A Bone Structural Basis for Fracture Risk in Diabetes

Running head: Bone Structure in Diabetes

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Abstract

**Context:** Elevated areal bone mineral density (aBMD) in type 2 diabetes mellitus is inconsistent with increased fracture risk at some skeletal sites.

**Objectives:** Since aBMD is an imperfect surrogate for bone strength, we assessed bone structure and strength more directly using quantitative computed tomography (QCT).

**Design:** Diabetic and non-diabetic subjects were evaluated in a cross-sectional study.

**Setting:** Subjects were recruited from a random sample of the Rochester, MN population.

**Participants:** Forty-nine subjects (28 women and 21 men) with type 2 diabetes were compared to age- and sex-matched non-diabetic controls.

**Main Outcome Measurements:** We measured bone geometry, strength and volumetric BMD (vBMD) at the hip, spine and wrist, along with hip aBMD, using central and peripheral QCT and estimated bone load to bone strength ratios at each site.

**Results:** Adjusted for differences in body mass index between cases and controls (29.8 vs. 27.6), hip aBMD was greater in diabetic subjects, but this was accounted for by greater trabecular vBMD. Cortical vBMD was similar in the two groups, as was bone cross-sectional area and cortical thickness. Bone strength measures were generally better in diabetic subjects, but bone loads were higher from their greater weight. Consequently, load to strength ratios (i.e., factor-of-risk) were similar.

**Conclusions:** Patients with type 2 diabetes enjoy little benefit from elevated aBMD in terms of improved bone load to strength ratios. With no deficit in bone density, the rationale for antiresorptive therapy in diabetic patients is uncertain, but potential adverse effects of diabetes on bone quality need more study.
Introduction
A recent meta-analysis concluded that hip fracture risk is elevated 1.7-fold among women with type 2 diabetes mellitus (1). However, some studies have either found no increase in hip fractures (2, 3) or else that risks were confined to patients with a longer duration of disease (4-7). The reports of increased fracture risk are somewhat unexpected since two-dimensional areal bone mineral density (aBMD) is consistently elevated among persons with type 2 diabetes (8), and higher aBMD is protective of fractures (9). This implies that diabetic individuals should be at decreased risk of fracture. Indeed, the average 0.27 SD increase in hip BMD in patients with type 2 diabetes (10) would be expected to result in a 10% reduction in fracture risk generally and an 18% reduction in hip fractures specifically (7). Moreover, the meta-analysis found no significant increase in fractures of the vertebrae or distal forearm in these patients (1).

At present, there is no clear explanation for this apparent contradiction. An increased risk of falling among diabetic patients (11) could account for elevated hip fracture risk in the face of normal aBMD since the forces delivered to the greater trochanter in a fall to the side are substantial. However, a recent report from the Women’s Health Initiative Observational Study (WHI-OS) found a 1.2-fold increase in fractures among diabetic subjects which was not accounted for by a 38% greater likelihood of falls nor by adjustment for a host of other potential risk factors, including aBMD in a subset of subjects (12). Of course, aBMD is not a perfect surrogate for bone strength, and it is possible that some aspect of bone “quality” plays a role here (13). Therefore, the purpose of this report was to evaluate aBMD, as well as three-dimensional volumetric bone density (vBMD), bone structure and bone strength by quantitative computed tomography (QCT), in a population sample of women and men with confirmed diabetes compared to age- and sex-matched community controls.

Methods

Study subjects
Following approval by Mayo Clinic's Institutional Review Board, subjects were recruited from an age-stratified random sample of Rochester, MN men and women selected from the medical records linkage system of the Rochester Epidemiology Project (14). The sample spanned ages from 20 to 97 years and included 375 women and 325 men (15). Reflecting the ethnic composition of the community, 98% of the subjects were white. Altogether, 49 subjects (28 women and 21 men) had been diagnosed with type 2 diabetes mellitus that was confirmed by stringent National Diabetes Data Group (NDDG) criteria (16), e.g., two consecutive fasting plasma glucose values ≥ 140 mg/dL, as recorded in their complete (inpatient and outpatient) medical records in the community that spanned a median 43 years prior to assessment. The cases were matched by sex and date of birth (± 1 year) to an equal number of control subjects from the same population sample who would not have qualified for a diagnosis of diabetes even by more generous American Diabetes Association (ADA) criteria (17) based on their recorded fasting plasma glucose values. All subjects provided written informed consent prior to participation in the study.

