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

Julius Simoni Leerea,⁎ Christian Krusea,c, Maciej Robaczykb, 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 osteoporosis.
osteoarthritis (De Geronimo et al., 2006; Vignali et al., 2009). Trabe-
cular 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
(Brøbøn 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 mi-
croarchitecture (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 cada-
veric bones and HRpQCT in clinical studies, to correlate strongly with
various measures of 3D trabecular microarchitecture such as con-
nectivity, 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 evalu-
ated TBS in patients with PHPT as a tool in assessing bone quality,
fracture risk and improvement in bone structure by medical and sur-
gical 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 de-
tecting and predicting VFx. Possible correlations between relevant
blood-derived biochemical markers (such as plasma calcium (p-calci-
um), plasma parathyroid hormone(p-PTH) and plasma -alcaline
phosphatase(p-ALP) and TBS in PHPT patients, have only been spar-
sely investigated (Eller-Vainicher et al., 2013; Walker et al., 2016).
Such correlations could be valuable, as they would possibly give in-
formation 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 corre-
lation 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 re-
sults 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 dif-
ferential 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 ex-
pected 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 au-
thor 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
hypercalcemia, or secondary hyperparathyroidism). The patients were
divided in two groups consisting of surgically treated patients (“surgi-
cally 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/m² 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/
cm²) 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 ≤ 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%. Bio-
chemical variables were measured by the Department of Clinical Bio-
chemistry at Aalborg University Hospital, which is subject to GLP
procedures and ISO90000 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


acquisition for both blood samples and DXA-scans. The blood samples
drawn closest to the date of the scan were selected for analysis. Bio-
chemical analyses were performed using a Modular (2006–June 2012)
or Cobas-8000 (June 2012–present) analyzer system (both Roche Di-
agnostics, Switzerland). The following biochemical variables were
analyzed and checked for correlation to the TBS-score of vertebrae
L1–L4: p-total calcium (norm. 2.20–2.55 mmol/l), p-calcium ion (norm.
1.18–1.32 mmol/l), p-PTH (norm. 1.3–7.6 pmol/l), p-vitamin-D2 + D3
(norm. 50–160 mmol/l), p-phosphorous (norm. 0.76–1.41 mmol/l), p-
creatinine (norm. 45–90 μmol/l), and p-ALP (norm. 35–105 U/l). Ad-
ditionally, the renal tubular maximum reabsorption rate of phosphate
to glomerular filtration rate (TmP/GFR), and the urinary calcium ex-
cretion to glomerular filtration rate (U-Ca/GFR) were calculated based
on data on fasting excretion of urinary calcium, phosphorous and
creatinine from the cohort. Demographic data on age (years), sex (m/f),
body weight(kilograms), height(cm) and BMI(kg/m²) were collected
from data obtained in relation to the DXA-scans to evaluate the re-
presentability of the selected cohort. From scrutinization of the in-
cluded patients' radiology reports and medical charts further informa-
tion on the diagnostic workup was obtained. This included, in addition
to ruling out differential diagnoses, information about results and
performance of parathyroid scintigraphy, ultrasound of the parathyroid
glands, incidence of low-energy major osteoporotic fractures (MOF),
use of antiresorptive agents or calcimimetics prior to the DXA-proce-
dure, genetic screening for multiple endocrine neoplasia and FHH,
previous and later parathyroid surgery (PTX) until 01/03/2018, and
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Fig. 1. Selection of cohort.
timespans from 1st visit in the outpatient clinic and/or previous PTX
until the investigated DXA procedure. Fractures were identified through
radiology reports provided by on-site radiologists. Fractures were in-
cluded if they were MOFs i.e. 1st of hip, humerus, forearm or vertebral
column (Klop et al., 2015), took place between June 1st 2006 to June
1st 2018, did not involve a history of a high energy trauma, and no
previous fracture was described at the same site (fractures at the spine
counted once from diagnosis of first vertebral fracture only). At Aalborg
University Hospital VFxs are diagnosed following guidelines based on
the semiquantitative visual assessment as described by Genant et al.
(1993).

