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Research Article

Trabecular Bone Scores and Bone Fractures in Diabetes Patients with and Without a Charcot Foot

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Abstract

The collapse of bones in the Charcot foot may be caused by other factors than decreased bone mineralization, such as the trabecular structure. The trabecular bone score (TBS) of the lumbar spine can be measured by dual energy x-ray absorptiometry as a measure of trabecular structure and may reflect resistance to fracture beyond that of bone mineral alone.

Thus, the aim of this study was to investigate whether TBS is lower in diabetes patients with a Charcot foot compared to diabetes patients without a Charcot foot, and to assess changes in TBS and occurrence of fractures over 8.5 years in these patients.

Methods: 41 patients with type 1 or type 2 diabetes, of which about half had a Charcot foot, were included in 2005-2007 and 21 of these were followed up after 8.5 years.

TBS and bone mineral density (BMD) of the lumbar spine were measured with Lunar Prodigy DXA-scanner and TBS iNsight software. The occurrence of bone fractures from baseline to follow-up was registered.

Results: There were no significant differences in TBS between those with and those without a Charcot foot neither at baseline nor at follow-up ($p>0.32$). Furthermore, there was no significant change in TBS from baseline to follow-up in neither those with nor those without a Charcot foot ($p>0.19$), and there was no significant difference in the change in TBS between the two groups ($p>0.21$).

All fractures had occurred in the diabetes patients with an acute Charcot foot (4 out of 10 patients at follow-up: i.e. 40%), which is statistically significant ($p<0.035$) compared to no fractures in the diabetes patients without a Charcot foot (11 patients at follow up).

There were no significant associations between BMD, TBS, and biochemical markers of bone turn over at baseline and later occurrence of fracture in the diabetes patients with Charcot foot.

Conclusion: There was no association of TBS of the lumbar spine and having a Charcot foot, or not, in diabetes patients, neither at baseline, nor after 8.5 years follows up. Diabetes patients with an acute Charcot foot seem to have an increased risk of fracture, which might not be revealed by measurement of TBS.

INTRODUCTION

Charcot osteoarthropathy (Charcot foot) is a rare but severe complication to diabetes mellitus and peripheral neuropathy (1). It manifests as an aseptic inflammation of bones and joints in the feet leading to progressive degeneration of the bone structures, which can cause deformity and ulceration [1,2]. The precise pathogenetic mechanism leading to the collapse of bones and joints in the Charcot foot is however unknown [3,4].

Measurement of bone mineral density (BMD) is considered as the gold standard for the diagnosis of osteoporosis. We have previously reported that diabetes patients with chronic Charcot foot, but not patients with an acute Charcot foot, may have reduced BMD in the calcaneus, but not elsewhere in the skeleton. On the other hand, patients with an acute Charcot foot have increased markers of bone turnover and inflammation [4]. However, when followed up 8 years later, the diabetes patients with a previous Charcot foot had similar BMD´s at hip, spine and calcaneus, as well as markers of bone turnover, as diabetes patients without a previous Charcot foot [5]. Thus, the BMD in diabetes patients with a Charcot foot does not seem to be significantly affected, why other components of the bones than bone mineral, such as the collagen and/or the trabecular structure or geometry, may be affected instead [6-8].

The trabecular bone score of the lumbar spine can be measured by dual energy x-ray absorptiometry as a measure of trabecular structure and may reflect resistance to fracture beyond that of BMD [9,10].

Thus, the **aim** is to investigate whether the trabecular bone score is lower in diabetes patients with a Charcot foot compared to diabetes patients without a Charcot foot, and to assess the changes in the Trabecular Bone Score over 8 years, in our previously well-described diabetes population with and

without a Charcot foot [4,5]. Furthermore, to assess the number of fractures in our population and to compare the BMD and TBS in those patients with fractures and those without fracture.

Population

The population and methods have been described in detail previously [4,5].

In brief, 49 patients with type 1 or type 2 diabetes were originally included in the study and were examined in 2005-2007 (baseline). Half of the patients had an acute or chronic Charcot foot at baseline, whereas the others did not have a Charcot foot [4].

In 2015, after a mean of 8.5 year (follow-up), 21 of the diabetes patients were examined again [5]. Of these, 10 patients had had an acute Charcot foot at baseline (DM+CF group), whereas 11 patients did not had had a Charcot foot at baseline (DM-CF group). None of the participants had a Charcot foot at follow-up [5].

