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Original Paper

Osteoporosis and Impaired Trabecular Bone Score in Hemodialysis Patients

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Key Words
Osteoporosis • Trabecular bone score • Hemodialysis

Abstract
Background/Aims: Small attention is paid to other types of bone diseases then chronic kidney disease-mineral and bone disorder in dialysis patients. The aim of our study was to assess the occurrence of osteoporosis and bone microarchitecture by trabecular bone score in this population. ***Methods:*** 59 patients (67.6 ± 13.1 years, 43 males) treated with hemodiafiltration underwent densitometry (Lunar Prodigy, TBS software 2.1.2) and laboratory assessment. ***Results:*** Osteoporosis was observed in 34% patients, high bone turnover was found in 80% of them, with SHPT (PTH > 300 ng/l) present in 69%. TBS was significantly decreased in 47.5% of the patients. TBS correlated with T- and Z-scores of the lumbar spine and proximal femur in the total population ($P < 0.0001$) and in men ($P < 0.00001$) and there were significant differences between TBS in groups with normal densitometry, osteopenia, and osteoporosis, both in total population ($P < 0.0001$; $P < 0.01$) and in men ($P < 0.001$; $P < 0.001$). ***Conclusions:*** Osteoporosis was found in about 1/3 of patients treated with hemodiafiltration. Normal TBS was found in only 1/4 of the dialysis population. TBS correlated with densitometric parameters and was significantly different relative to T-scores.

Introduction

Osteoporosis is probably the most prevalent metabolic bone disease characterized by decreased bone mineral density (BMD) and impaired bone micro architecture (MA). World Health Organization (WHO) has defined osteoporosis according to BMD obtained from the gold diagnostic standard method - densitometry (DXA) as T-score (standard deviation

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from the normal average BMD of young healthy population) ≤ - 2.5, whereas osteopenia ranges from -2.5 to -1 and normal BMD is considered to be higher than -1. The most serious complications of osteoporosis are fractures occurring in at least 40% women and up to 30% men [1-3].

Originally DXA had the potential to assess only one aspect of osteoporosis – BMD, but it was not able to assess MA. However, a trabecular bone score (TBS), which is a textural parameter expressed as different grey level values distribution, determined using special DXA software (TBS iNsight TM, Med-Imaps SASU, France) that correlates with assessments of MA using standard methods [4], has recently been established as an indirect measure of MA. Based on the risk of major osteoporotic fracture, normal TBS with no differences between the sexes has been recently suggested as TBS ≥ 1.31 (connected with the lowest risk), while a TBS 1.23 – 1.31 corresponds to partially impaired MA (and intermediate fracture risk), and a TBS ≤ 1.23 defines substantially impaired MA and the highest risk [5]. Additionally, TBS has been recently assessed in some types of secondary osteoporosis including patients with higher grades of chronic kidney disease (CKD), however, not in dialysis patients [6].

Chronic kidney disease - mineral and bone disorder (CKD-MBD) consists of three relevant parts: calcium-phosphate metabolism, renal osteopathy (entire bone involvement), and extra-osseal calcifications; and is common (80%) in patients with advanced CKD, mostly as a result of secondary hyperparathyroidism (SHPT) [7]. Renal osteopathy or renal bone disease is a heterogenic group of disorders which comprises of high turnover secondary hyperparathyroidism, low turnover adynamic bone, osteomalacia and mixed type of renal osteopathy. Bone biopsy remains the gold diagnostic standard of renal osteopathy and its description should address three parameters: bone turnover (high, normal, low), mineralization (normal, abnormal) and volume (low, normal, high) [8].

