reports concerning women with type II diabetes or non-insulin dependent diabetes have shown higher aBMD than controls without diabetes (10-15), however not always significant (8, 16)

Bone turnover has been extensively studied in diabetic disease. In pre-menopausal diabetic women the disease is accompanied by a high bone turnover (1, 3, 5). In elderly women with type II diabetes or non-insulin dependent diabetes mellitus it has been reported that bone turnover is decreased (11, 17-20), unchanged (16) or with a more mixed finding compared to in controls (13). The results are difficult to evaluate since many of the studies have been on patients with severe kidney disease or without taking age or type of diabetes into account.

Bone turnover is dependent on serum levels of vitamin D or parathyroid hormone. In diabetic patients, vitamin D metabolites and PTH have been studied in a few papers. It seems as if serum $1,25(OH)_2$ vitamin D and 25(OH) vitamin D are decreased in diabetic patients (20-23). Results from studies on serum PTH varies considerably from decreased values (18, 22), unaltered values (16, 20, 21) to increased PTH when diabetic patients with renal insufficiency were analysed (22).

Some studies have shown an increased rate of hip (15, 24, 25), proximal humerus (15, 26) and foot fractures (15) in women with diabetes. In another study, non-insulin dependent diabetes mellitus was associated with a decreased frequency of non-vertebral fractures (12), and in one study the association between diabetes and hip fracture risk disappeared after correction for confounders (25).

In order to gain a better understanding of the bone metabolic events taking place in diabetic disease it would be advantageous to compare diabetic individuals with non-diabetic controls of a defined and uniform age and gender. The intention of this paper was to compare elderly diabetic women with non-diabetic controls regarding: i) bone mass as assessed with DXA-technique and ultrasound, ii) bone turnover, serum 25(OH) vitamin D and serum PTH and iii) fracture susceptibility.

Material and Methods

Subjects

Between 1995 and 1999, 1604 women, all 75 years old, were invited to participate in the OPRA study. The women had been identified at random from the city files of Malmö, Sweden, and the invitation letter was sent out a week following the 75th birthday of each woman. Of these 1604 women, 1132 (71 %) responded to a questionnaire including information about whether they had diabetes or not, and if so when the disease had its debut and if they currently were treated with insulin or not. The questionnaire also comprised questions about time spent outdoors, menopausal age, any use of walking aid, and intake of milk, which in Sweden is fortified with vitamin D. A visual acuity test was made with a Snellen letter test chart (0.0-1.0).

Of the 1132 women 1028 (64 % of the entire cohort) participated also in a clinical investigation. Serum was available in 1000 women and urine in 1019 women. The reason for not participating was mainly unwillingness or illness. In addition a few of the women shortly died after the invitation and a few were not reached at all. No exclusion criteria were used for participation and the study was in all parts approved by the local ethics committee.

Bone mineral density

Areal bone mineral density (aBMD) of the femoral neck and lumbar spine (LII –IV) were assessed by DXA-technique (Lunar® DPX-L, Madison, WI, USA). The precision of this DXA-equipment as assessed by duplicate measurements on 14 healthy persons after repositioning has been determined to be 1.6% at the femoral neck and 0.5 % at the spine. Bone mass of the calcaneus was also determined using quantitative ultrasound. Measurement was done with a Lunar Achilles Plus ® (Lunar corporation, Madison WI, USA) and the

stiffness index was calculated from broadband attenuation and speed of sound using the formula provided by the manufacturer (stiffness index = (broadband attenuation x 0.67) + (speed of sound x 0.28) – (420)). The precision of this ultrasound equipment has been determined by duplicate measurements on 14 healthy individuals to be 1.5 %.

Bone markers

Non-fasting blood samples were obtained between 08.00 and 13.00. The blood samples were centrifuged within two hours after phlebotomy and serum was stored at –80° C. The urine samples were obtained as first morning void and stored at minus –80° C. All samples were analysed at the same time. Inter- and intra-assay coefficient of variation (CV) for the assays has been determined previously. Serum bone specific alkaline phosphatase (S-Bone ALP) was determined using the Alkphase-B immunoassay (Metra Biosystems, Seattle, USA), with inter- and intra-assay CV of 4.4 % and 3.6 %, respectively. Serum intact and N-Mid osteocalcin were determined using the Elecsys N-MID osteocalcin immunoassay (S-Total OC; N-MID®; Roche Diagnostics, Mannheim, Germany), with inter- and intra-assay CV of 2.4 % and 2.3 %, respectively.