Bone density and structure
As reported previously (15), central measurements of bone density and geometry at the lumbar spine and femoral neck were made by single energy QCT using a multidetector Light Speed QX-I scanner (GE Medical Systems, Waukesha, WI). Calibration standards scanned with the subject were used to convert CT numbers directly to equivalent vBMD in mg/cm$^3$. The correlation between bone density determined by our algorithm and that of the European Spine Phantom was $r = 0.998$. At each skeletal site, we evaluated total, trabecular and cortical vBMD as well as bone geometric variables (e.g., total cross-sectional area and cortical thickness, recognizing that true cortical thickness is overestimated in the lumbar spine due to volume averaging artifacts).

As also described elsewhere (15), peripheral QCT (pQCT) measurements of vBMD and bone structure were made at the distal radius using the Densiscan 1000 instrument (Scanco Medical AG, Bassersdorf, Switzerland).

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As also described elsewhere (15), peripheral QCT (pQCT) measurements of vBMD and bone structure were made at the distal radius using the Densiscan 1000 instrument (Scanco Medical AG, Bassersdorf, Switzerland).
aBMD of the total hip was estimated from the QCT hip scans using commercial software (QCT PRO, Mindways Software, Austin, TX).

**Bone strength**

Indices of bone strength were derived at each of the three skeletal sites as described in detail previously (18, 19). We used a bending strength index, i.e., flexural rigidity (EI) defined as the product of elastic modulus and area moment of inertia, to estimate bone strength at the femoral neck and distal radius (18). Vertebral compressive strength was estimated as the product of cross-sectional area and average elastic modulus (19). The elastic modulus was derived from previously published relationships between vBMD and compressive modulus in human trabecular bone (20).

In addition, we estimated bone loading under conditions specific for hip, spine and wrist fractures. The applied load at the hip was estimated from data on the kinematics of sideways falls with impact at the hip (18). The load applied to the wrist during a forward fall was estimated from data predicting impact forces on the upper extremity during falls on the outstretch hand (18). Since the events leading to vertebral fracture are ill-defined, we studied several daily activities with varying compressive force magnitudes on L3: Upright standing (0° flexion), forward flexion with the trunk at 45° and forward flexion with the trunk at 90° while lifting 10 kg (19). The largest of the daily loads (i.e., bending at the waist while lifting 10 kg) was used in this analysis.

Finally, we computed the ratio of applied bone loads to estimated whole bone strength (factor-of-risk, $\phi$). Theoretically, a fracture is predicted to occur when $\phi \geq 1$ (21), but no specific threshold for $\phi$ was established in this population, and not all load and strength components could be expressed in comparable units. Nonetheless, fracture risk should increase as the load to strength ratio rises.

**Statistical analysis**

Analyses were performed using SAS (SAS Institute Inc., Cary, NC) and Splus (Insightful Corp., Seattle, WA). Bone variables were summarized using means and standard deviations. Cases and controls were compared using paired t-tests for continuous variables and McNemar’s test for categorical variables. Percent change for variables was calculated for each case:control pair and reported as an overall average. Conditional logistic regression was used to adjust for differences in body mass index (BMI) between cases and controls, testing whether skeletal parameters were better (i.e., higher BMD, bigger bones, lower load to strength ratios) among the diabetic subjects.

