Skeletal changes in type-2 diabetic Goto-Kakizaki rats

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Abstract

We characterized appendicular and axial bones in rats with type-2 diabetes in five female Goto-Kakizaki (GK) rats, a strain developed from the Wistar rat showing spontaneous type-2 diabetes, and five age- and sex-matched non-diabetic Wistar rats. The humerus, tibia, metatarsals and vertebral bodies were analysed by peripheral quantitative computerized tomography (pQCT). In diabetic rats, the height of the vertebral bodies and length of the humerus were decreased while the length of the metatarsals was increased. A decreased cross-sectional area was found in the vertebral end-plate region and the tibial metaphysis. Notably, the diaphysis in all long bones showed expansion of periosteal and endosteal circumference. In tibia this resulted in increased cortical thickness, whereas in humerus and metatarsal it was unchanged. Areal moment of inertia was increased in all diaphyses suggesting greater bending strength. The most conspicuous finding in diabetic rats pertained to trabecular osteopenia. Thus, trabecular bone mineral density was significantly reduced in all bones examined, by 33–53%. Our pQCT study of axial and appendicular bones suggests that the typical feature of diabetic osteopathy in the GK rat is loss of trabecular bone and expansion of the diaphysis. The loss of metaphysial trabecular bone if also present in diabetic patients may prove to underlie the susceptibility to periarticular fracture and Charcot arthropathy. The findings suggest that the risk of fracture in diabetes varies according to the specific sub-regions of a bone. The approach described may prove to be useful in the early detection of osteopathy in diabetic patients who may be amenable to preventive treatment.

Introduction

It has been suggested that the risk of fracture is increased in diabetic patients (Forsen et al. 1999, Nicodemus & Folsom 2001, Schwartz et al. 2001). The fracture callus in diabetes is slow to appear and mature (Cozen 1972, Loder 1988). The complication rate of fracture treatment in diabetes is elevated because of increased susceptibility to infections, non-union, implant failure and redislocation (Bibbo et al. 2001). Moreover, diabetic patients are at risk to develop Charcot-type arthropathy in load-bearing joints (Jeffcoate et al. 2000).

A common finding in diabetic bone disease is osteopenia. Bone densitometry on type-1 diabetes patients fairly consistently show a decrease of bone mineral density (BMD), although in type-2 diabetes some studies have demonstrated decreased, some normal and some even increased BMD (Bouillon 1991, Buysschaert et al. 1992, Van Dael et al. 1995, Tuominen et al. 1999). Contradictory reports on bone changes in type-2 diabetes may be due to reliance on one single method such as dual energy X-ray absorptiometry (DEXA). Areal BMD, measured by DEXA, is affected by bone size and does not reflect volumetric BMD. In DEXA studies on diabetics the findings are not consistent across the skeleton suggesting that diabetic changes vary according to individual bone. Therefore, conventional scanning protocols for generalized bone diseases may not be entirely appropriate for assessment of diabetic osteopathy.

In a previous methodological study diabetic osteopathy was assessed in a rat model of spontaneous type-2 diabetes, the Goto-Kakizaki (GK) rat. Thus, tibia was examined by means of DEXA, peripheral quantitative computed tomography (pQCT) (Ahmad et al. 2003) and ash weight. pQCT seemed to provide the most relevant information. It demonstrated significant loss of volumetric BMD of the trabecular bone in the metaphysis and expansion of the diaphyseal cortex. In the present study, we used pQCT to explore whether trabecular osteopenia and diaphyseal cortical expansion are typical features of the diabetic rat skeleton by analysing different types of bones (axial, appendicular) as well as sub-regions (trabecular, cortical) within the individual bones.
Materials and Methods