However, other bone diseases occur very probably in progressed or end-stage CKD patients (e.g. osteoporosis) and recently, more attention has been paid to them [9-11]. Although Kidney Disease Improving Global Outcomes (KDIGO) has originally recommended strongly against routine DXA measurement in patients with CKD stages 3-5 due to the loss of BMD predictive value regarding the fracture risk [7], based on studies by Yenchek et al. [12] and Iimori [13] which confirmed BMD as an independent risk factor for fragility fractures in elderly patients with CKD stages 3-5, a working group has recently suggested a revision to original KDIGO recommendation regarding routine DXA testing in CKD stages 3 – 5 [14]. Despite the fact that bone biopsy remains the gold standard for the diagnosis of the type of bone disease in patients with CKD stages 3 – 5, the diagnosis in routine clinical practice is very often made by combination of more feasible methods (e.g. clinical assessment, DXA and laboratory assessment) because the wider use of bone biopsies is compromised by relatively high demands for the procedure itself, demanding work-ups of specimens, and limited numbers of specialized pathologists [8].

Fractures occur more frequently in dialysis patients compared to general population [15, 16] and the BMD of the dialysis patients is significantly lower compared to healthy controls [16]. No differences were found in BMD between hemodialysis and peritoneal dialysis [17]. Low BMD also represents an independent mortality risk factor [18].

Few studies have focused on MA in dialysis patients and they usually used quantitative computerized tomography with high resolution /QCT/ [9, 11, 19]. So far, only one study examined TBS in CKD patients, but not in dialysis patients. Authors concluded that CKD had a negative impact on TBS [20].

The rationale of our study is based on two facts discussed above: firstly, probable (and by some studies [e.g. 9, 10] also proved) occurrence of osteoporosis in dialysis patients, and secondly, recent introduction of TBS and its assessment in some types of secondary osteoporosis [6], however not in end-stage renal disease. Thus, in our study we focused on the frequency of osteoporosis and the assessment of TBS in a common, non-selected cohort of hemodialysis patients from one dialysis centre by methods feasible in routine clinical practice.

Patients and Methods

Seventy six non-selected patients of one dialysis centre treated with high-volume online hemodiafiltration on a Fresenius 5008 dialysis machine agreed to participate in the study and signed an informed consent. However, only 59 patients (37% diabetic patients): 43 (73%) males and 16 (27%) females completed all the procedures. Pregnancy was the only exclusion criterion. Our study was approved by the Ethical Committee and respected the principles of Helsinki declaration.

Densitometry

The study protocol comprised of densitometry and laboratory assessment. Densitometry was performed by a single trained operator using a Lunar Prodigy densitometer (GE-Lunar, Madison, USA, German reference population). TBS has been assessed using TBS iNsight TM v2.1.2. (Med-Imaps SASU, France). The assessment of densiometric findings (including reference databases for T-scores, standards for performing DXA for diagnosis, diagnosis of osteoporosis in postmenopausal women, men and premenopausal women and technical standards) respected the recommendation of International Society for Clinical Densitometry [21].

Laboratory methods

Serum calcium /S-Ca/ and serum phosphate /S-P/ were analyzed by automated analyzer, parathormone /PTH/ by chemiluminiscence immunoassay (Immulite 2000, DPC, coefficient of variation /CV/ < 6%), total 25-hydroxyvitamin D3 /25OHD/ by chemiluminiscence immunoassay, Roche Diagnostics, CV< 6%; markers of bone remodelling: marker of bone resorption β-cross laps /CTX/ and markers of bone formation N-terminal procollagen type 1 /P1NP/ and bone specific alkaline phosphatase by chemiluminiscence immunoassay, Roche Diagnostics, CV < 5.5%. Calcium was corrected to serum albumin levels [= total serum calcium + 0.020 x (41.3 – albumin)]. All the parameters were taken from blood samples during routine midweek morning sampling in the fasting state.

In patients with low T-scores, clinical diagnosis of primary osteoporosis was made *per exclusionem* after exclusion of causes of secondary osteoporosis using a standard battery of laboratory tests (except for calcium-phosphate parameters glycaemia, liver tests, blood count, sedimentation rate, thyroid stimulation hormone, testosterone in men, and anti-tissue transglutaminase antibody), X-ray imaging, and patient history including medication and personal history.