**Results**

The 49 subjects (28 women and 21 men) with type 2 diabetes (mean age ± SD, 72.2 ± 11.6 years) ranged in age from 38 to 88 years. They were matched to 49 comparably aged subjects (72.2 ± 11.6 years) of the same sex who had no evidence of diabetes. The diabetic subjects met diagnostic NDDG criteria a median of 6.5 years prior to baseline. The mean fasting plasma glucose value closest to the time of assessment (all within 8 months) among these unselected community residents with diabetes was 149 mg/dL (8.3 mmol/L), but only 100 mg/dL (5.6 mmol/L) in controls, while the mean hemoglobin A1c level was 6.7%. Altogether, 18 cases (37%) had been diagnosed with a diabetic complication, including polyneuropathy in 10, proteinuria in 10 and retinopathy in 8. Current treatment included insulin with or without other agents in 10 and oral agents in 26 (sulfonylureas in 12, biguanides in 10, combinations in 4); the rest were treated with diet alone.

Only one diabetic woman was premenopausal compared to 3 premenopausal controls, while 6 cases compared to 7 controls were on estrogen therapy. Conversely, the diabetic subjects were somewhat heavier than the non-diabetic controls (82.0 ± 18.6 kg vs. 77.6 ± 17.0 kg; $P = 0.180$) and slightly shorter (165.7 ± 7.6 vs. 167.3 ± 9.6 cm; $P = 0.175$) so that their BMI was significantly greater (29.8 ± 6.2 vs. 27.6 ± 4.6; $P = 0.038$). Altogether, 82% of the diabetic subjects compared to 71% of the controls were overweight (BMI ≥ 25), while
45% and 20%, respectively, were obese (BMI ≥ 30).

The various bone density, structure and strength variables are compared for diabetic and non-diabetic subjects in Tables 1, 2 and 3 for the hip, spine and wrist, respectively. Hip aBMD and the total vBMD variables were greater in the cases. However, when the compartments of bone were evaluated separately by QCT, it became evident that it was mainly trabecular vBMD which was elevated among the diabetic subjects. Increased trabecular bone density was seen at the hip, spine and distal radius, but there were few differences in cortical vBMD between diabetic cases and controls.

A less consistent picture was seen with respect to the bone structure and strength variables. The cross-sectional area of all bones was somewhat smaller for diabetic subjects, while cortical thickness was generally greater among the cases, but these differences were small. Resistance to compressive forces in the spine was greater among the diabetic subjects. By contrast, resistance to bending forces, i.e., flexural rigidity, at the hip and radius did not differ significantly.

The implications of these differences became clearer when selected bone strength variables were assessed relative to potential bone loads. Compared to control women, for example, the diabetic women had greater resistance to bending forces at the hip, but this was offset somewhat by a greater estimated traumatic load in a fall (Table 1). Estimated traumatic loads and femoral neck bending strengths were somewhat less in diabetic than nondiabetic men. Consequently, despite greater hip aBMD, the load-to-strength ratio (i.e., factor-of-risk) for hip fracture was no better in diabetic cases than in controls.

Larger compressive loads on the spine in diabetic women but not men were counteracted by greater resistance to compressive forces among the cases. Therefore, the mean load to strength ratio did not differ greatly between diabetic and non-diabetic subjects under the spinal loading condition of 90° forward bending at the waist while lifting 10 kg (Table 2).

With respect to a fall on the outstretched arm, the estimated traumatic load on the distal forearm was dictated more by height than weight and was similar in the two groups (Table 3). Compared to controls, resistance to bending forces in the distal radius was somewhat greater in diabetic women and somewhat lower in diabetic men, but the average load-to-strength ratio was again similar in cases and controls.

Discussion

These bone density and structure data help explain apparent inconsistencies with respect to fracture risk in diabetes. Thus, we confirm many previous reports that femoral neck aBMD is elevated among women and men with type 2 diabetes mellitus (10). However, aBMD is confounded by bone size (22), and the a priori expectation is that bone size might have increased to adapt diabetic skeletons to their presumably greater bone loads. In this study, however, aBMD was elevated among the diabetic subjects as a result of higher trabecular vBMD; cortical vBMD was mostly unchanged relative to controls. Bone cross-sectional area was actually slightly lower, in part because cases were 1.6 cm shorter on average and bone size is correlated with height.