Five female GK rats (Goto et al. 1976) bred in our animal department and five female Wistar rats (B&K Universal, Stockholm, Sweden) aged 12 months were used. The GK rat strain has been developed from the Wistar rat by selective inbreeding on the basis of elevated blood glucose levels. Thus, Wistar rats are the only relevant controls. The GK rats have spontaneous mild to moderate type-2 diabetes with onset early after birth (Abdel-Halim et al. 1994) and have been shown to develop chronic complications of diabetes such as neuropathy, retinopathy and nephropathy in long-standing disease (Östenson 2001). As these rats are not obese, they may reveal effects of diabetes on bone that could otherwise be masked by obesity seen in other animal models and in humans with type-2 diabetes. Animals were cared for in the animal department at Karolinska Hospital according to the Karolinska Institute’s protocol. The same diet, standard rat-chow, was available ad libitum to both diabetic and control rats. No treatment was given to the GK rats to correct the diabetes since such treatment would affect bone turnover. Notably, insulin is a growth factor for bone. Calorific restriction would impair bone formation due to undernutrition because these rats are not obese. All animal experiments were performed with approval from the Ethics Committee for Animal Research, North Stockholm, Sweden.

To establish the diabetic state, an intraperitoneal (i.p.) glucose tolerance test was performed (Östenson 2001). Animals were fasted overnight and fasting glucose was measured in tail blood. An i.p. injection of glucose solution (2 g/kg body weight) was given and blood glucose was measured after 2 h. Rats were killed by decapitation under an overdose of Hypnorm (Janssen Pharmaceutica, Beerse, Belgium). The lumbar vertebrae including part of the pelvis, whole humerus, tibia and 3rd metatarsal bones were dissected, cleared of soft tissue and stored in 70% ethanol.

Tomographic measurements were made as described previously (Ahmad et al. 2003) using the Stratec XCT Research M (Norland, Fort Atkinson, WI, USA) which has a voxel resolution of 70 microns. In brief, for trabecular bone analysis the humerus and tibia were scanned at the proximal metaphysis while in the spine, L4 and L5 vertebral bodies were scanned in their mid-portion and near the distal end-plate (85% of vertebral body height). No metaphyseal scan was taken in the metatarsal for technical reasons because of the small size of the bone and very short metaphysis. For identifying trabecular bone we selected the area protocol which is a standard in the CT software and a convention applied by others (Tuukkanen et al. 2000, McHugh et al. 2003). The cutoff of inner 45% of the bone cross-section has a high correlation to trabecular bone volume/tissue volume as measured by conventional histomorphometry. Analysis gave the cross-sectional area and volumetric BMD (total and trabecular). For cortical bone analysis in diaphyseal bone, the humerus was scanned at 70% of its length from the proximal end, the tibia at 75% from the proximal end, and the metatarsal in its middle. Data on volumetric cortical BMD, cross-sectional area, cortical thickness, peristeal and endosteal circumferences, and cross-sectional moment of inertia were obtained. Tomographic bone-strength index was calculated as a product of cross-sectional moment of inertia and volumetric BMD. This index has been shown to correlate strongly with mechanically tested bending strength (Ferretti et al. 1996) in non-diabetic rats. The inter-assay coefficients of variation for the pQCT measurements, assessed previously in our laboratory by scanning bones five times after repositioning, were less than 2%.

Statistics

Mean and standard deviation were used to summarize the measurements. Parametric tests were used for all group comparisons after confirming absence of severe skewness. t-test was used for comparisons of means between control and diabetic groups. An α-level of 5 percent was chosen.

Results

Diabetes and body weight

The presence of diabetes in the GK rats was confirmed by fasting glucose levels and glucose tolerance test (Table 1). The mean weight of the diabetic rats was 9-5% lower compared with controls, but the difference was not significant.

Bone size and form

Analysis of bone morphology considered length, cross-sectional area, circumference and cortical thickness (Table 2). In diabetic rats, there was a significant decrease in cross-sectional area of the humeral and tibial metaphyses but, notably, a significant increase in the diaphyses. A similar pattern was seen in the vertebral body in the sense that the end-plate region exhibited a decreased cross-sectional area, whereas it was unchanged in the mid-portion.