Serum C-terminal cross-linked telopeptides of type I collagen (S-CTX) were determined using the Elecsys ß-CrossLaps immunoassay (Roche Diagnostics) (intra-assay CV 5.9%, inter-assay CV 5.8%). Urinary deoxypyridinoline (U-DPD) was determined by the Pyrilinks-D assay (intra-assay CV of less than 12%, inter-assay CV of less than 10%) (Metra Biosystems).

Urinary creatinine and plasma creatinine were determined in accordance with kinetic Jaffé reaction with a Beckman synchron LX20-4, with CV´s of 3% or less.

Vitamin D

The serum concentration of 25(OH) vitamin D was used as a measure of vitamin D status. The analysis was done with the Nichols Advantage assay (Nichols Institute Diagnostics, CA, USA), which utilizes chemiluminescence detection. According to the manufacturer, the reference range is 10-68 ng/mL and the intra-assay coefficient of variation (CV) is less than 10 % for 25 (OH) vitamin D levels between 8.4 and 75.1 ng/mL. The intra-assay CV was 8.7% in this specific cohort as determined by duplicate measurements in 37 individuals.

PTH

Serum concentration of PTH was measured with the Elecsys PTH immunoassay (Roche Diagnostics, Mannheim Germany) with a reference range of 1.6-6.9 pmol/L. Intra- and inter-assay CVs were 1.6 and 5.7 % respectively.

Fracture registration

In addition to the information about retrospective fractures given in the questionnaire the files of the Department of Radiology at the Malmö University Hospital were searched. This is the only hospital serving the city (260.000 inhabitants). Due to the unique personal identification number of each Swedish citizen, retrieval of such data is possible as is avoidance of double entries.

Prospectively sustained fractures with a minimum follow-up of 3 years and a maximum follow-up of 6.5 years (mean 4.6 years) were ascertained by 2 means. Firstly the same files of the Department of Radiology were searched and secondly at prospective follow-up visits at 1,

3 and 5 years all women were asked whether they had sustained any fracture since the previous visit or not. The information was confirmed against files.

Statistics

Shapiro Wilks test of normal distribution was applied to all variables and when non-normal distribution was found (SW-W $\leq$ 0.95) non-parametric statistics was applied. Comparisons of levels of aBMD and stiffness of the calcaneus as well as of levels of biochemical markers of bone metabolism were made between women with and without diabetes. Correcting for difference in body weight, plasma creatinine or time spent outdoors was performed with analysis of covariance. Fracture comparisons between diabetic and non-diabetic women were made by Chi-square tests, Fisher exact tests and logistic regression.

Results

Of the 1604 women, 1132 responded to the questionnaire about diabetic disease. Seventy four (7 %) had diabetes and 1058 had not. The average duration of diabetes was 9.8 years (range 0.04 to 61 years). Out of the 74 diabetic women 26 were currently taking insulin while 48 were not. Of the 1028 women that also participated in the clinical investigation 67 had diabetes and 961 had not.

Body weight and all bone mass variables were normally distributed. Women with diabetes were on average 5 kilo heavier than the others (Table 1). In comparison with non-diabetics the diabetic women tended to spend less time outdoors both during summer (30 minutes less, p=0.02) and winter (15 minutes less, p=0.04). On the other hand there was no difference in intake of milk, usually fortified with vitamin D (p=0.51).

