



A new corrective model to evaluate TBS in obese post-menopausal women: a cross-sectional study

Gloria Bonaccorsi¹ · Francesco Pio Cafarelli² · Carlo Cervellati³ · François De Guio⁴ · Pantaleo Greco¹ · Melchiorre Giganti⁵ · Giuseppe Guglielmi^{2,6}

Received: 13 May 2019 / Accepted: 10 August 2019
© Springer Nature Switzerland AG 2019

Abstract

Introduction The relationship between post-menopausal osteoporosis and obesity has been mainly investigated using bone mineral density (BMD) as marker of bone health. Since BMD does not reflect bone microarchitecture, another analytical tool, the Trabecular Bone Score (TBS), has been recently developed for this purpose. In this study, we intended to investigate the validity of TBS as marker of bone quality in obese post-menopausal women.

Methods and materials Three hundred fifty-two post-menopausal women were consecutively enrolled in the study and underwent anthropometric and dual-energy X-ray absorptiometry (DXA) examination. DXA-based BMD was used to classify subjects into osteoporotic (9%), osteopenic (58%), and controls (33%) categories. As TBS is sometimes sensitive to the effects of increased image noise with higher BMI, a corrected version of the TBS (TBS*) was also used to assess bone microarchitecture quality in this cohort.

Results As expected, BMI was positively and negatively related to total BMD ($r=0.22$, $p<0.0001$) and TBS ($r=-0.12$, $p<0.05$), respectively. TBS* was found positively and significantly correlated with femoral neck BMD ($r=0.40$, $p<0.001$), total hip ($r=0.33$, $p<0.001$) and lumbar spine BMD ($r=0.50$, $p<0.001$).

Conclusion TBS, once removed the effect of BMI, can serve as a good surrogate maker of bone microarchitecture in obese post-menopausal women in addition to BMD.

Keywords Body mass index · Trabecular Bone Score · Post-menopausal age · Obesity · Osteoporosis

Introduction

Nowadays, osteoporosis and obesity represent two major public health problems, and need to be contextualized and correctly addressed to a prevention plan [1, 2].

Osteoporosis is the most common osteometabolic disorder affecting post-menopausal women [3]. The menopause-related estrogen deprivation is the main etiopathogenic cause of this disorder, which is characterized by reduction in bone mineral density (BMD) and deterioration of microarchitecture, leading to an increased risk of fractures [4–6]. The diagnosis of osteoporosis is currently based on BMD as assessed by the gold standard dual X-ray absorptiometry (DXA) [6]. Low BMD is an important component of fracture risk. However, aging leads in both women and men to a worse “quality” of bone, intended as alteration of microstructure that also contributes to skeletal fragility. Historically, the gold standard technique for quantification of bone quality has involved obtaining a highly invasive bone biopsy

✉ Giuseppe Guglielmi
giuseppe.guglielmi@unifg.it

¹ Department of Morphology, Surgery and Experimental Medicine, Menopause and Osteoporosis Centre, University of Ferrara, Via Boschetto 29, 44124 Ferrara, Italy

² Department of Clinical and Experimental Medicine, Foggia University School of Medicine, Via L. Pinto, 1, Foggia, Italy

³ Department of Biomedical and Specialist Surgical Sciences, Section of Medical Biochemistry, Molecular Biology and Genetics, University of Ferrara, Via Luigi Borsari 46, 44121 Ferrara, Italy

⁴ Medimaps, Canéjan, France

⁵ Department of Morphology, Surgery and Experimental Medicine, Section of Radiology, University of Ferrara, Via Ludovico Ariosto 35, 44121 Ferrara, Italy

⁶ Department of Radiology, University of Foggia, Viale Luigi Pinto 1, 71100 Foggia, Italy

[7]. More recently, a novel, safe, and more accessible DXA-based technique for detecting bone microarchitecture has been developed, Trabecular Bone Score (TBS). Notably, recent epidemiological/clinical data have consistently shown that TBS is a predictor of fracture incidence independently of BMD and clinical risk factors [7, 8].