2.3. Statistical analysis

For statistical analysis SPSS 24 (IBM Corp., USA) and STATA 14.1
(StataCorp LP, USA) were used. Standard normal distribution was
checked using QQ-plots and histograms. As some of the included pa-
tients had surgery performed prior to the included analyses, data were
analyzed for treated and active disease subgroups separately. Cut-off
level of p-total calcium in the adjudication procedure was 2.55 mmol/l,
although results from patients with marginal disease was included if the
patients previously had repeated calcium levels above this cutoff.
Variables were reported in terms of percentages, means ± SD or
medians derived from logarithmic transformation with ranges as ap-
licable and depending on normality. Confidence intervals (95%) were
calculated for all reported data. Statistical significance was determined
using Chi-square test, Students t or Wilcoxon rank-sum tests depending on the type of data, normality, variance and distribution (F-test). Missing data were left out of analysis, no imputations were made, and number of subjects (n) was reported for each variable. Scatter-plots were used to evaluate possible correlations between TBS for L1-L4 and the various tested biochemical variables. Finally, multivariate regression analyses were computed for the whole verified population using TBS and BMD for L1-L4 as the dependent variables separately, and evaluating subgroup, sex, age, BMI, p-calcium levels, p-total D$_2$ + D$_3$, p-ALP, p-creatinine, p-PTH, p-phosphorous, use of antiresorptive agents and time since diagnosis as possible predictors. Model assumptions of the distribution of residuals were checked using residual statistics outcomes, histograms and pp-plots.

This paper is written in accordance with the recommendations of the STROBE Statement on the reporting of cross-sectional studies (von Elm et al., 2007).

3. Results

3.1. Demography

A total of 563 patients had been diagnosed with PHPT and followed in the outpatient clinic, Aalborg University Hospital, from 2006 until 2016. Of those, 437 patients had a DXA-scan performed in the timespan of 2009–2015. 220 patients were randomly selected of this cohort for further analysis. Judged from the medical charts 178 had active PHPT at the time of the DXA-scan and 29 were surgically treated (see Fig. 1). When evaluating the validity of the PHPT-diagnosis cohort, 13 were found not to have PHPT and were thus excluded from the study. Of these, one did not meet diagnostic criteria, five had FHH, and seven had secondary hyperparathyroidism (four due to vitamin D deficiency and three due to renal failure). This gives a total diagnostic precision of 207/220 = 94.1% (95% CI: 90.1%; 96.8%).

12 patients were removed from further analysis due to BMIs outside the recommended range for TBS-analysis (10 with active PHPT and 2 surgically treated, all with BMIs above 37.0 kg/m$^2$).

The diagnostic workup included a parathyroid scintigraphy in 75.0% vs. 92.3% (active vs. surg. treated; p < 0.05) of cases, and 65.9% vs 83.3% (p = 0.09) of the scanned patients had one or more adenomas visualized by this procedure. 85.1% vs 84.6% had ultrasound of the neck performed during the investigation, and 65.0% vs 63.6% of those scanned had visualization of suspected adenomas by this method. Twelve patients (7.1%) in the active disease subgroup had undergone at least one failed parathyroidectomy prior to the DXA-procedure. Eighty-three (49.4%) of the same subgroup had surgery performed in the follow-up period (ending 01/03/2018). Three patients in the surgically treated subgroup had elevated p-PTH above normal range post-PTX, of whom none were hypercalcemic.

Median timespan from 1st visit in the outpatient clinic until time of the included DXA-procedure was 3.77 (95% CI: 2.73; 5.20) months in the active disease subgroup vs 25.2 (95% CI: 15.3; 41.5) months (p < 0.001) in the surgically treated subgroup. Median time from surgery until time of DXA-procedure was 14.5 (95% CI: 7.8; 26.9) months in the surgically treated subgroup.