Femoral neck vBMD, which is not confounded by bone size, was 19% higher among the diabetic subjects and cortical thickness was somewhat greater. This, in turn, was associated with a slightly greater resistance to bending forces (EI) in the femoral neck, which was offset by a slightly greater estimated traumatic load given a fall on the hip due to their greater weight. The net result was that the likelihood of hip fracture, given a fall, was similar in both cases and controls. Therefore, the increased hip aBMD (about 0.86 SD) observed by our group and others (10) did not translate into any significant protection among those with diabetes, and their increased risk of hip fracture (1) might be related more to a greater likelihood of falling (11).

Likewise, an increase in total lumbar spine vBMD among the cases, in conjunction with comparable cross-sectional areas, resulted in a 20% greater resistance to axial compression but little absolute difference in load to strength ratios. Thus, the increased lumbar spine aBMD observed by DXA in most earlier investigations
(10), and the increased trabecular vBMD observed by us and some (23) but not all others (24), does not contradict reports that vertebral fracture risk is no lower in diabetic than nondiabetic subjects (1).

At the ultradistal radius, total vBMD was 14% greater but cross-sectional area was 4% less among the cases, and cortical thickness was similar. Consequently, their resistance to bending forces in a fall on the outstretched arm did not differ significantly from that of controls. This is again consistent with most studies (1), which find no association of diabetes with distal forearm fractures.

Our study has several notable strengths. First, the subjects were recruited from an age-stratified random sample of community men and women. Diabetes was confirmed by fasting plasma glucose values using stringent NDDG criteria (16). The control subjects did not meet ADA fasting plasma glucose criteria for diabetes as judged from four decades of prior community medical record documentation. Three-dimensional bone density and structure in diabetic cases and their community controls were evaluated with central QCT in the hip and spine and pQCT in the distal radius. Also, we estimated failure loads (~ strength) from the QCT parameters, and related bone strength to a range of spine loads encountered routinely in daily life and to traumatic loads that might be expected from a lateral fall on the hip or a forward fall on the outstretched arm.

There are also some corresponding limitations. In particular, we had available only a limited number of subjects with diabetes, and the analysis was cross-sectional. Both osteoporosis and diabetes increase with age and are more common in women than men, but those effects were matched for in this analysis. The patients with type 2 diabetes had greater BMI, but that should be protective of fractures (25). There is also the theoretical possibility that single-energy QCT could be affected by the fat content of the marrow, but changes in vertebral vBMD over life have shown good agreement between single- and dual-energy CT (26). Moreover, we obtained similar results with pQCT at the ultradistal radius where this should not be an issue. Finally, hip aBMD was estimated from the QCT scans, and we did not have aBMD measurements for the spine and wrist. However, recent clinical practice recommendations focus on hip aBMD (27, 28).

In addition, the bone strength indices that we used (i.e., compressive and flexural rigidities) are theoretically associated with structural failure, but their relations to whole bone strength at the hip and wrist have not been described (18). Our strength estimates relied on empirical relationships between vBMD and bone biomechanical properties derived from cadavers. It is not known whether these relationships would differ in diabetic bone, which may have altered bone matrix properties. For instance, non-enzymatic collagen cross-linkage with advanced glycation end products is higher in persons with diabetes (29), and this has been shown to influence both cortical and trabecular bone biomechanical properties (30, 31). Unfortunately, current imaging methodologies do not allow for direct assessment of the type or degree of collagen cross-linking.

The prevalence of diabetes mellitus is increasing rapidly in the population (32) so adverse outcomes of the condition are likely to grow in importance as well. Considerable concern has been expressed about fracture risk in these patients (33), and fractures might be prevented by the efficacious treatments now available (34). Although patients with diabetes share fracture risk factors with the general population (7), this research shows that there is no deficit in trabecular or cortical bone among the diabetic subjects. Thus, no clear rationale exists for treating such patients with antiresorptive agents, and an insufficient knowledge base exists to permit the design of prophylaxis better tailored to this group (35). By default, management recommendations have emphasized interventions to reduce the risk of falling (11, 36). Additional research is needed to better define the determinants of bone strength in diabetic individuals, including abnormal material properties of bone that might respond to treatment of the diabetes itself.
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Table 1. Bone density, structure and strength at the femoral neck, comparing Rochester, MN residents with Type 2 diabetes mellitus (cases) to age- and sex-matched community controls (40 matched pairs)