Women without diabetes had a mean visual acuity of 0.5 and women with diabetes had a mean visual acuity of 0.4, a difference which was non-significant (p=0.06). The diabetic women used a walking aid to a greater extent than non-diabetics (22% vs 10%, p=0.003. One (1%) of the women in the diabetic group used potent estrogens vs 17 (2%) of the women in the non-diabetic group (p=0.63). The menopausal age between women with and without diabetes did not differ (p=0.32).

aBMD was higher in diabetic women, both in the femoral neck (11 %, p<0,001) and in the lumbar spine (8 %, p=0.002) whereas there were no significant differences in ultrasound of the calcaneus (Table 1). There were no significant correlations between duration of diabetes and aBMD (r between –0.10 and -0.23, p between 0.08 and 0.47). With multiple regression analysis the influence on bone density of the presence of diabetes was tested after correcting

for body weight. Women with diabetes had still higher aBMD of the femoral neck ($p<0.001$) and lumbar spine ($p<0.03$) (Table 2).

Plasma creatinine was non-significantly higher in the diabetic women compared with the non-diabetic women ($p=0.88$) (Table 1). Among women with diabetes, those treated with insulin had a higher plasma creatinine than those without insulin treatment (Table 1).

None of the bone turnover markers were normally distributed. S-OC was lower by 26 % ($p<0.001$), U-DPD/crea lower by 9 % ($p=0.001$) and S-CTX lower by 31 % ($p<0.001$) in diabetics compared to non-diabetics. After correcting for the covariance of body weight and for plasma creatinine, S-OC ($p<0.001$) and S-CTX ($p<0.001$) were still lower in women with diabetes compared to in non-diabetic women (Table 2).

25(OH) vitamin D was 10 % ($p=0.008$) lower in women with diabetes. Using multiple regression analysis, including correction for differences in time spent outdoors and body weight, the diabetic women did not differ in serum 25(OH) vitamin D compared with the non-diabetics ($p=0.13$).
There was no difference in S-PTH between diabetic women and non-diabetic women ($p=0.39$).

There were no significant correlations between duration of diabetes and bone markers or between duration of diabetes and 25OHD or PTH (r between –0.07 and 0.13, p between 0.40 and 0.97).

In neither of the bone mass variables nor the bone markers including 25(OH) vitamin D and PTH was there any significant difference between diabetic women taking insulin or not (Table 1).

There was no difference in lifetime fracture prevalence between diabetic and non-diabetic women (Table 3). The odds ratio (OR; 95% confidence interval) to sustain a fracture for women with diabetes was 0.78 (0.49-1.26) when compared to women without diabetes. Neither was there any difference in fracture prevalence if only prospective fractures, i.e. fractures sustained after the age of 75, were taken into account (Table 3). The OR for women with diabetes to sustain a fracture after the age of 75 was 0.72 (0.36-1.44).

When weight, aBMD, use of walking aid, or visual acuity were included in the logistic regression, the OR for fracture for women with diabetes was not significantly altered. For women with diabetes, there was no difference in duration of diabetes between women with and without life-time fractures (p=0.87) or fractures after the age of 75 (p=0.61). The median age for the occurrence of a first fracture during life-time was for diabetic women 62 years and for non-diabetic women 59 years (p=0.22). The corresponding ages for the first fracture after the age of 75 was 78 and 77 years (p=0.08).

Regarding the degree of trauma, 2% of the life-time fractures in the diabetic women were caused by traffic accidents or similar high-energy trauma compared to 4% of the life-time fractures among the non-diabetic women (p=0.30). After the age of 75, 0% and 5% were caused by traffic accidents or similar high-energy trauma in the diabetic and non-diabetic group, respectively (p=1.00).

Discussion

In this study, by analysing bone mass and markers of bone turnover together with the calcium regulating hormones 25(OH) vitamin D and PTH, we have made an effort to cover both the metabolic events eventually leading to diabetic bone disease and ultimately the result, i.e. fracture, of such disease. Elderly women with diabetes had higher bone density in the hip and in the spine than non-diabetic women, even when correcting for body weight. There was no evident influence of diabetic disease on the calcaneus as assessed with ultrasound. The increased bone density of the axial skeleton is accompanied by decreased bone turnover; both bone formation and bone resorption.

When adding the present study to earlier studies, there is evidence that elderly women with diabetes have better bone mass in the central skeleton than non-diabetic controls, also after correction for body weight. The reason for this could be the low bone turnover found in these women. Also, the higher body weight and fat mass in these women and therefore greater endogenous estrogen production could be added as a possible explanation for the higher bone mass (27).