Time from blood-sample to scanning was checked, and did, except for p-ALP, not deviate significantly from the time of scanning; median time for each analysis was: p-calcium: 9 days, p-PTH: 24 days, p-creatinine: 19.5 days, p-vitamin D: 39 days, p-phosphorous: 15.5 days, p-calcium ion: 33 days, and p-ALP: 337 days.

In the active disease subgroup 21 patients (12.5%) received antiresorptive therapy prior to the DXA-session. A significantly larger proportion (29.6%; p = 0.02) of the surgically treated received antiresorptives at the time of scanning. Two patients in the active disease subgroup were treated with cinacalcet at the time of scanning.

Results on demography are displayed in Table 1. In the active disease fraction subjects were on average 64.1 ± 14.2 years old, 73.8% were women, and they were slightly overweight (BMI: 27.2 kg/m$^2$ (95% CI: 26.7; 27.9)). They did not significantly differ in age, sex, BMI, p-calcium levels, p-total D$_2$ + D$_3$, p-ALP, p-creatinine, p-PTH, p-phosphorous, use of antiresorptive agents and time since diagnosis as possible predictors. Model assumptions of the distribution of residuals were checked using residual statistics outcomes, histograms and pp-plots.

3.2. Biochemistry

The mean p-total calcium in the untreated subgroup was 2.74 ± 0.176 mmol/l (Ca$^{2+}$-ion: 1.46 ± 0.11 mmol/l) vs 2.31 ± 0.15 mmol/l (p < 0.001) (Ca$^{2+}$-ion: 1.21 ± 0.064 mmol/l) in the treated subgroup. As expected median p-PTH was significantly higher in the active disease cohort (12.36 vs 4.68 pmol/l (p < 0.001)). P-phosphorous was correspondingly lower in active disease patients (0.79 ± 0.185 vs 1.03 ± 0.19 mmol/l (p < 0.001)), and they also had significantly lower p-total 25 vitamin D (65.95 ± 26.67 vs 79.12 ± 34.21 nmol/l (p < 0.05)). No significant differences in urinary-Ca$^{2+}$/GFR, TMP/GFR-ratio, p-creatinine or p-alkaline phosphatase levels were found between the subgroups (See Table 1).

3.3. BMD and TBS-values

There was no significant difference in mean aBMD values for L1-L4 between the two subgroups (p = 0.09) vs treated) or T-score (−1.51 ± 1.36 vs −1.63 ± 1.18 (p = 0.68)). There was a trend for mean TBS-scores for L1-L4 being lower in the active disease-group: 1.28 ± 0.10 vs. 1.32 ± 0.12 in the active disease and treated subgroups respectively (p = 0.07), the first being within the partially degraded range, the latter in the normal range (See Table 2).

In the active disease subgroup 66 subjects (39.29%) had a TBS-score ≥ 1.31 indicating a normal bone structure/low fracture risk, 42 subjects (25.00%) had a TBS-score between 1.23 and 1.31, signifying partial degradation/intermediate fracture risk and 60 subjects (35.71%) had a TBS-score ≤ 1.23 indicating a degraded structure/high fracture risk. Corresponding figures for the treated subgroup were ≥ 1.31: 15 (55.56%); 1.23 < TBS < 1.31: 6 (22.22%); and ≤ 1.23: 6 (22.22%).

When excluding the subjects with osteoporosis (T-score < −2.5) the distribution was similar as follows:

Active disease: n = 115, TBS-score ≥ 1.31: 49 (42.60%); 1.23 < TBS < 1.31: 30 (26.10%); and TBS ≤ 1.23: 36 (31.30%).

Surgically treated: n = 15, TBS-score ≥ 1.31: 9 (60.0%); 1.23 < TBS < 1.31: 3 (20.0%); and TBS ≤ 1.23: 3 (20.0%).