However, even if TBS has already shown several strength points, as recently reported by Martineau and Leslie, it is also affected by some limitations [9]. The main caveat reported so far is related to the effects of soft tissues on TBS measurement; indeed, high amount of soft tissues is associated with high noise in DXA image. As a consequence, DXA-based measurements are impacted by such increased noise in the image. TBS is decreasing with increasing soft tissue thickness as demonstrated by ex vivo experiments where soft tissue layers can be simulated and varied [9]. To cope with this artefactual decrease unrelated to biological variations, a correction has been implemented in TBS based on patient BMI. This correction is not perfect under some conditions. For example, as reported in some studies using Hologic devices, a negative and significant correlation has been observed between TBS and BMI, leading to densitometer-specific differences. That being said, TBS limits of use are set to a maximum BMI of 37 kg/m² to avoid incoherent TBS values in these subjects. Besides, it has been reported that TBS reproducibility was not affected up to 6 cm of increasing soft tissue thickness and was even less influenced by fat than BMD [10]. Another study reported that no significant differences were found for TBS precision error when comparing BMI groups (normal, overweight, class I obesity) and waist circumference groups (less or greater than 88 cm) [11].

Finally, a new TBS corrective algorithm has been recently developed to remove this residual correlation. This correction is based on the estimated tissue thickness determined from the DXA device. This enables to have a more precise and robust assessment of soft tissues compared to the BMI measure. It has been shown that this correction leads to a positive correlation with BMI as observed for the BMD and that it improves TBS clinical performance, reproducibility, and follow-up.

Within this study, the new correction method for TBS was not yet available but we made use of the known correlation between TBS and BMI to correct the effects of the latter to the DXA-derived parameter. This is an alternative to the new correction that will be integrated in TBS v4 when using TBS v3.

Despite the increasing use of TBS in clinical setting and the well-documented good performance in risk stratification, a little has been reported on the clinical relevance of using this novel index of bone health in obesity.

The purpose of the present study was to investigate the possible role of a corrected version of TBS (TBS*) in obese

post-menopausal patients in evaluating bone texture, to stratify the fracture risk in this particular group of patients.

Methods

Subjects

Between January 2015 and December 2017, 412 consecutively female outpatients, referred for osteoporosis management to the Menopause and Osteoporosis Center of the University of Ferrara, were enrolled in the study. Each subject was evaluated by a questionnaire that included demographic information, medical and reproductive history, and main lifestyle habits. The inclusion criteria were: female sex, Caucasian race, post-menopausal status, defined as cessation of menses for at least 1 year, and BMI between > 30 and 37 kg/m². Women were excluded from the study whether: affected by diseases, such as chronic kidney disease, rheumatoid arthritis, etc., which are well-recognized cause of secondary osteoporosis; were under pharmacological/hormonal (e.g., corticosteroid) treatment during the last months prior to blood withdrawal. Major details in the study design are reported in similar previous studies [12, 13].

The study was undertaken within the framework of a protocol approved by the Medical School Ethics Committee. All participants provided informed consent. Table 1 shows the baseline characteristics of patients. Three hundred fifty-two women were finally enrolled in the study. Figure 1 shows the flowchart of patients enrollment.

Study protocol

The protocol considered an interview that included the gathering of the clinical risk factors, skeletal and extra-skeletal factor identified by DeFra algorithm [5]. Data were collected to evaluate BMI, family, and personal history of hip

Table 1 General characteristics of the study sample ($N=352$)

Age (years)	65 ± 8 (43–84)
Years since menopause, (months)	48 ± 12
BMI, kg/m ²	32 ± 2
DXA-assessed parameters	
Lumbar spine BMD, g/cm ²	0.940 ± 0.14
Lumbar spine T score	– 1.1 (– 1.9; 0.2)
Femoral neck BMD, g/cm ²	0.722 ± 0.09
Total hip BMD, g/cm ²	0.881 ± 0.01
TBS	1.16 ± 0.15
TBS*	1.18 ± 0.15

Data are expressed as mean ± standard deviation/median (interquartile range) when the variable is normally/not normally distributed, respectively

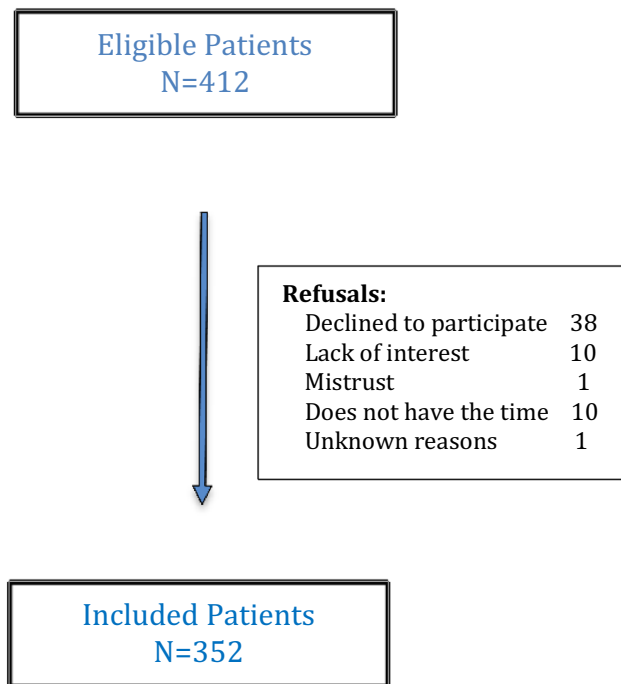


Fig. 1 Flowchart of patients enrollment

or vertebral fragility fractures. The study considered the use of BMD, TBS evaluation with DXA.