Statistics

All statistical analyses were performed with SPSS-PC version 13. Group comparisons were analyzed by tests from ANOVA test group (Student-Newman-Keuls, Tukey-Kramer and Duncan test) with similar statistical significance and Duncan test was selected as a test of choice by our statistician in the presentation of the results. Correlations were calculated using Pearson correlation coefficients. $P < 0.05$ was considered to be statistically significant.

Results

Characteristics of the patients including skeletal parameters are shown in Table 1, whereas standard dialysis parameters are shown in Table 2.

Normal densitometric findings (T-scores ≥ –1) were found in 18 patients (30%), osteopenia/decreased BMD was present in

Table 1. Characteristics of the patients including skeletal parameters

Patients´characteristics	Average ± S.D.
Age (years)	67.6 ± 13.1
BMI (kg/m^2)	27.6 ± 5.4
S – Ca (mmol/l)	2.1 ± 0.2
S – P (mmol/l)	1.5 ± 0.4
PTH (ng/l)	396.9 ± 384.4
CTX (ug/l)	1.6 ± 1.0
Bs-ALP (ug/l)	9.5 ± 5.4
P1NP (ug/l)	298.0 ± 193.6
25 – OH vitamin D (nmol/l)	106.2 ± 47.6
T – lumbar spine	-0.5 ± 1.8
T – proximal femur	-1.4 ± 1.6
TBS	1.26 ± 0.14

S – Ca – serum calcium, S – P – serum phosphate, PTH – parathormone, CTX – cross laps, Bs-ALP – bone specific alkaline phosphatase, P1NP – N-terminal procollagen type 1

Table 2. Dialysis parameters of the patients

Patients´characteristics	Average ± S.D.
Vintage of dialysis treatment (months)	53.8 ± 46.3
Effective weekly treatment time (minutes/week)	792 ± 72.2
Blood volume processed per week (L/week)	293.4 ± 53.1
Infusion volume per week (substitution volume) (L/week)	73.9 ± 11.9
Effective infusion volume (L/week)	24.6 ± 3.4
Kt/V	1.74 ± 0.28
Blood flow - Qb (ml/min)	371 ± 54

BMI – body mass index, L – litre, Kt/V – quantifies the adequacy of dialysis, K - dialyzer clearance of urea, t - dialysis time, V - volume of distribution of urea, approximately equal to patient's total body water, ml/min – millilitre/minute

21 patients (36%), whereas osteoporosis was present in 20 patients (34%) - 11 men (25% of all the male participants) and 9 women (56% of all the female participants).

Table 3. Differences in laboratory and skeletal parameters among groups according to T – scores

	T > -1	-1 ≤ T ≥ -2.5	T ≤ -2.5	P
CTX (ug/l)	1.7 ± 0.4	1.7 ± 0.9	1.8 ± 1.2	NS
PTH (ng/l)	325 ± 233	347 ± 295	507 ± 531	NS
P1NP (ug/l)	319 ± 274	303 ± 223	366 ± 273	NS
25-OH D (nmol/l)	113 ± 47	110 ± 55	95 ± 38	NS
S – Ca	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	NS
TBS	1.37 ± 0.16	1.26 ± 0.09	1.17 ± 0.12	P < 0.01

CTX – cross laps, PTH – parathormone, P1NP – N-terminal procollagen type 1, 25-OHD – 25- OH vitamin D, S – Ca – serum calcium, TBS – trabecular bone score

Bone turnover measured by cross laps did not differ among groups with different T-scores (Table 3). High bone turnover was present in 16 (80%) patients with T-scores ≤ −2.5 (average 2.2 ± 0.9 ug/l). Eleven of the 16 patients (69%) had PTH values above the recommended range /150 – 300 ng/l/ for dialysis patients. Three of the 11 patients had severe secondary hyperparathyroidism (PTH 2500 ng/l, 1064 ng/l and 968 ng/l). The remaining 8 of 11 patients had average PTH values of 432.3 ± 110.1 ng/l. There were no significant differences in PTH, 25-OH vitamin D, or P1NP among the patients according to T – scores (Table 3).