We failed to show any significant difference in bone mass as assessed by ultrasound of the calcaneus. The reason for this may of course be a true reality. We believe, however, that is partly a reflection of lack of power for this specific measurement. Although not exactly comparable, the difference between diabetics and non-diabetics in stiffness of the calcaneus was almost as large as that obtained with DXA of the spine and hip (Table 1).

This study confirms the results of most of earlier studies where bone turnover has specifically been investigated in diabetic patients. After reviewing the literature and with the confirmatory findings of this study we are inclined to conclude that elderly women with diabetes, provided the diabetic disease is not accompanied by severe renal disease, have low bone formation and low bone resorption. It is not difficult to relate low bone turnover to an increased bone mass when comparison is made with the physiologically high bone turnover accompanying post-menopausal bone loss. Also, after pharmacological treatment of osteoporosis, the bone mass gain is accomplished by a decreased bone turnover (both resorption and formation). The physiological basis of this low bone turnover in diabetic disease is not totally evident but the close connection between insulin and insulin-like grow factor system components and their relationships to bone metabolism should be involved (4).

Vitamin D deficiency is regarded as a risk factor for bone loss and fracture. We found, in accordance with others (20, 21, 23), that elderly women with diabetes have a comparable vitamin D deficiency. High weight and low sun exposure may explain some of these differences (28). When controlling for these factors in a multiple regression analysis the difference in 25(OH) vitamin D levels was eliminated.

Plasma creatinine was marginally but not significantly increased in the diabetic compared to the non-diabetic women, indicating that renal disease was not significantly involved in these women. Further evidence that this cohort of diabetic women was not generally renally insufficient was the finding that serum PTH was not significantly altered in the diabetics compared to the controls. However, plasma creatinine was slightly higher in the insulin treated women indicating a higher degree of renal impairment than in the non-insulin treated diabetic women.

Data on fracture occurrence in diabetic disease should be judged cautiously as a potential combination dependent not only on bone mass but also on other disease-associated factors such as for instance impaired vision or gait disturbances. In the largest study (n=35,444) performed so far on this subject (25) it was found that diabetics (type I or type II) had more hip fractures than others but this finding was no longer significant after correcting for confounders. Others have shown that type II diabetics may have an increased hip fracture risk (15, 24, 29), but is contrasted to findings of fewer non-vertebral fractures among non-insulin dependent diabetics (12). The data from our study does not support any difference in fracture rate among diabetics and non-diabetics, also after correction for possible confounders. Due to few fractures in the present study, the lack of power to find an increased or decreased fracture risk in this population has to be taken into account. Fractures not remembered by the subject and not x-rayed at our hospital may not be identified in this study. However, in an earlier study it was estimated that only 3% of all fractures occurring in Malmö were x-rayed at one of two the private x-ray departments (30). These are likely to be fractures not requiring specific treatment at the hospital. There is no reason to believe that this possible loss of fracture data would differ between diabetic and non-diabetic women.

The increased bone density in diabetic patients may be accompanied by concomitant diabetic complications neutralising the positive implication of increased bone mass on fracture susceptibility. Nevertheless, it does not seem like non-complicated diabetes is a disease with strong influence, in either direction, on fracture susceptibility.

The participation rate in this study was high. All women, with or without diabetes, were recruited concomitantly and in the same way, a methodology seldom used but one that should minimize selection bias. All women were of the same age, not making it necessary to correct

for age differences which otherwise may have impact on bone mass and bone turnover results. However, it is possible that frail women, for example those with diabetes and severe co-morbidity did not volunteer. Diabetic women were subgrouped according to treatment (insulin or not). We recognize that this does not completely differentiate type I and type II diabetes women. However, bone mass data and bone marker data did not differ between these groups, although it must be recognized that insufficient power of the study due to few diabetic women may be a reason for lack of differences between diabetic and non-diabetic women.

In conclusion, elderly women with diabetes, with and without insulin treatment, and without severe renal insufficiency, have in comparison with women without diabetes better bone mineral density and also a low bone turnover. These differences are not related to differences in body weight or kidney function. The higher bone mass and low bone turnover in diabetics is not likely to have a strong influence on fracture susceptibility.