DXA assessment

Areal bone density was measured in each participant by Discovery dual energy X-ray absorptiometry scanner (Hologic Inc, Bedford, MA, USA) in accordance with manufacturer and International Society for Clinical Densitometry (ISCD) guidelines. Precision error (%) for BMD was 0.1 at lumbar spine, femoral neck, and total hip. For lumbar spine BMD the L1–L4 was chosen for the analysis. Osteoporosis was diagnosed when BMD *T* scores (the number of SDs below the average for a young adult at peak bone density) were lower than 2.5 SDs from BMD peak at either the femoral neck (FN) or lumbar spine (LS) according to World Health Organization (WHO) guidelines; osteopenia with *T* scores between -2.5 and -1.0 ; normal with *T* scores > -1.0 .

TBS Insight software (Medimaps, France) was used to assess TBS values, scored in same spinal regions (lumbar spine vertebrae L1–L4) where DXA scans were performed to measure the lumbar spine BMD. The average TBS scored value of the L1–L4 vertebrae was utilized for the statistical analyses in the study.

We applied a mathematical approach to remove the negative correlation between TBS and BMI, correcting the linear

trend of TBS as a function of BMI ($TBS^* = TBS + (BMI - 30) \times 0.00753$) where 30 is the reference BMI and -0.00753 is the negative slope of TBS as a function of BMI in these data.

Statistical analysis

Continuous variables following a normal distribution (height, weight, BMI, BMD) were expressed as mean \pm standard deviation, and comparisons between groups were performed using the *t* test. The multivariate analysis was run with a logistic regression analysis taking as outcome the presence of fracture and as exposure variables the factors significantly associated with fracture in the univariate analysis (taking a *p* value < 0.05).

Statistical analysis was performed using Statistical Package for Social Sciences version 23.0 software (SPSS, Chicago, IL, USA). A *p* value of < 0.05 was considered statistically significant.

Results

Table 1 summarizes baseline characteristics of the 352 postmenopausal women included in the present study. According to BMD *T* score, 9% of patients were classified as osteoporotic (*T* score < -2.5), 58% as osteopenic (*T* score between -2.5 and -1), and 33% as normal (*T* score > -1).

The calculated correct TBS* was slightly higher than TBS (mean value 1.18 vs. 1.16). Regarding the correlation analysis among the anthropometric and DXA measures, BMI was negatively ($r = -0.12$, $p = 0.03$) and positively ($r = 0.22$, $p < 0.001$) correlated with TBS and BMD, respectively. TBS* showed a negative correlation with age ($r = -0.29$, $p < 0.0001$). More specifically, the linear decrease was -0.004 unit of TBS*/year for whole sample (352 women), but between age 45 and 65, the decrease was -0.005 unit of TBS/year (177 women), which is similar to the observed decrease in the European reference curve (-0.0045) [14].

TBS* was also positively correlated with femoral neck BMD ($r = 0.40$, $p < 0.001$), total hip BMD ($r = 0.33$, $p < 0.001$), lumbar spine BMD ($r = 0.50$, $p < 0.001$). Notably, no significant association was found between TBS* and menopausal age ($p > 0.05$).

All osteoporotic women according to BMD *T* score definition have a low TBS. For osteopenic women, 62% of them have a low TBS and for “normal” women, always according to BMD *T* score thresholds, 42% of them have a low TBS. Table 2 gives the proportion of patients according to both BMD and TBS thresholds. We consider thresholds (1.23 and 1.31) based on tertiles defined from the meta-analysis by McCloskey et al. [8].