25-OH vitamin D levels were normal (above 75 nmol/l) in 43/59 patients (73%), 8/59 (13.5%) were deficient, and the remaining 8/59 (13.5%) were insufficient (50 – 75 nmol/l). The deficient group had significantly lower serum calcium compared to the insufficient group (2.02 ± 0.13 mmol/l versus 2.2 ± 0.16 mmol/l; P < 0.05) although the level was not significantly different from the group with normal 25-OH vitamin D levels (2.12 ± 0.16; NS). However, there were no significant differences in serum phosphate, PTH, cross laps, P1NP, or densitometric parameters among those groups.

Almost one fourth (14/59) of the patients were treated with oral cholecalciferol, with median dose 5000 IU weekly and 33/59 (56%) were treated with active analogues (either alphacalcidiol /n = 1/ (3 ug weekly) or 1,25 calcitriol /n = 32/ (median dose 1 ug weekly). Dual treatment (i.e. cholecalciferol plus an active analogue of vitamin D) was administered to 9/59 (15%) patients with no documented episode of hypercalcemia in these patients.

Average TBS was 1.26 ± 0.14; 47.5% of the patients had TBS in the range corresponding to severely damaged micro architecture (≤ 1.23; average 1.15 ± 0.06), whereas 32% had a normal TBS (1.43 ± 0.09) and 20.5% impaired TBS (average 1.27 ± 0.02). There were significant differences between TBS among groups with normal densitometry (1.37 ± 0.16) and osteopenia/decreased bone mineral density (1.26 ± 0.09; P < 0.0001) and normal densitometry and osteoporosis (1.17 ± 0.12; P < 0.01). Correspondingly, T-scores both of

Table 4. Differences in laboratory and skeletal parameters among groups according to TBS groups

	TBS ≥ 1.31	1.23 > TBS < 1.31	TBS ≤ 1.23	P
CTX (ug/l)	1.9 ± 1.3	1.5 ± 0.7	1.7 ± 1.2	NS
PTH (ng/l)	514 ± 399	251 ± 151	384 ± 231	NS
P1NP (ug/l)	404 ± 315	262 ± 180	310 ± 231	NS
25-OH D (nmol/l)	116 ± 51	107 ± 46	99 ± 46	NS
S – Ca	2.1 ± 0.2	2.1 ± 0.1	2.1 ± 0.2	NS
LP-T	1.0 ± 1.7*	0.7 ± 1.6^	-1.1 ± 2.0*^	P = 0.002* P = 0.006^
PF-T	-0.8 ± 1.3*	-1.1 ± 1.4	-1.9 ± 1.7*	P = 0.03*

CTX – cross laps, PTH – parathormone, P1NP – N-terminal procollagen type 1, 25-OHD – 25- OH vitamin D, S – Ca – serum calcium, TBS – trabecular bone score, LP-T – T-score in lumbar spine, PF-T – T-score in proximal femur

lumbar spine and of proximal femur significantly differed among TBS groups – decreased with the decrease in TBS (Table 4). However, no differences were found in either bone turnover parameters (cross laps, P1NP, bone specific alkaline phosphatase) or in calcium-phosphate metabolism parameters (serum calcium, phosphate, PTH, 25-OH vitamin D), age, body mass index or dialysis parameters among group with normal, impaired and severely impaired TBS (Table 4).

A significant negative correlation was found between TBS and age ($r = -0.33$; $P < 0.05$) and positive correlations were found only between TBS with T- and Z-scores of the lumbar spine ($r = 0.49$; $P < 0.0001$ /Figure 1/ and $r = 0.33$; $P < 0.01$) and T- and Z-scores of the proximal femur ($r = 0.46$; $P < 0.0001$ /Figure 2/ and $r = 0.49$; $P < 0.0001$); correlations of TBS with other studied parameters did not reach a statistical significance.