3.4. Correlations between TBS and biochemistry (Table 3)

No significant correlations were found between the investigated biochemical variables and TBS for L1-L4 in either patients with active PHPT or in those surgically treated (Fig. 2). Scatterplots for the other investigated variables were similar to that of TBS vs. p-total calcium. Two multivariate regression analyses were performed using TBS and BMD of L1–L4 as the dependent variables, and sex, age, BMI, p-total calcium levels, p-total vitamin D$_2$ + D$_3$, p-ALP, p-creatinine, p-PTH, p-phosphorous, use of antiresorptive drugs and timespan from diagnosis to DXA-procedure as possible predictors (Table 3). Model assumptions were not violated. The explanatory strength of the models as measured by R$^2$ were 0.223 for TBS and 0.241 for BMD. The analyses revealed no significant correlations between TBS or BMD and any of the evaluated biochemical markers. Similarly, there was no association between treatment status (subgroup) or timespan from diagnosis to DXA-procedure and either TBS or BMD. BMI and absence of antiresorptive use was significantly positively correlated with BMD. TBS was significantly negatively associated with age and BMI (age: −0.002 ± 0.001(p < 0.001)), (BMI: −0.005 ± 0.002 (p = 0.006)). The negative correlation between TBS and BMI was confirmed when plotting TBS against corresponding BMI values (Fig. 3).
3.5. TBS, BMD and fragility fractures

28 patients were diagnosed with a total of 36 MOFs in the selected timespan. Of these 25 patients (with 32 fractures) were in the active disease subgroup. The fractures in the active disease group were distributed as follows: Hip: 3; Humerus: 3; Forearm: 15; Spine: 11.

TBS-scores were on average significantly lower in the subgroup who experienced fractures (fractures vs no-fractures: 1.23 ± 0.10 vs. 1.29 ± 0.10; \( p = 0.007 \)). BMD and T-scores followed a similar pattern, although with somewhat lesser statistical significance; BMD:

Table 1
Demography and biochemical variables, active disease vs. surgically treated fraction.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Surgically treated subgroup</th>
<th>Active disease subgroup</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD/(Median)</td>
<td>(Ranges) [95% CI]</td>
<td>Mean ± SD/(Median) [95% CI]</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td></td>
<td>(n)</td>
</tr>
<tr>
<td>Age, years</td>
<td>60.0 ± 14.3 (31; 87)</td>
<td>[54.3; 65.6] (n = 27)</td>
<td>64.1 ± 14.2 (18; 93) [61.9; 66.3] (n = 168)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>164.1 ± 10.62 (147.8; 199.8)</td>
<td>[160.0; 168.3] (n = 27)</td>
<td>165.6 ± 9.71 (144.6; 194.0) [164.1; 167.1] (n = 168)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>(70.0)</td>
<td>[63.5; 77.1] (n = 27)</td>
<td>74.6 ± 13.3 (45.1; 112.3) [72.6; 76.6] (n = 168)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 ± 5.1 (18.4; 36.99)</td>
<td>[24.5; 28.6] (n = 27)</td>
<td>27.2 ± 4.2 (16.4; 36.8) [26.6; 27.9] (n = 168)</td>
</tr>
<tr>
<td>P-total calcium, mmol/l</td>
<td>2.31 ± 0.15 (1.78; 2.50)</td>
<td>[1.78; 2.50] (n = 27)</td>
<td>2.74 ± 0.17 (2.36; 3.23) [2.72; 2.77] (n = 168)</td>
</tr>
<tr>
<td>P-calcium ion, mmol/l</td>
<td>1.21 ± 0.064 (1.00; 1.33)</td>
<td>[1.19; 1.24] (n = 27)</td>
<td>1.46 ± 0.11 (1.23; 1.83) [1.44; 1.48] (n = 168)</td>
</tr>
<tr>
<td>P-PTH, pmol/l</td>
<td>(4.68)</td>
<td>(12.36) [11.45; 13.34] (n = 168)</td>
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</tr>
<tr>
<td>P-tot-25-D vitamin, nmol/l</td>
<td>79.12 ± 34.21 (17.0; 155.0) [65.00; 93.24] (n = 25)</td>
<td>65.95 ± 26.67 (13.0; 148.0) [61.82; 70.1] (n = 168)</td>
<td></td>
</tr>
<tr>
<td>P-phosphorous, mmol/l</td>
<td>1.03 ± 0.19 (0.59; 1.50)</td>
<td>[0.96; 1.11] (n = 26)</td>
<td>0.79 ± 0.185 (0.19; 1.47) [0.764; 0.825] (n = 163)</td>
</tr>
<tr>
<td>P-creatinine, µmol/l</td>
<td>(73.86)</td>
<td>(75.16) [38.86; 179.5] (n = 168)</td>
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<tr>
<td>P-alkaline phosphate, U/l</td>
<td>73.41 ± 21.5 (43.0 ± 117.0) [64.90; 81.91] (n = 27)</td>
<td>(80.4) [72.9; 278.7] [76.06; 84.96] (n = 152)</td>
<td></td>
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<tr>
<td>U-Ca²⁺/GFR</td>
<td>(0.040)</td>
<td>(0.031) [0.027; 0.036] (n = 90)</td>
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<tr>
<td>TMP/GFR</td>
<td>0.67 ± 0.16 (0.46; 0.98)</td>
<td>[0.56; 0.78] (n = 11)</td>
<td>0.61 ± 0.17 (0.08; 1.39) [0.57; 0.64] (n = 90)</td>
</tr>
</tbody>
</table>