Table 2 Distribution of patients according to both BMD and TBS thresholds

DXA categories	Corrected Trabecular Bone Score (TBS*)		
	< 1.23	1.23–1.31	> 1.31
Normal (<i>T</i> score > -1)	42% (<i>n</i> .49)	36% (<i>n</i> .42)	22% (<i>n</i> .25)
Osteopenic (<i>T</i> score < -1 and > -2.5)	62% (<i>n</i> .127)	35% (<i>n</i> .70)	3% (<i>n</i> .7)
Osteoporotic (<i>T</i> score < -2.5)	100% (<i>n</i> .32)	0% (<i>n</i> .0)	0% (<i>n</i> .0)

Discussion

BMD is commonly used for the diagnosis of osteoporosis and for evaluating disease risk stratification and monitoring individual patients' responses to therapy [6]. Moreover, the combination of BMD (at the femoral neck) and clinical risk factors into the WHO fracture risk algorithm (FRAX), is presently regarded as an effective tool for the estimation of 10-year probability of major osteoporotic fracture (spine, hip, proximal humerus, and distal forearm) and the 10-year probability of hip fracture [15]. However, epidemiological data consistently showed that more than 50% of incident fractures occur in women with either normal BMD or osteopenia [16]. Bone strength depends not only on bone mass but also on bone quality. This feature of bone can be properly quantified by TBS, a new gray-level textural measure that can be extracted from the two-dimensional lumbar spine DXA image to estimate trabecular microstructure [17, 18]. An elevated TBS value correlates with better skeletal texture (a reflection of better microarchitecture); a low TBS value correlates with weaker skeletal texture (a reflection of degraded microarchitecture). The relationship between TBS texture parameters and 3D microarchitecture parameters has been documented by several *ex vivo* studies that have reported significant correlations between TBS and various microstructural parameters of bone assessed by micro-computed tomography [19].

However, one of the essential point in evaluating fracture risk is to develop a most suitable and integrated system, able to predict better this condition: to go beyond this limit, FRAX and DeFRA adjusted for increasing the global diagnostic accuracy to stratify better the patient risk profile have been developed [5, 6].

As a consequence of all these considerations, has to be taken into account, as already stated, the need to implement the role of DXA examination in patient with increased soft tissue thickness, such as in obese patients, due to potential interference of abdominal fat.

A limitation of our study is the use a surrogate maker of abdominal fat with BMI, instead of a body composition evaluation, since it is still not recommended the use of TBS in patients with BMI major than 37 kg/m².

The aim of the study is to evaluate whether TBS can be used for osteoporosis risk stratification among obese

post-menopausal women. In the attempt to limit the potential, and widely acknowledged, interference of BMI on TBS, we generated a novel parameter from this DXA-derived parameter, TBS* and checked its potentials as alternative bone strength measure. The aforementioned influence of BMI on TBS is due to the fact that it could be suffered from the soft tissue bias due to an overattenuation of X-rays; to overcome this possible confounding effect, we introduced a coefficient of correction. Of note, this mathematical procedure is performed by a commercially available specific software.

Our population included *n*.352 obese women. The statistical analyses showed that BMD was strongly correlated with BMI, while neither TBS nor TBS* showed a significant relationship with this anthropometric measure. In this light, we concluded that both TBS and TBS* in this setting of patients could be used in place of BMD.

The interesting aspect of this evidence is that, as already highlighted in the largest prospective study performed in the Canadian province of Manitoba, among 29,407 post-menopausal women, since TBS was a fracture predictor as well as BMD, it could be possible to use TBS in obese post-menopausal woman as BMD, with the same power [7, 20]. A recent publication of European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) Working Group, supports the role and the importance of TBS and its specific use in clinical practice [21, 22]. Indeed, authors report the potential value of TBS as an independent adjunct to risk assessment using DXA BMD and/or FRAX in settings such as post-menopausal and secondary osteoporosis, and its potential use in assessment of response to treatment.

Hence the major part of population has a low TBS (208 pts with < 1.23), and the proportions of patients with low TBS are higher than expected in a population-based cohort even if, to note, reference population has an inferior mean BMI.

Above all, among women with normal *T* score and osteopenic, up to 50% has a low TBS. These data could suggest a better ability of TBS in this sub-group of our cohort, to better stratify the fracture risk as already reported in OFELY study [19, 22].

In conclusion, after matching for age and BMI, TBS has smaller values when compared to a reference population.

In addition, even if there is a statistical correlation between TBS and BMD, there is a high proportion of patients with low TBS comparatively to a low proportion of patients with low BMD. These results have to be taken with extreme caution as there is no control with BMI < 30 kg/m² and still now the true TBS–BMI relationship is better clarified. However, data presented are consistent with the previous findings, reported by Shin et al. [23].

However, some confounding factors could influence these data, in particular is still now developing the importance of the role of functional muscle–bone unit that should be taken into account [24].

It seems that TBS* values are smaller compared to a reference population, even after matching for age and BMI. There is a high proportion of patients with low TBS* comparatively to a low proportion of patients with low BMD.