When divided according to sex and the presence of osteoporosis, there were significant differences between TBS among males with normal densitometry (n = 13; 1.44 ± 0.12) and (i) males with decreased BMD (n = 19; 1.26 ± 0.09; $P < 0.001$) and (ii) males with osteoporosis, (n = 11;1.19 ± 0.14; $P < 0.001$), however no significant differences were found among females with normal BMD (n = 5; 1.18 ± 0.05) and (i) females with osteopenia (n = 2; 1.22 ± 0.06, NS) and (ii) females with osteoporosis, (n = 9; 1.15 ± 0.08).

Similarly, the significant correlation between TBS and T- and Z-scores, was only present in males (N = 43; T- and Z-scores of the lumbar spine: $r = 0.53$; $P < 0.00001$ /Figure 3/; $r = 0.44$; $P < 0.01$; T- and Z-scores of the proximal femur: $r = 0.55$ /Figure 4/; $P < 0.00001$; $r = 0.61$; $P < 0.00001$).

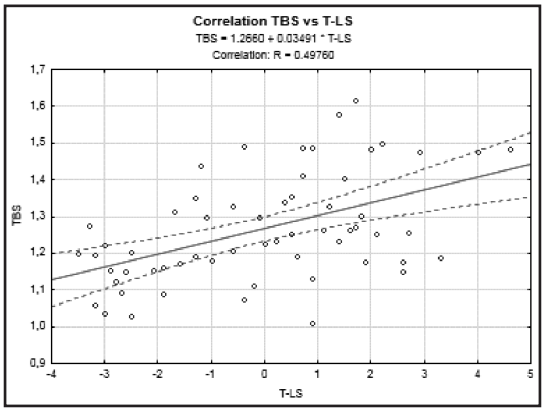

Fig. 1. Correlation of TBS and T-score of lumbar spine in the total population.

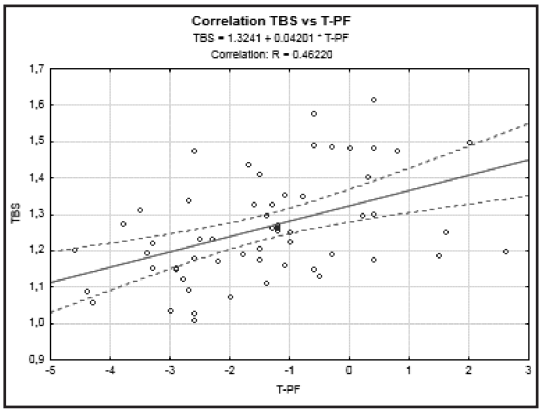

Fig. 2. Correlation of TBS and T-score of proximal femur in the total population.

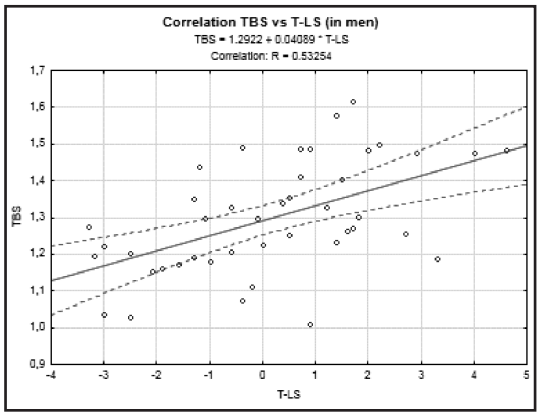

Fig. 3. Correlation of TBS and T-score of lumbar spine in men.