Volumetric bone mineral density

In the metaphyseal region, the BMD was reduced in all bones (10% to 22%) in diabetic rats compared with controls (Table 3). On separate analysis of the trabecular compartment, a substantially greater loss of BMD was observed, ranging from 33% to 53%. The greatest loss was in the humeral metaphysis, followed by the middle of the vertebral body, the tibial metaphysis and the vertebral...
end-plate. BMD of the cortical bone of the diaphyses was slightly but significantly reduced in the humerus but unchanged in the tibia and the metatarsal.

**Estimated bending strength**

Both estimates of bending strength, i.e. cross-sectional moment of inertia and the tomographic bone strength index, showed a significant increase in the diabetic rats suggesting greater diaphyseal strength (Table 4).

**Discussion**

This study shows that there are typical changes in bones of the diabetic GK rat. In both the appendicular and axial skeleton there is a significant loss of trabecular bone. In long bones there is also diaphyseal expansion.

In the previous pQCT study of rat tibia, we found that the metaphysis was narrower and the diaphysis was wider in diabetic rats (Ahmad et al. 2003). In the present study we again found a significant narrowing of the metaphysis in tibia and a similar trend in the humerus. Also, the subchondral end-plate region of the vertebral bodies was significantly narrower in diabetic rats. Furthermore, expansion of the diaphysis was observed in all long bones examined. Thus, changes in size and form seem to be a consistent feature throughout the diabetic rat skeleton.

In another study based on X-ray measurements, we measured an index of cortical thickness (ratio of periosteal to endosteal diameter) in the humerus, metatarsal and tibia in 8-month-old male GK rats (Östenson et al. 1997) and found that it was significantly lower in the humerus and metatarsal, but not in the tibia in diabetic rats. From our present data, calculation of the cortical thickness index gave similar results (data not shown). However, this index

**Table 1** Animal characteristics

<table>
<thead>
<tr>
<th>Control (n=5)</th>
<th>Diabetes (n=5)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>312·2 ± 37·8</td>
<td>282·4 ± 34·14</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>3·8 ± 0·35</td>
<td>7·8 ± 1·67</td>
</tr>
<tr>
<td>Fasting 2 hours</td>
<td>5·2 ± 0·79</td>
<td>12·7 ± 3·38</td>
</tr>
</tbody>
</table>

**Table 2** Size and form of bones

<table>
<thead>
<tr>
<th>Control (n=5)</th>
<th>Diabetes (n=5)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>29·7 ± 0·76</td>
<td>27·4 ± 0·82</td>
</tr>
<tr>
<td>Tibia</td>
<td>40·6 ± 0·72</td>
<td>39·7 ± 0·95</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>15·3 ± 0·18</td>
<td>15·8 ± 0·17</td>
</tr>
<tr>
<td>Vertebral body L4, L5</td>
<td>6·3 ± 0·28</td>
<td>5·8 ± 0·17</td>
</tr>
<tr>
<td>Cross-sectional area (mm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus Metaphysis</td>
<td>8·66 ± 0·932</td>
<td>7·80 ± 0·348</td>
</tr>
<tr>
<td>Diaphysis</td>
<td>4·71 ± 0·273</td>
<td>5·31 ± 0·265</td>
</tr>
<tr>
<td>Tibia Metaphysis</td>
<td>17·91 ± 1·582</td>
<td>13·23 ± 0·270</td>
</tr>
<tr>
<td>Diaphysis</td>
<td>4·90 ± 0·172</td>
<td>5·61 ± 0·241</td>
</tr>
<tr>
<td>Metatarsal Diaphysis</td>
<td>1·45 ± 0·091</td>
<td>1·67 ± 0·017</td>
</tr>
<tr>
<td>Vertebral body End plate</td>
<td>6·93 ± 0·625</td>
<td>6·28 ± 0·360</td>
</tr>
<tr>
<td>Middle</td>
<td>6·16 ± 0·550</td>
<td>6·11 ± 0·210</td>
</tr>
<tr>
<td>Circumference (mm) – diaphysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus Periosteal</td>
<td>7·69 ± 0·224</td>
<td>8·16 ± 0·203</td>
</tr>
<tr>
<td>Endosteal</td>
<td>3·09 ± 0·167</td>
<td>3·55 ± 0·104</td>
</tr>
<tr>
<td>Tibia Periosteal</td>
<td>7·85 ± 0·138</td>
<td>8·39 ± 0·181</td>
</tr>
<tr>
<td>Endosteal</td>
<td>3·74 ± 0·224</td>
<td>3·85 ± 0·134</td>
</tr>
<tr>
<td>Metatarsal Periosteal</td>
<td>4·27 ± 0·132</td>
<td>4·59 ± 0·023</td>
</tr>
<tr>
<td>Endosteal</td>
<td>1·96 ± 0·134</td>
<td>2·29 ± 0·026</td>
</tr>
<tr>
<td>Cortical thickness (mm) – diaphysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>0·73 ± 0·026</td>
<td>0·73 ± 0·042</td>
</tr>
<tr>
<td>Tibia</td>
<td>0·65 ± 0·036</td>
<td>0·72 ± 0·027</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>0·37 ± 0·004</td>
<td>0·37 ± 0·006</td>
</tr>
</tbody>
</table>
Bone strength index (mm\(^4\) / gc m\(^3\))

