Effect on Trabecular Bone Score (TBS) of Tissue-Selective Estrogen Complex (TSEC) in early post-menopausal women: case report

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Summary

Early post-menopause is a critical period for bone metabolism. It is well known hormonal status strongly influences skeletal health in association with other clinical risk factors. Different hormonal replacement therapies used to treat vasomotor symptoms, including classical HRT (Hormonal Replacement Therapy consisting of estrogens plus progestin for women with intact uteri), ERT (Estrogen Replacement Therapy without progesteron for women without uteri) or Tibolone, can precociously protect bone from loss of Bone Mineral Density (BMD), bone quality and vertebral and non vertebral fragility fracture risk. The Tissue-Selective Estrogen Complex (TSEC), a new pharmacological compound composed by conjugated estrogens (CE), 0.45 mg/day associated with 20 mg/day bazedoxifene (BZA) recently approved for treatment of menopausal symptoms, resulted an effective and safe therapy even in order to preserve bone. However, there are still few data about the possible effects of TSEC assumption on bone quality parameters other than serum bone turnover markers. Trabecular Bone Score (TBS) is a new direct measure of bone quality obtained from dual-energy X-ray absorptiometry (DXA) analysis. It offers an innovative parameter to add to BMD assessment a reproducible numerical evaluation of bone integrity on the basis of standard DXA. The combination of both methods could give more information about bone health analyzing skeletal status from different aspects and help clinicians to better document the impact of pharmacological therapies. Here, we describe two clinical cases regarding two young postmenopausal women treated with TSEC and their short-term response to therapy concerning BMD and TBS score.

KEY WORDS: TSEC; bone strength; bone quality; TBS.

Introduction

Osteoporosis is largely recognized as an important social and public health problem, affecting million of people of both sexes worldwide (1). Typical progressive loss of female hormones of the climacteric period still represents the main cause of physiological reduction of bone density and quality of perimenopause (2). In fact, normally ovarian hormones play a key role in bone metabolism, as they are usually involved in bone resorption – through the direct regulation of osteoclastogenesis induced by estrogens – and in bone formation – firstly sustained by Progesterone activity on osteoblastic cells (3, 4). On the other hand, menopause negatively impacts on bone health not only because of loss of all these hormones usually produced by all women in reproductive age, but also owing to the general modifications of body composition and the possible influence of other factors, such as comorbidities, drugs, lifestyle and diet (5).

Vasomotor disturbances, the most frequent symptoms of perimenopausal period, are considered the main indication for HRT (Hormonal Replacement Therapy consisting of estrogens plus progestin for women with intact uteri) or ERT (Estrogen Replacement Therapy without progestin for women without uteri). At the same time, HRT/ERT, if not contraindicated, can protect women from bone deterioration preventing vertebral and femoral fractures since from early post menopause, when bone turnover is particularly enhanced due to hormonal modifications (6). Data about use of each type of menopausal hormonal therapy still suggest to initiate treatment of symptomatic women as soon as possible – ideally within 60 years old and/or 10 years after the last menstrual cycle – in order to optimize its potential benefits (7).

In the last few years, one interesting new kind of hormonal therapy has been approved: it is called Tissue-Selective Estrogen Complex (TSEC). TSEC is an association between a Selective Estrogen Receptor Modulator (SERM), such as 20 mg bazedoxifene (BZA) with an estrogen compound, like the conjugated estrogens (CE), 0.45 mg/day (8). Recent studies demonstrate TSEC can reduce frequency and intensity of hot flushes and have also clear positive effects on vagina, libido, energy levels and bone tissue (8). TSEC is characterized by a particular pharmacological profile which confers a peculiar neutrality on breast and uterus, as it is without any usual progestinic action: in fact, opponent effects balancing tissutal stimulation induced by CE are interestingly linked to BZA (9). This is the main aspect which makes TSEC different from previous traditional menopausal hormonal therapies (10, 11). Therefore, nowadays TSEC is largely considered a new safe treatment with recognized efficacy. The effects of the TSEC on bone tissue was demonstrated in two clinical trials (SMART-1 and SMART-5) (12, 13). In particular, in the SMART trial 1 (12), in all patients in menopause for more than five years treated with BZA 20 mg/CE 0.45 mg, a sig-

nificant increase from baseline of mean lumbar spine and hip BMD resulted after 24 months of therapy and differences in BMD between treatment groups (BZA 20 mg/CE 0.45 mg or BZA 20 mg/CE 0.625 mg) and placebo were reported at each time point (p<001 at 6, 12, and 24 months). In addition, the Authors interestingly observed a significant change in markers of bone turnover (BTM) following treatment with all BZA/CE doses compared with placebo (p<0001), suggesting TSEC may improve both bone density and bone quality. These results were confirmed by the double-blind, randomized, placebo-controlled SMART-5 where BZA 20 mg/CE 0.45 mg (–40.86% and –42.38%) and BZA 20 mg/CE 0.625 mg (–50.06% and –43.58%) groups showed significantly greater decreases from the baseline in both serum markers of bone resorption, C-telopeptide and procollagen I N-terminal propeptide, *vs* the PBO (–5.52% and –11.13%, respectively), evaluated at 12 months ($P < .001$ for all) (13).