<table>
<thead>
<tr>
<th>Variables (units)</th>
<th>Women</th>
<th>Men</th>
<th>Both sexes combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Δ</td>
</tr>
<tr>
<td>Bone density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral neck (FN)</td>
<td>0.68±0.15</td>
<td>0.57±0.11*</td>
<td>22</td>
</tr>
<tr>
<td>FN total vBMD (mg/cm$^3$)</td>
<td>337±81</td>
<td>279±58</td>
<td>25</td>
</tr>
<tr>
<td>FN trabecular vBMD (mg/cm$^3$)</td>
<td>216±69</td>
<td>173±49</td>
<td>30</td>
</tr>
<tr>
<td>FN cortical vBMD (mg/cm$^3$)</td>
<td>573±76</td>
<td>522±67*</td>
<td>12</td>
</tr>
<tr>
<td>Bone structure</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Total area (cm$^2$)</td>
<td>7.0±0.7</td>
<td>6.9±0.8</td>
<td>3</td>
</tr>
<tr>
<td>Endocortical area (cm$^2$)</td>
<td>4.6±0.8</td>
<td>4.8±0.8</td>
<td>-1</td>
</tr>
<tr>
<td>Cortical “thickness” (mm)</td>
<td>3.0±0.6</td>
<td>2.7±0.5</td>
<td>18</td>
</tr>
<tr>
<td>Bone strength relative to load</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall load (N)</td>
<td>6763±957</td>
<td>6316±637</td>
<td>8</td>
</tr>
<tr>
<td>Flexural rigidity (EI, kN x cm$^2$)</td>
<td>440±75</td>
<td>366±79</td>
<td>25</td>
</tr>
<tr>
<td>Ratio (fall load ÷ EI x 100)</td>
<td>1.6±0.3</td>
<td>1.8±0.3</td>
<td>-6</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01 adjusted for differences in body mass index
Table 2. Bone mineral density, structure and strength at the lumbar spine, comparing Rochester, MN residents with Type 2 diabetes mellitus (cases) to age- and sex-matched community controls (47 matched pairs)

| Variables (units) | Women | | | Men | | | Both sexes combined | | |
| | Cases | Controls | Δ | Cases | Controls | Δ | Cases | Controls | Δ |
| | \( \bar{x} \pm \text{SD} \) | \( \bar{x} \pm \text{SD} \) | % | \( \bar{x} \pm \text{SD} \) | \( \bar{x} \pm \text{SD} \) | % | \( \bar{x} \pm \text{SD} \) | \( \bar{x} \pm \text{SD} \) | % |
| Bone density | | | | | | | | | |
| Total lumbar spine (LS) vBMD (mg/cm\(^3\)) | 180±55 | 156±46 | 21 | 195±56 | 165±41 | 25 | 186±55 | 160±44* | 23 |
| LS trabecular vBMD (mg/cm\(^3\)) | 141±46 | 121±41 | 26 | 149±44 | 125±32 | 26 | 144±45 | 123±37** | 26 |
| Bone structure | | | | | | | | | |
| Total area (cm\(^2\)) | 10.5±1.4 | 10.6±1.2 | 1 | 13.9±1.9 | 14.3±1.8 | -1 | 11.9±2.4 | 12.1±2.4 | 0 |
| Endocortical area (cm\(^2\)) | 8.8±1.5 | 8.9±1.2 | 0 | 11.6±1.6 | 12.1±1.7 | -3 | 10.0±2.0 | 10.3±2.1 | -1 |
| Apparent cortical “thickness” (mm) | 1.6±0.3 | 1.5±0.3 | 9 | 1.9±0.5 | 1.7±0.3 | 15 | 1.7±0.4 | 1.6±0.3 | 11 |
| Bone strength relative to load | | | | | | | | | |
| Compressive load, 90° forward bending and lift 10 kg (N) | 3754±900 | 3332±554 | 15 | 3811±578 | 4042±747 | -3 | 3778±772 | 3636±729 | 7 |
| Vertebral strength (N) | 4045±1006 | 3576±995 | 19 | 5914±1816 | 5104±1043 | 21 | 4840±1675 | 4226±1262* | 20 |
| Ratio (90° + 10 kg load ÷ strength) | 1.0±0.2 | 1.0±0.2 | 0 | 0.7±0.2 | 0.8±0.2 | -10 | 0.8±0.2 | 0.9±0.2* | -4 |