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length di

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bending strength of the diaphysis in all diabetic long bones.

and the bone strength index. We found a higher calculated

which permit analysis of cross-sectional moment of inertia

the cortex is placed further away from the centre of the

periosteal diameter increases mechanical strength because

which bear more weight (hindlimb) were not. Possibly the growth response to mechanical loading is abnormal in diabetic rats. This shortening of certain bones seems to be a characteristic of GK rats and is more likely related to the underlying disease than altered growth per se.

Individual bone lengths may relate to other parameters analysed. The magnitude of changes in the trabecular bone and the cortical dimensions could not be satisfactorily explained by the bone length differences. In the GK rats, cortical expansion was seen in the humerus despite a reduction in length. If the length was greater, we would expect the expansion also to be greater. Moreover, met-

physal osteopenia is unlikely to be due to a smaller bone because volumetric BMD is not affected by differences in bone size. This is one of the main advantages of BMD assessments by pQCT as compared with DEXA (Seeman 1998).

A limitation of this study is that we have not established whether the skeletal changes in the GK rats are due to diabetes or due to genetic differences between the GK and Wistar rats. However, since the GK rats were bred from Wistar rats, they are expected by virtue of the breeding procedure to be genetically more similar to the Wistar than any other strain. Moreover, the type-2 diabetes in the GK rat is likely to be polygenetic, since the same is true for clinical type-2 diabetes, implying that it would be impossible for a diabetic rat to be genetically identical to a non-diabetic rat. Quite possibly, the genes responsible for diabetes may affect bone.

As for the mechanisms underlying the bone changes observed, a wide variety of factors are presumably involved. Indeed, in diabetes abnormalities of the endocrine organs such as the hypothalamus, the pituitary, adrenal, thyroid and parathyroid glands and the gonads as well as the endocrine function of the adipose tissue and the vitamin D system have been reported (Alrefai et al. 2002), all of which may affect bone turnover. Data on the GK rat are scanty, but there are findings of low growth hormone levels (Ismail et al. 1995) and low serum insulin-like
does not consider that wider bones are stronger. Increase in periosteal diameter increases mechanical strength because the cortex is placed further away from the centre of the bone (Turner & Burr 1993). In the current study we analysed the actual cortical thickness and circumference, which permit analysis of cross-sectional moment of inertia and the bone strength index. We found a higher calculated bending strength of the diaphysis in all diabetic long bones. Since pQCT can only provide data on mineral density but not on other aspects of bone quality, mechanical studies are required to ascertain the combined effect of the above factors on bone strength.