\* \( p < 0.05 \).

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3.5. TBS, BMD and fragility fractures

28 patients were diagnosed with a total of 36 MOFs in the selected timespan. Of these 25 patients (with 32 fractures) were in the active disease subgroup. The fractures in the active disease group were distributed as follows: Hip: 3; Humerus: 3; Forearm: 15; Spine: 11.

TBS-scores were on average significantly lower in the subgroup who experienced fractures (fractures vs no-fractures: 1.23 ± 0.10 vs. 1.29 ± 0.10; \( p = 0.007 \)). BMD and T-scores followed a similar pattern, although with somewhat lesser statistical significance; BMD:

Table 2
BMD and TBS, surgically treated vs. active disease fraction.

<table>
<thead>
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</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td></td>
</tr>
<tr>
<td>TBS-L1–L4</td>
<td>1.32 ± 0.12 (1.62; 1.54) [1.27; 1.37]</td>
<td>1.28 ± 0.10 (0.99; 1.54) [1.26; 1.30]</td>
<td>( p = 0.07 )</td>
</tr>
<tr>
<td>BMD-L1–L4, g/cm²</td>
<td>0.88 ± 0.13 (0.66; 1.17) [0.83; 0.94]</td>
<td>0.90 ± 0.15 (0.49; 1.42) [0.88; 0.92]</td>
<td>( p = 0.57 )</td>
</tr>
<tr>
<td>T-score, lumbar spine</td>
<td>–1.63 ± 1.18 (–3.6; 0.7) [–2.13; –1.13]</td>
<td>–1.51 ± 1.36 (–5.16; 3.40) [–1.73; –1.30]</td>
<td>( p = 0.68 )</td>
</tr>
</tbody>
</table>
Multivariate Linear Regression, treated and untreated subgroups: TBS/BMD-L1–L4 as dependent variable.

