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Associations between trabecular bone score and biochemistry in surgically vs conservatively treated outpatients with primary hyperparathyroidism: A retrospective cohort study

Julius Simoni Leere[a,*], Christian Kruse[a,c], Maciej Robaczyk[b], Jesper Karmisholt[a,b], Peter Vestergaard[a,b,c]

[a] Department of Clinical Medicine, Aalborg University, Denmark
[b] Department of Endocrinology, Aalborg University Hospital, Denmark
[c] Steno Diabetes Center North Jutland, Denmark

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ABSTRACT

Purpose: Trabecular Bone Score (TBS) is a software-based method for indirect assessment of trabecular bone structure of the spine, based on analysis of pixels in dual energy x-ray absorptiometry (DXA) images. Few studies describe the use of TBS in patients with primary hyperparathyroidism (PHPT). This study aimed at further describing this relationship, investigating possible correlations between biochemistry, body mass index (BMI), fracture incidence and TBS.

Methods: Cross-sectional study of 195 patients with verified PHPT, surgically (27) or conservatively (168) treated at the Department of Endocrinology, Aalborg University Hospital. TBS was acquired by reanalyzing DXA-images of the included subjects from the outpatient clinic. Biochemical variables were obtained from clinical routine blood samples taken in relation to the DXA-scans. History of fractures and medical history was obtained from radiology reports and medical charts.

Results: Patients with active PHPT had a TBS-score signifying a partly degraded bone structure, whereas surgically treated patients had a normal bone structure as judged by TBS, though the difference in TBS-score was not statistically significant. Use of antiresorptive treatment was negatively associated with BMD but not TBS. No correlations between the biochemical variables and TBS were found. A negative correlation between TBS and BMI in patients with PHPT was present. Patients experiencing a fragility fracture had a significantly lowered TBS, BMD and T-Score.

Conclusion: Biochemistry does not seem to predict bone status in terms of TBS in patients with PHPT. TBS is negatively correlated to BMI, which is also seen in patients not suffering from PHPT. The lack of a predictive value for antiresorptive treatment for TBS may raise concern. TBS appears to have a predictive value when assessing risk of fracture in patients with PHPT.

Mini abstract: This cross-sectional study investigates possible correlations between biochemical variables, body mass index (BMI) and trabecular bone score (TBS) in 195 patients with primary hyperparathyroidism. It finds no correlation between biochemical variables and TBS, but finds a negative correlation between TBS and BMI and a clear association between fracture incidence and low TBS-score.

1. Introduction

Primary Hyperparathyroidism (PHPT) is often an asymptomatic condition at the time of diagnosis (Mosekilde, 2008). Despite lack of symptoms PHPT often leads to bone loss, osteoporosis and increased risk of fractures (Rubin et al., 2008; Valdemarsson et al., 1998; Vestergaard et al., 2000). Hence, to predict and prevent fractures, guidelines suggest close monitoring of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA)-technology (J.P. et al., 2014). BMD, however, appears to lack sensitivity with regards to predicting fractures in patients with PHPT, and many vertebral fractures (VFx) are diagnosed in patients suffering from osteopenia rather than

* Corresponding author at: Department of Endocrinology, Aalborg University Hospital, Medicinerhuset, Mølleparkvej 4, DK-9000 Aalborg, Denmark.
E-mail addresses: j.leere@rn.dk (J.S. Leere), c.kruse@rn.dk (C. Kruse), mgr@rn.dk (M. Robaczyk), jsk@rn.dk (J. Karmisholt), p.vestergaard@rn.dk (P. Vestergaard).

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osteoporosis (De Geronimo et al., 2006; Vignali et al., 2009). Trabecular BMD appears less affected in PHPT as opposed to BMD at cortical sites, such as the distal forearm (Dempster et al., 2007; Silverberg et al., 1989).

Studies utilizing high resolution periphery quantitative computed tomography (HRpQCT) have shown that the microarchitecture in both cortical and trabecular bone is degraded by PHPT (Bandeira et al., 2014; Hansen et al., 2010; ; Stein et al., 2013) which could explain the increased incidence of vertebral fragility fractures in patients with the disease (Khosla et al., 1999). Evaluation of bone microarchitecture seems relevant for refining risk estimation for fractures and for selecting patients for surgical treatment. QCT-technology is limited in its utility by being expensive and lack of distribution. Recently trabecular bone score (TBS)-software applied to DXA-images of the lumbar spine have shown somewhat promising results in fracture risk assessment in both primary osteoporosis and various forms of secondary osteoporosis (Bréban et al., 2012; Leslie et al., 2013b; Pothuaud et al., 2009; Rabier et al., 2010). TBS is a pixel-based grey-level tissue-texture analysis using experimental variograms adapted from 2 D lumbar spine DXA-images that provides a measurement that correlates to the bone microarchitecture (Hans et al., 2011). Thus, TBS does not directly reflect bone microarchitecture, but rather variations in the grey-tones of the DXA-image. TBS has been shown, when compared with μCT in cadaveric bones and HRpQCT in clinical studies, to correlate strongly with various measures of 3D trabecular microarchitecture such as connectivity, density, trabecular number and trabecular spacing, and thus provides an indirect estimate of the bone structure quality.(Hans et al., 2011; Pothuaud et al., 2008; Silva et al., 2013) A low TBS value is associated with a weak bone structure and an increased risk of fragility fractures partly independent of BMD (Harvey et al., 2016; Silva et al., 2014). A few studies, all based on relatively small cohorts, have evaluated TBS in patients with PHPT as a tool in assessing bone quality, fracture risk and improvement in bone structure by medical and surgical treatment of the condition (Cipriani et al., 2017; Eller-Vainicher et al., 2013; Lee et al., 2017; Rolighed et al., 2014; Romagnoli et al., 2013; Silva et al., 2013; Walker et al., 2016). These studies have shown that TBS is reduced in patients with PHPT, that TBS correlates with HRpQCT indices in these patients, and that TBS alone or in combination with lumbar spine-BMD appear more accurate than BMD alone in detecting and predicting VFx. Possible correlations between relevant blood-derived biochemical markers (such as plasma calcium (p-calcium), plasma parathyroid hormone(p-PTH) and plasma -alkaline phosphatase(p-ALP)) and TBS in PHPT patients, have only been sparsely investigated (Eller-Vainicher et al., 2013; Walker et al., 2016). Such correlations could be valuable, as they would possibly give information about a given patient's bone-microarchitecture from a simple blood sample.