We have previously reported that the GK rats grow less than the corresponding Wistar rats (Östenson 2001). In the current study, the alteration of bone lengths was inconsistent across the skeleton in diabetic rats. Hence, the length differences are unlikely to be due solely to difference in growth. The bones bearing relatively less weight in the rat (axial and forelimb) were shortened, while those which bear more weight (hindlimb) were not. Possibly the growth response to mechanical loading is abnormal in diabetic rats. This shortening of certain bones seems to be

Table 3 Bone mineral density (mg/cm\(^3\))

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 5)</th>
<th>Diabetes (n = 5)</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total – metaphyseal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humeral metaphysis</td>
<td>758.4 ± 77.26</td>
<td>655.8 ± 17.94</td>
<td>-13.5% (0.0201)</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>628.6 ± 65.83</td>
<td>613.5 ± 29.88</td>
<td>-10.1% (0.0650)</td>
</tr>
<tr>
<td>Vertebral body</td>
<td>747.1 ± 74.92</td>
<td>600.0 ± 47.50</td>
<td>-19.7% (0.0060)</td>
</tr>
<tr>
<td>Middle</td>
<td>666.2 ± 73.04</td>
<td>517.2 ± 26.43</td>
<td>-22.4% (0.0027)</td>
</tr>
<tr>
<td>Trabecular – metaphyseal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humeral metaphysis</td>
<td>339.2 ± 81.74</td>
<td>160.6 ± 33.36</td>
<td>-52.7% (0.0019)</td>
</tr>
<tr>
<td>Tibial metaphysis</td>
<td>431.9 ± 90.07</td>
<td>272.5 ± 32.23</td>
<td>-36.9% (0.0058)</td>
</tr>
<tr>
<td>Vertebral body</td>
<td>576.5 ± 79.01</td>
<td>383.2 ± 58.88</td>
<td>-33.5% (0.0023)</td>
</tr>
<tr>
<td>Middle</td>
<td>459.8 ± 75.10</td>
<td>269.1 ± 18.24</td>
<td>-41.5% (0.0006)</td>
</tr>
<tr>
<td>Cortical – diaphyseal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>1437.3 ± 5.74</td>
<td>1399.1 ± 16.35</td>
<td>+2.7% (0.0012)</td>
</tr>
<tr>
<td>Tibia</td>
<td>1331.3 ± 9.36</td>
<td>1314.6 ± 22.04</td>
<td>+1.2% (0.1593)</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>1277.9 ± 12.11</td>
<td>1281.8 ± 7.42</td>
<td>+0.3% (0.0504)</td>
</tr>
</tbody>
</table>

Table 4 Estimated strength of diaphysis

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 5)</th>
<th>Diabetes (n = 5)</th>
<th>Difference (P-value)</th>
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</thead>
<tbody>
<tr>
<td>Cross-sectional moment of inertia (mm(^4))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>3.96 ± 0.436</td>
<td>5.52 ± 0.672</td>
<td>+39.5% (0.0024)</td>
</tr>
<tr>
<td>Tibia</td>
<td>3.84 ± 0.297</td>
<td>5.56 ± 0.565</td>
<td>+44.4% (0.0003)</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>0.29 ± 0.033</td>
<td>0.37 ± 0.011</td>
<td>+29.9% (0.0005)</td>
</tr>
<tr>
<td>Bone strength index (mm(^4) / g cm(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humerus</td>
<td>5.68 ± 0.615</td>
<td>7.72 ± 0.989</td>
<td>+35.9% (0.0045)</td>
</tr>
<tr>
<td>Tibia</td>
<td>5.11 ± 0.402</td>
<td>7.31 ± 0.692</td>
<td>+43.0% (0.0003)</td>
</tr>
<tr>
<td>Metatarsal</td>
<td>0.37 ± 0.042</td>
<td>0.48 ± 0.016</td>
<td>+30.3% (0.0006)</td>
</tr>
</tbody>
</table>

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growth factor-I levels (authors' unpublished data), which may reduce bone formation. On the other hand, serum insulin levels are elevated (Östenson 2001), which may increase bone formation. Thus the hormonal profile does not seem to reveal a pattern consistent with all the bone changes observed. In-depth assessment of the function of relevant endocrine organs and levels of other systemic factors of concern may provide useful mechanistic information, but is beyond the scope of the present study. However, from our results it appears that the complex regional bone changes are unlikely to be caused exclusively by systemic factors. In fact, the site-specific changes can best be explained by local factors regulating bone turnover.