<table>
<thead>
<tr>
<th>Predicting variable</th>
<th>TBS L1-L4: Unstandardized B coefficient ± Std. error; (p-value)</th>
<th>BMD L1-L4: Unstandardized B coefficient ± Std. error; (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>−0.037 ± 0.034; (p = 0.278)</td>
<td>0.011 ± 0.048; (p = 0.821)</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.017 ± 0.022; (p = 0.438)</td>
<td>−0.055 ± 0.032; (p = 0.087)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>−0.002 ± 0.001; (p &lt; 0.001)</td>
<td>−0.001 ± 0.001; (p = 0.494)</td>
</tr>
<tr>
<td>P-total calcium, mmol/l</td>
<td>−0.005 ± 0.002; (p = 0.006)</td>
<td>0.013 ± 0.003; (p &lt; 0.001)</td>
</tr>
<tr>
<td>P-PTH, nmol/l</td>
<td>−0.041 ± 0.065; (p = 0.525)</td>
<td>−0.024 ± 0.093; (p = 0.796)</td>
</tr>
<tr>
<td>Plasma Calcium (Total)</td>
<td>−0.001 ± 0.001; (p = 0.391)</td>
<td>−0.003 ± 0.002; (p = 0.082)</td>
</tr>
<tr>
<td>P-Vitamin D (D2 + D3), nmol/l</td>
<td>−2.13 × 10⁻⁵ ± 0.000; (p = 0.948)</td>
<td>0.000 ± 0.000; (p = 0.323)</td>
</tr>
<tr>
<td>P-Alkaline phosphatase, U/l</td>
<td>0.000 ± 0.000; (p = 0.303)</td>
<td>−2.22 × 10⁻⁵ ± 0.000; (p = 0.954)</td>
</tr>
<tr>
<td>P-Creatinine, μmol/l</td>
<td>0.000 ± 0.000; (p = 0.472)</td>
<td>0.000 ± 0.001; (p = 0.664)</td>
</tr>
<tr>
<td>Antiresorptive therapy</td>
<td>−0.030 ± 0.023; (p = 0.193)</td>
<td>−0.062 ± 0.079; (p = 0.431)</td>
</tr>
<tr>
<td>Time from diagnosis</td>
<td>0.000 ± 0.000; (p = 0.451)</td>
<td>5.78 × 10⁻⁶ ± 0.000; (p = 0.794)</td>
</tr>
<tr>
<td>Model strength: $R^2 = 0.223$ (n = 153)</td>
<td>Model strength: $R^2 = 0.241$ (n = 147)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.

(0.84 ± 0.14 vs. 0.91 ± 0.14; p = 0.029); T-score: (−2.05 ± 1.26 vs. −1.42 ± 1.36; p = 0.045). Data reported here are for the active disease subgroup solely. Data on the total cohort and surgically treated subgroup can be found in the electronically submitted supplementary.

4. Discussion

4.1. TBS and BMD values

This study shows a trend for TBS being improved post-PTX in PHPT-patients, although not statistically significant. Thus, subjects with active, conservatively managed PHPT had a mean TBS within the partially degraded range, whereas surgically treated PHPT patients had a mean score within the normal range tertile.

No significant differences between the subgroups could be found for the corresponding BMDs and BMD-derived T-scores. The level of degradation, based on their TBS, in the active disease subgroup is in line with previously published studies on patients with PHPT (Cipriani et al., 2017; Lee et al., 2017; Rolighed et al., 2014; Silva et al., 2013; Walker et al., 2016). The distribution of patients between the TBS tertiles within each subgroup remained roughly unchanged even when excluding patients with osteoporosis as diagnosed by T-score below −2.5, confirming the independence of TBS from BMD.

Although there was a clear trend, the lack of statistical significance in the TBS-scores between treated and untreated patients, contrasts with what has been reported in some previous studies. Eller-Vainicher et al. (2013) and Rolighed et al. (2014) both reported increasing TBS-values 24 and 6 months after PTX, respectively. Other studies have conflicting results: Cipriani et al. (2017) found no change in TBS 18 months post PTX, and Donovan Tay et al. (2018) found no improvement in either obese or non-obese patients 24 months post-PTX. It has been suggested that this conflicting evidence could be explained by differences in the evaluated cohorts’ stages of the disease prior to surgery, and also that it may take longer for TBS to improve compared to BMD (Donovan Tay et al., 2018). The absence of a more pronounced difference in mean TBS-scores between the subgroups reported in this study could alternatively be explained by the difference in timing of the scan. Time from diagnosis to DXA was much longer in the treated group (25 months) than in the patients with active disease (3.7 months). The time that thus has passed since the surgical procedure (median 14.5 months) would at least allow a reasonable catch-up in bone density. Patients offered surgical treatment generally must be expected to have more advanced disease prior to surgery, and may therefore have had a lower T-score, BMD and TBS-score at the time of surgery, the two former known to improve post-PTX (Bollerslev et al., 2007; Rao et al., 2004).