None of the diabetes patients were taking antiosteoporotic drugs prior to, or during, the study.

METHODS

Baseline measurements were performed in 2005-2007 and again after 8.5 years on average, as described previously [5]. BMD of the anteroposterior lumbar spine (L2-L4) had been assessed with a Lunar Prodigy DXA-scanner (GE, Madison, WI, USA, with encore 2005 software, version 9.15.010).

For the measurement of the Trabecular Bone Score (TBS) of the lumbar spine, the original scan data were restored from archive. After quality control and adjustments of the ROIs over the lumbar spine if needed, using Encore software version 16.20.059, the data were exported to a separate PC running the TBS software (TBS iNsight, version 3.0.2.0). Calibration of the TBS software was performed with the TBS_phantom_V3, serial number 0028.

The BMD and TBS T-scores were calculated by the DXA software using normal reference material (provided by the scanner software) of age, sex and ethnicity values. The BMD T scores are used for diagnosis of osteoporosis (T-score < -2.5) and osteopenia (-2.5 < T-score > -1) [11].

The occurrence of bone fractures from baseline to follow-up was registered.

Statistical analysis

Data are expressed as [means ±1SD] for normally distributed data, and as [median ±range] for data not normally distributed. Normal distribution in data was controlled by Shapiro-Wilks tests (no transformations were used). Student's t-tests (unpaired and paired) were used to test for differences between groups in normally distributed data sets. In groups not normally distributed, the non-parametric test Mann-Whitney rank sum test was used. For matched groups not normally distributed (e.g. baseline versus follow-up) Wilcoxon signed rank tests were used.

Statistics and general data handling was done using IBM SPSS Statistics v. 23 by IBM Corporation, SIGMAPLOT v. 11.0.0.77 by Systat Software Inc., Microsoft Excel 2000 v. 9.0.2812 by Microsoft Corporation and Apache OpenOffice 4.0.1 by The Apache Software Foundation.

RESULTS

TBS results were available from 41 patients at baseline (eight missing), whereas TBS results were available from all 21 patients at follow up.

Baseline characteristics of the patients with available TBS results are shown in Table 1, and the TBS results at baseline and at follow-up are shown in Table 2. There were no significant differences in TBS between those with and those without a Charcot foot at baseline or at follow-up (p=0.95 and p=0.32, respectively). Furthermore, there was no significant change in TBS from baseline to follow-up in neither those with nor those without a Charcot foot (p=0.998 and p=0.19, respectively), and there was no significant difference in the change in TBS between the two groups (p=0.21).

- At the follow up, 4 patients had had fractures between baseline and foOne patient had had a Colles fracture on two different occasions, one of each wrist,
- One had had a vertebral fracture,
- One had had a fracture of the ankle (traumatic, not in the previous Charcot foot) and a fracture of the calcaneus of the previous acute Charcot foot (which was not considered to be a relapse of Charcot),

Table 1: Baseline characteristics of the diabetes patients with or without a previous Charcot foot, who had available TBS results.

	Previous Charcot	No Previous Charcot
n (#)	22	19
Age (years) [median; range]	57; 25	62; 23
Sex (Male/Female)	17/5	15/4
BMI (kg/m^2)	30.6 ±5.3	29.0 ±5.1
Diabetes type (I/II)	5/17	3/16
Diabetes duration (years) [median; range]	15; 39	14; 40
HbA1c (mmol/mol)	63 ±19	63 ±15

Table 2: Trabecular Bone Scores (TBS) of the Lumbar Spine L2-L4 at baseline (BL) and after 8.5 years of follow-up (FU) in diabetes patients with or without a Charcot foot at baseline.

	Baseline (n=41)		
	Charcot foot	No Charcot Foot	P-value
TBS (g/cm^2)	1.277 ±0.123	1.274 ±0.121	p=0.948
	Follow-up (n=21)		
TBS (g/cm^2)	1.312 ±0.081	1.361 ±0.130	p=0.323
*Change in TBS from BL to FU	0.000 ±0.118	0.053 ±0.126	p=0.349

TBS: Trabecular Bone Scores, BL: Baseline, FU: after 8.5 years of follow-up.
*Change in TBS in diabetes patients who had available measurements both at Baseline and at Follow-up

- One had had a fracture in the foot (in the previous acute Charcot foot) due to a moderate-energy trauma.