Further studies are required to definitively prove this hypothesis, considering that TBS could represent an added value to BMD.

Conclusion

Since BMD is demonstrated to be influenced by BMI, TBS and TBS* can support BMD for stratifying obese women in post-menopausal age.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Burge R, Dawson-Hughes B, Solomon DH et al (2007) Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res* 22:465–475
- Becker DJ, Kilgore ML, Morrisey MA (2010) The societal burden of osteoporosis. *Curr Rheumatol Rep* 12:186–191
- Cram P, Rosenthal GE, Ohsfeldt R et al (2005) Failure to recognize and act on abnormal test results: the case of screening bone densitometry. *Jt Comm J Qual Patient Saf* 31:90–97
- McClung MR (2005) The relationship between bone mineral density and fracture risk. *Curr Osteoporos Rep* 3:57–63
- Bonaccorsi G, Fila E, Cervellati C et al (2015) Assessment of fracture risk in a population of postmenopausal Italian women: a comparison of two different tools. *Calcif Tissue Int* 97:50–57. <https://doi.org/10.1007/s00223-015-0009-2>
- Kanis JA, Cooper C, Rizzoli R et al (2019) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 30:3–44
- Harvey NC, Glüer CC, Binkley N et al (2015) Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. *Bone* 78:216–224
- McCloskey EV, Odén A, Harvey NC et al (2016) A meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res* 31:940–948
- Martineau P, Leslie WD (2018) The utility and limitations of using trabecular bone score with FRAX. *Curr Opin Rheumatol* 30:412–419
- Messina C, Poloni A, Chianca V et al (2018) Increasing soft tissue thickness does not affect trabecular bone score reproducibility: a phantom study. *Endocrine* 61:336–342. <https://doi.org/10.1007/s12020-018-1647-8>
- Messina C, Uselli FG, Maccario C et al (2019) Precision of bone mineral density measurements around total ankle replacement using dual energy X-ray absorptiometry. *J Clin Densitom* S1094–6950:30250–30256. <https://doi.org/10.1016/j.jocd.2019.01.006>
- Cervellati C, Pansini FS, Bonaccorsi G et al (2009) Body mass index is a major determinant of abdominal fat accumulation in pre-, peri- and post-menopausal women. *Gynecol Endocrinol* 25:413–417
- Cervellati C, Bonaccorsi G, Bergamini CM et al (2016) Association between circulatory levels of adipokines and bone mineral density in postmenopausal women. *Menopause* 23:984–992
- Dufour R, Winzenrieth R, Heraud A et al (2013) Generation and validation of a normative, age-specific reference curve for lumbar spine trabecular bone score (TBS) in French women. *Osteoporos Int* 24:2837–2846
- Kanis JA, Cooper C, Rizzoli R et al (2019) Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). Executive summary of European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Aging Clin Exp Res* 31:15–17. <https://doi.org/10.1007/s40520-018-1109-4>
- Lee JE, Kim KM, Kim LK et al (2017) Comparisons of TBS and lumbar spine BMD in the associations with vertebral fractures according to the T-scores: a cross-sectional observation. *Bone* 105:269–275
- Silva BC, Leslie WD, Resch H et al (2014) Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 29:518–530
- Bazzocchi A, Ponti F, Diano D et al (2015) Trabecular bone score in healthy ageing. *Br J Radiol* 88:20140865
- Hans D, Barthe N, Boutroy S et al (2011) Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. *J Clin Densitom* 14:302–312
- Leslie WD, Caetano PA, MacWilliam LR et al (2005) Construction and validation of a population-based bone densitometry database. *J Clin Densitom*. 8:25–30
- Leslie WD, Anderson WA, Metge CJ et al (2007) Clinical risk factors for fracture in postmenopausal Canadian women: a population-based prevalence study. *Bone* 40:991–996
- Boutroy S, Hans D, Sornay-Rendu E et al (2013) Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study. *Osteoporos Int* 24:77–85

23. Shin YH, Gong HS, Lee KJ et al (2017) Older age and higher body mass index are associated with a more degraded trabecular bone score compared to bone mineral density. *J Clin Densitom* 22:266–271. <https://doi.org/10.1016/j.jocd.2017.06.006>
24. Zhang Y, Guo J, Duanmu Y et al (2018) Quantitative analysis of modified functional muscle-bone unit and back muscle density in patients with lumbar vertebral fracture in Chinese elderly men: a case-control study. *Aging Clin Exp Res*. <https://doi.org/10.1007/s40520-018-1024-8>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.