Noteworthy is also the fact that there was no correlation between the use of antiresorptive treatment and TBS-levels in the regression...
analysis (Table 3), whereas, as expected, a significant impact was found when applying BMD as the dependent variable (−0.088 ± 0.034; (p = 0.01)). The negative correlation found between use of antiresorptive agents and BMD suggests that the patients treated with these drugs have a more deteriorated bone structure than those not offered treatment, which is expectable as they must have fulfilled diagnostic criteria for osteoporosis prior to commencing the treatment. The lack of a predictive value for antiresorptive treatment for TBS found in our analysis, however, may raise concern in a way: Do we treat the right patients suffering from PHPT with bisphosphonates, when we simultaneously find indications that TBS has a predictive value in identifying fractures? Can TBS form the basis for commencing treatment on its own? It is intriguing that a similar correlation could not be found when analysing TBS, especially when considering it is the same image effects by antiresorptive drugs on TBS are similar to, although less pronounced than the impact on BMD, though the partial independency of TBS from BMD may be another factor that explains this finding (Clarvey et al., 2016). This study finds no correlation between age and BMD, but a significant negative interaction between age and TBS (−0.002 ± 0.001 (p < 0.001)). This is similar to what is reported by Donovan Tay et al. (2018).

4.2. TBS and biochemistry

Fig. 2 shows, and the multivariate regression model confirms that no significant correlations of clinical importance were found between any of the investigated biochemical parameters and TBS, in either surgically treated patients or patients with active disease. This is in accordance with previously published poster-abstracts (E., 2012, 2010; Manzanares, 2014), and as briefly stated by Eller-Vainicher et al. (2013) and Walker et al. (2016)).

P-vitamin D levels were statistically lower in the subgroup with active disease, which is expectable as patients with PHPT have an increased turnover of vitamin D (Rolighed et al., 2014). We found no association between vitamin D levels and TBS scores. This corresponds well with the results reported by two recent cross-sectional studies by Lee et al. (2017) and Walker et al. (2016). None of those studies found differences in TBS-levels when comparing vitamin D sufficient and vitamin D insufficient patients with PHPT. Our results also align with the lack of effect on TBS by vitamin D-treatment in patients with PHPT found by Rolighed et al. (2014). The difference between the treated and active disease groups in terms of p-phosphorous and p-vitamin D confirm that the surgically treated patients are indeed cured, as they differ significantly on these parameters which in addition to p-calcium and PTH are affected in PHPT. Three patients in the surgically treated subgroup had elevated p-PTH, one had years after PTX developed renal impairment, and two had suspected hungry bones syndrome (Brasier and Nussbaum, 1988; Lee et al., 2006).

4.3. TBS and BMI

This study is among the first ones to report a negative correlation between TBS and BMI in patients with PHPT irrespective of surgical status. The association remains negative when removing the 12 patients having BMI-values outside the working ranges recommended by TBSiNight (15 to 37 (McCloskey et al., 2016)). This confirms the association described between TBS and weight by Walker et al. and underlines the associations found between TBS and BMI by Donovan Tay et al. (2018) and Walker et al. (2016).

This controversial negative correlation between TBS and BMI has been previously reported in various studies on other diseases than PHPT (Hernández et al., 2016; Langsetmo et al., 2016; Romagnoli et al., 2016; Shin et al., 2017). It is interesting since BMD is generally known to increase with increased bodyweight (Evans et al., 2015; Leslie et al., 2013a), which was also the case in this study (0.013 ± 0.003; (p < 0.001)). A recent publication by Mazzetti et al. (2017) demonstrated a significant difference in the relationship between TBS and BMI depending on the densitometer used (the manufacturer). The study concluded that a negative correlation was apparent when using densitometers from Hologic, but not from GE Lunar. This can be due to differences in how the densitometers accommodate soft tissues, e.g. interposed fat tissue, which must be adjusted for in the TBS-processing (Mazzetti et al., 2017). Langsetmo et al. show in their study in older men that the correlation between lumbar spine volumetric BMD and TBS is attenuated by increasing BMI, potentially indicating a waning association between TBS and incident fractures in patients with higher levels of BMI (Langsetmo et al., 2016). We used DXA-images derived from densitometers produced by Hologic Inc. Thus, our results are in keeping with those described by Mazzetti et al., and indicate that the
described relationship between TBS and BMI can also be present in cohorts with PHPT. This correlation, being a result of either an actual weakened bone structure, or attenuated precision of TBS due to noise from the interposed tissue, may be important if TBS is used in clinical assessment, as it could potentially lead to an overestimation of the fracture risk in patients. This could be of particular importance when evaluating patients suffering from PHPT, keeping in mind that PHPT is usually associated with an elevated BMI (Bolland et al., 2005), finding also observed in the patient cohorts in this study.