All the fractures had occurred in the diabetes patients with an acute Charcot foot at baseline (4 out of 10 patients at follow-up: i.e. 40%), which is statistically significant ($p<0.035$) compared to no fractures in the diabetes patients without a Charcot foot (11 patients at follow up).

The BMD of the four patients with fractures was significantly lower compared to the other Charcot patients without a fracture (0.988 ±0.166 g/cm^2 vs 1.391 ±0.129 g/cm^2, respectively, $p=0.001$), whereas the TBS of the four patients with fracture was not significantly different from the other Charcot foot patients (six) without fracture (1.264 ±0.102 g/cm^2 vs 1.312 ±0.089 g/cm^2, $p=0.432$).

The individual T-scores derived from TBS at baseline (BL) and follow up (FU) of the four patients with fractures were BL: -1.2; FU: missing, BL: -2.3; FU: -2.4, BL: -3.4 ; FU: -1.8 and BL: -1.6; FU: -0.9, respectively, whereas the corresponding individual T-scores derived from BMD at the lumbar spine were: BL: -2.2; FU: -3.0, BL: -3.7; FU: -3.3, BL: -1.7; FU: -0.7 and BL: -0.4; FU: +0.2. Thus, based on the BMD T-score at baseline, one of the four patients with fracture had osteoporosis and two had osteopenia, whereas the patients were somewhat different classified using the TBS T-scores.

There were no significant associations between BMD, TBS, and biochemical markers of bone turn over at baseline and later occurrence of fracture in the diabetes patients with acute Charcot foot.

As most of the patients were men, the analyses were performed omitting women, which did not change the results of the primary analyses, which were performed including both men and women.

DISCUSSION

Trabecular Bones Scores (TBS) have not been reported in diabetes patients with a Charcot foot before and no one have reported on long term changes in TBS and occurrence of bone fractures in diabetes patients with Charcot foot. However, due to the small number of participants and fractures, conclusions should be drawn with precaution.

There was no association of TBS of the lumbar spine and having a Charcot foot, or not, in diabetes patients, neither at baseline, nor after 8.5 years follows up. As previously reported, this was the same for the BMD of the lumbar spine as well as for the hips [5]. However, in the present study, the diabetes patients with an acute Charcot foot had a high incidence of bone fracture, i.e. 40% had fractures over a period of 8.5 years. This suggests that measurements of BMD or TBS by DXA do not adequately describe the increased risk of fractures in diabetes patients with a previous Charcot foot, compared to diabetes patients without a Charcot foot. Methods that can measure other components of the bones than BMD and TBS, such as the collagen and/or the trabecular structure, geometry or bone strength, such as micro indentation [12,13], should be studied in diabetes patient with Charcot.

Besides treating the acute Charcot foot, osteoporosis, if present, should also be treated to prevent osteoporotic fractures in these patients, but it remains to be proven with which drug. Drugs used for treatment of osteoporosis have been tried for treatment of acute Charcot in diabetes patients, but so far all have failed [2]. Thus, for instance, zoledronic acid seems to worsen the acute Charcot foot [14] and the effect on subsequent bone fractures in this special subpopulation of diabetes patients is not known.

In the acute Charcot foot, blood flow and markers of inflammation and bone resorption (IL-6 and the RANKL/OPG ratio) are increased [3,15], and an optimal medical treatment of the acute Charcot foot as well as of osteoporosis may be an inhibition of bone resorption and inflammation targeting the RANKL/OPG system. Denosumab®, which is monoclonal antibodies against RANK-L, efficiently inhibits bone resorption, and is approved for treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures [16]. A recent study has indicated that Denosumab is effective in treating the acute Charcot foot, decreasing the time needed for offloading [15]. However, there is no data yet on the prevention of bone fractures with Denosumab in diabetes patients with an acute Charcot foot and with osteoporosis, - or without osteoporosis for that matter. Such studies are needed.

CONCLUSION

In conclusion, there was no association of TBS of the lumbar spine and having a Charcot foot, or not, in diabetes patients, neither at baseline, nor after 8.5 years follows up. Diabetes patient with an acute Charcot foot may have an increased risk of fracture, which may not be captured by measurement of TBS.

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