This study contributes to the existing sparse literature in the field with a larger cohort including PHPT patients with active disease as well as surgically treated. We sought to examine further the use of TBS in PHPT, aiming to investigate, by the means of multivariate regression analysis, whether a correlation between commonly used blood analyses and TBS scores could be identified in patients suffering from PHPT. We also studied the association between TBS and incidence of low-energy fractures, and finally to further clarify whether an association could be found between TBS-scores and body mass index (BMI) in patients with PHPT. The latter was a main target for the study, as previous studies have shown conflicting evidence, and a controversial negative correlation between TBS and BMI has been described recently by Donovan Tay et al., despite using newer versions of the TBS-software (Donovan Tay et al., 2018; Hernández et al., 2016; Langsetmo et al., 2016; Leslie et al., 2013a; Romagnoli et al., 2016). Patients suffering from PHPT are generally overweight (Bolland et al., 2005), and knowledge of a BMI correlation to TBS could therefore be of value in interpreting TBS results in clinical as well as research settings.

2. Methods

2.1. Study cohort

Eligible subjects were patients diagnosed with PHPT and followed in the outpatient clinic of the Department of Endocrinology, Aalborg University Hospital, Denmark, throughout the past 10 years up to the date of TBS analysis. The diagnosis was made according to international guidelines, as repeated elevated p-calcium and corresponding elevated or inappropriate normal p-PTH, in patients without any relevant differential diagnoses. A power calculation was conducted to ascertain that the available number of subjects would be statistically sufficient to detect relevant differences. Due to lack of previous experience with the usage of TBS at this facility, the power calculation was based on expected difference in BMD between the untreated and surgically treated subgroups. Assuming a 0.75% difference in BMD between the two subgroups, a risk of type 1 errors of 5%, a desired power of 80%, and a standard deviation of 1% of the DXA-measurements of BMD, the number of needed subjects in each subgroup should comprise a minimum of 25 subjects. A sample of 220 subjects of the available cohort was therefore deemed more than sufficient by the authors.

Thus, a random sample of 220 consecutive PHPT patients, who had a DXA-scan performed between 2009 and 2015, were selected for TBS analysis. The diagnosis of PHPT was then adjudicated by the first author by scrutinizing the patients' medical charts, investigating whether relevant differential diagnoses had been ruled out (e.g. correction of possible vitamin D deficiency, familial hypocalciuric hypercalcaemia (FHH), explanatory malignancy or granulomatous disease, iatrogenic hypercalcaemia, or secondary hyperparathyroidism). The patients were divided in two groups consisting of surgically treated patients (“surgically treated subgroup”) or patients with active disease (“active disease subgroup”) prior to the DXA in question (Fig. 1). Misdiagnosed patients were removed from the following analysis. Similarly patients with a BMI lower than 15 or above 37 kg/m^2 were removed from the analyses in accordance with the recommendations by The International Society of Clinical Densitometry and the manufacturer's guidelines (Silva et al., 2015).

2.2. Data acquisition

TBS was analyzed using TBSiNsight™-software (v. 2.2.0, Medimaps Group SA, Switzerland). All analyses were performed on March 22nd, 2016. In case more DXA-scans were available for the individual subject, the most recent was chosen for analysis. TBS-values for vertebrae L1–L4 of the spine were obtained together with the corresponding BMD (g/cm^2) and T-score (lumbar spine). Interpretation of the TBS-value was based on a tertile approach using the thresholds from a recent meta-analysis on TBS in fracture risk prediction by McCloskey et al. (2016), which has been used in a similar fashion in previous studies (Cipriani et al., 2017; Donovan Tay et al., 2018; Silva et al., 2013; Walker et al., 2016). Bone status in terms of TBS-score was thus graded as follows: A score ≥ 1.310 was considered low risk of fracture, $1.310 > TBS > 1.230$ was considered intermediate, and $TBS \leq 1.230$ was considered high risk. DXA images used for TBS-analysis were created using either a Hologic Discovery A or a Hologic Horizon A DXA-scanner (both Hologic Inc., MA, USA). For LS-BMD the in vivo precision (CV%) at our facility is 0.90%, for Total Hip 1.00% and for the femoral neck 1.79%. Biochemical variables were measured by the Department of Clinical Biochemistry at Aalborg University Hospital, which is subject to GLP procedures and ISO9000 accredited. Data on biochemical variables were collected in the timespan from September 28th, 2006 to the date of data extraction. Data was extracted on November 25th, 2015 from the LABKA II-system (CSC Denmark A/S), the clinical laboratory information system of the North Denmark Region, Aalborg University Hospital. Biochemical data were matched to the date of the DXA-scans and patients using personal identification numbers and the dates of