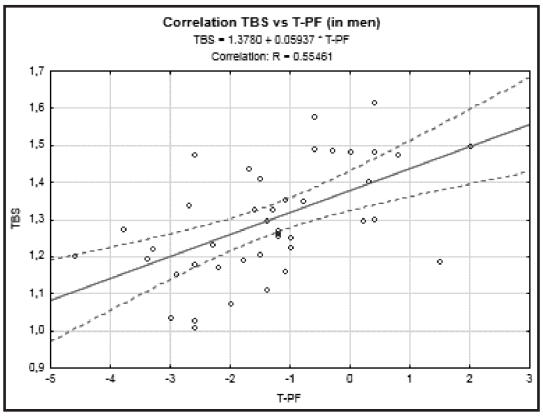

Fig. 4. Correlation of TBS and T-score of proximal femur in men.

There were no significant correlations found between TBS and parameters of calcium-phosphate metabolism or bone turnover in groups divided based on sex or groups divided based on T-scores.

Secondary osteoporosis was diagnosed in 4 (20%) of the osteoporotic patients – 1 man suffered from steroid osteoporosis (Crohn´s disease with long term steroid therapy), 1 patient was diagnosed with Turner syndrome (the patient had a history of refusing hormonal replacement therapy) and two female patients, who were treated with anastrazole for breast cancer. Surprisingly, the majority of men with low T-scores displayed serum testosterone levels within normal range relative to age (secondary hypogonadism with significantly decreased testosterone levels 1.5 ng/ml was measured in only one 76 year-old polymorbid patient).

Low number of osteoporotic fractures observed in our cohort (only in two patients) unfortunately prevented further analysis of these patients and from the same reason the calculations of predictive values of TBS or osteo-markers regarding the fracture risk were not possible to perform.

Discussion

Our study showed a high prevalence (34%) of low BMD ($T \leq -2.5$), i.e. osteoporosis, as defined by the WHO criteria. Our data fully correspond with recently published studies – e.g. in a study by Malluche et al. [9] 1/3 of the cohort (81 patients) met the criteria for osteoporosis and similarly, another group of Czech patients [10] described T-scores in the osteoporotic range in 35% of patients starting regular hemodialysis treatment. Regarding the sex distribution, a study from Saudi Arabia found lower prevalence of osteoporosis – 27% of women and 9% of men treated with hemodialysis [22] in comparison with 56% of women and 25% of men in our study. Surprisingly, the prevalence of secondary osteoporosis in our male patients with low T-scores was relatively low 2/11 (18%), although men are generally more prone to suffer from secondary osteoporosis [23].

In general, the presence of osteoporosis in patients with ESRD could have possible therapeutic implications which could decrease the fracture risk and improve the prognosis of the patients. Although the treatment of osteoporosis in this population is not routinely recommended [7], some smaller studies have already proved the efficacy of various antiosteoporotic agents, e.g. bisphosphonates, denosumab, raloxifene or teriparatide [24-27].

Bone turnover assessed by biochemical markers on one side represents a key parameter for determining the best treatment strategy and on the other side could be used as an alternative to histomorphometric evaluation since this examination is commonly available. However, it faces several concerns, the major of them being possible accumulation of these markers in progressed CKD. We selected three routinely available markers – P1NP, bone specific alkaline phosphatase and cross laps. The two former should not be influenced by the stage of CKD, however, the latter could [7]. Palička et al. described probable retention of both cross laps and P1NP in ESRD (with different kinetics in hemodialysis versus hemodiafiltration) [28] but we measured the markers before the initiation of hemodiafiltration sessions, thus they were not influenced by the dialysis procedure itself. At the same time he showed that these markers reflected bone turnover in dialysis patients so that they still had information value in its assessment [28]. Another relatively new marker, sclerostin, studied in progressed CKD or transplanted population [9, 29] would be of interest, unfortunately we did not include it into the analyses.

Serum markers of bone resorption and formation were high in the majority (4/5) of our patients with low BMD (osteoporosis) and in almost 70% of them secondary hyperparathyroidism was present. Although it is difficult to compare our results with other studies using a similar design, because of the different osteo-markers [30] used, our data seems to be consistent with the expected rates of high bone turnover secondary hyperparathyroidism CKD-MBD in the population of maintenance hemodialysis patients with low BMD despite standard PTH – lowering therapy. Again, in terms of possible treatment options, the presence of high bone turnover in this population may represent the rationale for antiresorptive treatment (e.g. bisphosphonates or denosumab) [31], however, larger studies are highly warranted.