The literature suggests that neuropathy and angiopathy may be the main features behind diabetic osteopathy (Edelman et al. 1987, Rix et al. 1999, Jeffcoate et al. 2000). Abnormal blood flow has been demonstrated in diabetic patients (Edmonds et al. 1982, 1985), possibly due to autonomic neuropathy. Notably, increased bone resorption has been observed in the presence of abnormal blood flow (Gross et al. 1999, Laroche 2002). One of the main theories on the mechanisms underlying Charcot joint formation, the neuro-vascular theory, considers osteopenia to be a result of disturbed vasoregulation caused by neuropathy (Rajbhandari et al. 2002). Neuropathy may also have direct effects on bone through neurotransmitter action on bone cells (Bjurholm et al. 1992, Lerner 2002). Moreover, disturbances in the interactions of neurotransmitters with growth factors and cytokines may explain the development of osteopathy caused by neuropathy. Recently, the sympathetic nervous system has been found to be involved in leptin-mediated regulation of bone mass (Takeda et al. 2002). Serum levels of leptin, a hypothalamic hormone, are abnormal in type-2 diabetes patients (Abdelgadir et al. 2002, Fischer et al. 2002, Sayeed et al. 2003). Since autonomic neuropathy is common in diabetes, both the neuropathy and abnormal leptin levels may contribute to osteopathy. We found that the diabetic skeleton shows different changes within individual bones; trabecular and cortical bone seem to be regulated differently. These observations suggest that a complex interplay of systemic hormones and local factors may underlie diabetic osteopathy.

Regardless of the exact mechanism, diabetic rats, due to the decreased trabecular density, appear to have weaker metaphyses. A pQCT study examining metaphyseal bone in diabetic patients demonstrated a significant reduction in trabecular BMD (Z-score) of the distal radius (Hirano et al. 1999). Presumably, the clinical implication is greater risk of metaphyseal, juxta-articular and intra-articular fractures in diabetes. Metaphyseal fractures of the proximal humerus have been noted to occur more frequently in the diabetic population even after correction for age, body mass index and differences in BMD (Schwartz et al. 2001). Recently, a multi-centre study of patients sustaining distal radius fractures (Vogt et al. 2002) reported that the risk of intra-articular fracture, but not that of extra-articular fracture, was increased twofold in diabetics. These reports support our findings, and reinforce the notion that the bone weakens in diabetes pertains not to the diaphyses of long bones, but to the regions rich in trabecular bone. Moreover, osteopenia has been suggested as one of the factors behind the development of Charcot joint (Young et al. 1995, Jeffcoate et al. 2000). Trabecular osteopenia in the metaphysis presumably predisposes to subchondral bone collapse. Notably, increased levels of markers of osteoclastic bone resorption have been found in Charcot arthropathy (Gough et al. 1997).

Our pQCT study suggests that certain sub-regions of a diabetic bone, i.e. the metaphyses, are more susceptible to fracture, while others, i.e. diaphyses, are not. In a recent editorial (Nelson & Jacober 2001) on fractures in diabetes it was stated that ‘...a normal bone mass, as conventionally assessed by DXA and related modalities, can be offset by bone fragility at certain fracture sites and the likelihood of injury to these sites.’ Thus, the most commonly used non-invasive tool for the detection of osteopenia, i.e. DEXA, may be inadequate for detection of diabetic osteopathy because it measures areal BMD and cannot separately analyse trabecular and cortical bone. Specifically, this applies to the assessment of trabecular BMD and cortical dimension.

In the diabetic patient population, a screening of different bones by pQCT may identify the typical bone and sub-region having the most pronounced osteopenia as compared with controls. Routine pQCT of such a site may enable detection of early diabetic osteopathy. This could be used to establish the indication for preventive treatment to reduce the risk of fracture and development of Charcot joint. The approach may also be applied to diabetic patients having sustained a fracture to detect the subset at increased risk of developing post-traumatic osteopenia and/or Charcot joint (Kristiansen 1980, Bibbo et al. 2001).

Acknowledgements

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