4.4. TBS, BMD and fragility fractures

This study finds TBS, when used in a tertile approach, to be at least comparable with BMD in predicting fragility fractures in patients with PHPT. TBS was significantly lower in patients enduring a fragility fracture throughout the study-period compared to those who did not. As also shown by the level of significance, this difference appears more pronounced for TBS than that for LS-BMD and corresponding T-score, which was in the osteopenic range. These results are in line with previous findings reported elsewhere (Eller-Vainicher et al., 2013; Romagnoli et al., 2013).

5. Strengths and limitations

A strength of this study is the relatively large sample of patients. This gives the study high power, which is relevant when a negative result is reported. The inclusion of both surgically treated patients and patients with active PHPT is another advantage, as it allows for direct comparison and indirect studying of the effect of PTX. The subgroups are demographically well matched, and the subgroups do, although they differ in size, both live up to the number dictated by the power calculation. The rather large variations of age in the patients within each subgroup gives a real life picture, and although this diversity in the cohort can influence the results, age was included in the regression analysis, and thereby adjusted for when evaluating other parameters. The inclusion of patients treated with antiresorptive agents can potentially affect the TBS analysis; however excluding this subgroup would also impose different limitations to the study, as these would likely be the patients with the most advanced stage of the disease. The method of data acquisition, being based on a diagnosis-classification system (ICD-10) can, when combined with scrutinizing the medical charts, give a valuable impression of the patients’ medical history. The diagnostic precision appears to be high even before scrutinizing the medical charts, and so data validity can be assumed high. However, the study also has limitations. The difference in time from diagnosis to the DXA (27 months in the treated group vs 2.5 months for patients with active disease), and the time that has passed since the surgical procedure to the DXA procedure for patients in the treated subgroup, complicates the interpretation when comparing TBS and BMD values directly for the two subgroups, but is of less importance in the evaluation of possible correlations with biochemical markers and demographic variables.

Therefore, we cannot provide time-defined estimations of development in e.g. BMD. The median timespan from scanning procedure to blood sampling was adequately short for most variables. However, for p-ALP the timespan was significantly longer, which can possibly be attributed to the mean-values being in the normal level in both subgroups (Table 1), and that this test is performed on a rarer basis than the other tests. The impact of this time-difference on the results seems therefore to be limited. The cross-sectional design and the lack of a healthy control group impose limitations on evaluation of causality but is adequate for fulfilment of the aims in this project by allowing identification of possible correlations between variables.

6. Conclusion

Patients with PHPT have on average a partly degraded bone structure when assessed by TBS, but the score seems to improve post PTX. This study found no clinically relevant correlations between p-total calcium, p-Ca\(^{2+}\)-ion, p-PTH, p-ALP, p- total-25- vitamin D and TBS irrespective of surgical status of the patient. The lack of a predictive value of antiresorptive treatment for TBS may raise concern. TBS is negatively associated with increasing BMI in PHPT-patients even when removing the subgroup of patients with BMI > 37 kg/m\(^2\). TBS is significantly lowered in PHPT-patients who suffer fragility fractures. These associations, however, warrants further study.

Transparency document

The Transparency document associated with this article can be found, in online version.

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Declarations of interest

None.

Ethical approval

For this type of study formal consent is not required. The project has been notified to the Danish Data Protection Agency.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2018.08.001.

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