*P < 0.05; **P < 0.01 adjusted for differences in body mass index
Table 3. Bone density, structure and strength at the distal radius, comparing Rochester, MN residents with Type 2 diabetes mellitus (cases) to age- and sex-matched community controls (47 matched pairs)

<table>
<thead>
<tr>
<th>Variables (units)</th>
<th>Women Cases ±SD</th>
<th>Controls ±SD</th>
<th>Δ %</th>
<th>Men Cases ±SD</th>
<th>Controls ±SD</th>
<th>Δ %</th>
<th>Both sexes combined Cases ±SD</th>
<th>Controls ±SD</th>
<th>Δ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone density</td>
<td></td>
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</tr>
<tr>
<td>Total distal radius (DR) vBMD (mg/cm$^3$)</td>
<td>526±80</td>
<td>462±105</td>
<td>19</td>
<td>552±104</td>
<td>524±107</td>
<td>8</td>
<td>538±91</td>
<td>490±110*</td>
<td>14</td>
</tr>
<tr>
<td>DR trabecular vBMD (mg/cm$^3$)</td>
<td>256±59</td>
<td>202±80*</td>
<td>51</td>
<td>299±77</td>
<td>286±61</td>
<td>8</td>
<td>275±71</td>
<td>240±83*</td>
<td>32</td>
</tr>
<tr>
<td>DR cortical vBMD (mg/cm$^3$)</td>
<td>1573±89</td>
<td>1564±96</td>
<td>1</td>
<td>1604±72</td>
<td>1603±72</td>
<td>0</td>
<td>1587±83</td>
<td>1581±87</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Bone structure</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total area (cm$^2$)</td>
<td>2.7±0.3</td>
<td>2.7±0.3</td>
<td>0</td>
<td>3.8±0.6</td>
<td>4.3±1.0*</td>
<td>-10</td>
<td>3.2±0.7</td>
<td>3.4±1.1*</td>
<td>-4</td>
</tr>
<tr>
<td>Endocortical area (cm$^2$)</td>
<td>1.8±0.3</td>
<td>1.9±0.3</td>
<td>0</td>
<td>2.6±0.5</td>
<td>3.1±0.9</td>
<td>-10</td>
<td>2.2±0.6</td>
<td>2.4±0.9*</td>
<td>-5</td>
</tr>
<tr>
<td>Cortical “thickness” (mm)</td>
<td>2.0±0.3</td>
<td>1.9±0.4</td>
<td>9</td>
<td>2.3±0.4</td>
<td>2.4±0.3</td>
<td>-3</td>
<td>2.1±0.4</td>
<td>2.1±0.4</td>
<td>4</td>
</tr>
<tr>
<td>Bone strength relative to load</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall load (N)</td>
<td>2662±45</td>
<td>2662±46</td>
<td>0</td>
<td>2752±39</td>
<td>2780±57</td>
<td>-1</td>
<td>2701±62</td>
<td>2713±77</td>
<td>0</td>
</tr>
<tr>
<td>Flexural rigidity (EI, kN · cm$^2$)</td>
<td>300±63</td>
<td>285±65</td>
<td>10</td>
<td>642±197</td>
<td>777±255</td>
<td>-6</td>
<td>453±220</td>
<td>505±303</td>
<td>3</td>
</tr>
<tr>
<td>Ratio (90° fall load ÷ EI x 100)</td>
<td>0.9±0.2</td>
<td>1.0±0.2</td>
<td>-2</td>
<td>0.5±0.1</td>
<td>0.4±0.1</td>
<td>30</td>
<td>0.7±0.3</td>
<td>0.7±0.4</td>
<td>12</td>
</tr>
</tbody>
</table>

*P < 0.05 adjusted for differences in body mass index