Regarding the prediction of fracture risk, markers of bone turnover have brought some results, although, they have not been overly consistent [9, 32]. In our study, low number of fragility fractures did not enable the assessment of the predictive value of selected biomarkers on fracture risk.

The majority (3/4) of patients had surprisingly sufficient 25-OH vitamin D levels, which was discrepant with published accounts of very high prevalence of low 25-OH vitamin D levels in hemodialysis patients [33]. The results can be partially explained by the season of 25-OH vitamin D sampling (early summer) and by cholecalciferol supplementation used by part of our studied population. Dual therapy (cholecalciferol plus active analogues of vitamin D) was used in 15% of our patients with no documented side effects (particularly hypercalcemia), thus our study contributed to the recently published data [33] on the safety of this combination therapy in dialysis patients with low 25-OH vitamin D levels and hyperparathyroidism. Frequent administration of active vitamin D analogues (n = 33), paricalcitol (n = 10) or cinacalcet (n = 1) could explain the relatively low prevalence of severe secondary hyperparathyroidism observed in our studied group.

As far as we are aware, this is the first study to describe bone MA in dialysis patients using TBS. There was a good correlation between TBS and QCT [34], and QCT reflected the histomorphometric parameters [11]. Thus, TBS seems to be an effective and non-invasive indirect marker of bone MA. We confirmed a high occurrence of severely impaired bone MA in dialysis patients, which was also described by other groups predominantly using QCT [35, 36].

Although Silva [4] suggested that TBS could be independent of DXA-derived BMD, in our study on hemodialysis patients TBS correlated with both T- and Z-score of lumbar spine and proximal femur in the total studied population and in men. In addition, significant differences in TBS were found in males with normal and decreased BMD and those with osteoporosis. These data showed that TBS was not independent on BMD since low BMD was connected with impaired micro architecture in our population of dialysis patients. Enigmatic question remains about the predictive value of combination of low TBS and low BMD regarding the fracture risk, which would further stratify the patients according to

the urgency of the treatment. However, currently, from our available data it is not possible to perform such analysis. Surprisingly, the correlation between TBS and BMD was not statistically significant in women. Whether the dependence between TBS and BMD is gender (male) specific or whether the reason for non-significant differences in women could be explained by the relatively low number of women in the groups remains to be elucidated by a larger study. Unfortunately, due to low number of fractures in our population we were not able to perform the analysis on the predictive value of TBS on fracture risk, which would be of clinical significance. However, the clinical follow-up of the patients is ongoing in order to perform such analysis.

The major limitation of our study is the absence of a histomorphometric correlate that could validate the densitometric findings in the specific population subgroup used in our study. However, two recently published studies showed a significant correlation between selected serum markers of bone turnover and histomorphometry [37] and acceptable sensitivity and specificity of BMD measured by DXA relative to low bone volume assessed by histology [38]. As such the combination of DXA and osteo-markers offers the potential for non-invasive assessment of different types of CKD-MBD.

Conclusion

Based on clinically feasible methods (densitometric findings, laboratory and clinical assessment) we can confirm a relatively high prevalence of osteoporosis in non-selected cohort of ESRD treated with on-line high volume hemodiafiltration from one dialysis centre. The majority of patients with low BMD had high bone turnover (measured by osteo-markers) with secondary hyperparathyroidism (despite treatment) being the most common cause. Almost ½ of the dialysis patients had severely impaired bone micro architecture measured using TBS. TBS correlated significantly with densitometric parameters, but only in men.

This paper contributes to the recent controversial questions regarding the occurrence and diagnosis of osteoporosis in patients with end stage renal disease and our findings may have an implication for potential treatment options.

Disclosure Statement

None declared by any of the authors.

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