Table 1. Body weight, bone mass and bone markers in 75-year-old women with or without diabetic disease. In addition, diabetic women currently on insulin treatment are compared with diabetic women without. For some of the variables not all women were investigated. (n=number of women)

	Women with diabetes n=67	Women without diabetes n=961	Difference between diabetic and non-diabetic women (p-value)	Diabetic women with insulin n=25	Diabetic women without insulin n=42	Difference between diabetic women with and without insulin (p-value)
Body weight (kg)	72.2 ± 11.4	67.4 ± 11.6	P<0.001	69.5 ± 11.0	72.9 ± 11.6	ns
Plasma-creatinine (μmol/L)	82 ± 42	77 ± 18	ns	97 ± 61	74 ± 21	p=0.009
Bone mass:						
BMD Femoral Neck (g/cm^2)	0.82 ± 0.16	0.74 ± 0.13	p< 0.001	0.76 ± 0.18	0.84 ± 0.14	ns
BMD Lumbar Spine (g/cm^2)	1.07 ± 0.23	0.99 ± 0.19	p= 0.002	1.00 ± 0.22	1.10 ± 0.23	ns
Ultrasound stiffness index	70.1 ± 14.0	66.5 ± 13.1	ns	67.0 ± 17.6	70.7 ± 13.1	ns
Bone markers:						
S-OC (μg/L)	21.6 ± 9.9	29.3 ± 12.9	p<0.001	22.6 ± 11.8	20.9 ± 8.7	ns
S-Bone ALP (U/L)	21.7 ± 5.9	22.7 ± 8.8	ns	21.4 ± 6.0	22.2 ± 5.8	ns
U-DPD/crea (nmol/mmol)	7.4 ± 3.2	8.6 ± 4.6	p=0.001	7.4 ± 2.9	7.3 ± 3.4	ns
S-CTX (ng/L)	217 ± 173	313 ± 203	p<0.001	253 ± 214	194 ± 138	ns
Vitamin D and PTH:						
S-25(OH) vit D (ng/mL)	34.3 ± 13.2	38.3 ± 11.9	p=0.008	31.7 ± 10.4	36.2 ± 14.2	ns
S-PTH (pmol/L)	4.5 ± 2.4	4.7 ± 2.1	ns	4.3 ± 2.7	4.5 ± 2.2	ns

Table 2. Adjusted means for bone mass after correction for body weight. Adjusted means for serum osteocalcin (S-OC), urinary deoxypyridinoline/urinary creatinine (U-DPD/crea) and serum C-terminal cross-linked telopeptide of type I collagen (S-CTX) after correction for body weight and plasma creatinine.

	Women with diabetes n=67	Women without diabetes n=961	Adjusted difference between diabetic and non-diabetic women (p-value)
Bone mass:			
BMD Femoral Neck (g/cm^2)	0.81	0.75	p<0.001
BMD Lumbar Spine (g/cm^2)	1.05	1.00	p<0.03
Bone markers:			
S-OC (µg/L)	21.8	29.1	p<0.001
U-DPD/crea (nmol/mmol)	7.4	8.5	ns
S-CTX (ng/L)	217	315	p<0.001

Table 3. There were no differences in fracture susceptibility when comparing women with and without diabetes. The table shows number of women (%) with at least one fracture (any type or hip, forearm or vertebral) compared to all other women.

	Life-time fractures				Fractures after the age of 75		
Fracture type	Women without diabetes n=1058	p	Women with diabetes n=74		Women without diabetes n=1058	p	Women with diabetes n=74
Any	606 (57%)	0.31[a]	39 (52%)		188 (18%)	0.35[a]	10 (14%)
Hip	101 (10%)	0.30[b]	4 (5%)		48 (5%)	1.00[b]	3 (4%)
Forearm	252 (24%)	0.08[a]	12 (16%)		39 (4%)	0.75[b]	2 (3%)
Vertebral	105 (10%)	0.30[b]	4 (5%)		46 (4%)	0.76[b]	2 (3%)

[a] Chi^2-test

[b] Fisher exact test

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