In the last few decades, the concept of bone quality had been studied and different methods were proposed to better investigated bone structure, besides biochemical analysis of BTMs (14). The assessment of Trabecular Bone Score (TBS) is one of the most interesting and promising method of bone quality evaluation, as it can give rapid and precocious important informations about bone integrity simultaneously with dual-energy X-ray absorptiometry (DXA) (15).

We present two clinical cases about the skeletal effect of TSEC in two postmenopausal patients, describing our data of significant rapid amelioration of BMD and bone turnover accompanied with enhancement of TBS value, since after few months of therapy, suggesting the rapid effect of TSEC on bone.

Materials and methods

Two menopausal women were admitted to Endocrinological Gynecology, Menopause and Osteoporosis Clinic, Policlinico Gemelli Foundation IRCCS, for the appearance of troublesome vasomotor symptoms. They were both affected by frequent hot flashes, sweating, and arthralgia and declaired amenorrhea since about 1 year and half. They had not other specific symptoms, medical history or particular risk factors for other causes of secondary osteoporosis. On physical examination, they seemed to be healthy, showing a normal weight without relevant clinical signs. In particular, we tested in the blood calcium, phosphorus, parathyroid hormone, (PTH) and vitamin D. Bone Mineral Density was evaluated with dual-energy X-ray absorptiometry (DXA) (GE-Lunar Prodigy Advance). Trabecular bone Score (TBS) was assessed at lumbar site simultaneously with DXA using Lunar Prodigy® with TBS Insight® program.

Considering normal results of general laboratory tests, their mammograms and pelvic ultrasound studies and absence of significant contraindication for assumption of menopausal hormonal replacement therapy, we prescribed TSEC as HRT. DXA measurements associated with TBS study were performed at baseline and repeated after 6 months of therapy in the same centre under the same methods and conditions.

Results

For both patients, vitamin D levels were within the normal range of laboratory (25dihydroxy-vitamin D ≥ 30 ng/ml) before and after TSEC therapy.

Patient n.1 (age 52 years) showed a basal lumbar (L1-L4) BMD of 1,271 g/cm^2; femoral neck BMD of 0,983 g/cm^2; total femur 0,941 g/cm^2; 25OHD was 41 ng/ml; PTH was 28 pg/ml. At 6 months spine and total/neck femoral BMD were increased, as respectively measured 1,274 g/cm^2; 1,034 g/cm^2 and 1,009 g/cm^2. TBS was also ameliorated, as its basal evaluation indicated a median level of 1,353, while the second one reported after treatment with TSEC was 1,360 (Figures 1, 2).

Patient n.2 (age 51 years) had lumbar BMD 1,227 g/cm^2, femoral neck BMD 0,985 g/cm^2, total femoral BMD 0,926 g/cm^2; vitamin D level was 38 ng/ml; PTH was 40 pg/ml. On the other hand, her TBS L1-L4 showed a modest reduction compared to normal range at baseline (1,252). After 6 months BMD values resulted: lumbar BMD 1,276 g/cm^2; femoral neck BMD 0,997 g/cm^2; total femoral BMD 0,947 g/cm^2. TBS L1-L4 was markedly increased after treatment (1,372) (Figures 3, 4).

Discussion and conclusions

Bone loss in perimenopausal period still represents an important matter of discussion. Sometimes, that phenomenon remains underdiagnosed and underestimated, as the major national guidelines suggest to perform the first densitometric evaluation at about 65 years of age for all women without evident clinical risk factors (16, 17). On the other side, bone strenght deterioration is usually much more rapid and prevalent in early period of menopause, whose median age is 51 years. Different studies demonstrated bone structure alterations may anticipate the definitive disappearance of menses (18).

In fact, the initial reduction of progesterone, which usually precedes the unrelenting loss of estrogens, may negatively impact on bone health formation and on general remodelling cycle, as this ovarian hormone is considered an important regulator of osteoblastic function (18). All those paraphysiological hormonal modifications possibly accompanied with other fragility fracture risk factors, like family hystory, aging, comorbidities, drug intake and oxidative stress, could promote a precocious loss of bone density and/or bone quality (19).

Nowadays, assessment of Bone Mineral Density through DXA analysis represents the mainstay for the diagnosis of osteopenia/osteoporosis, giving a largely recognized and reliable stratification of fracture risk (20). However, limit of that method consists of the absence of informations about inner bone structure, referring to bone geometry and microarchitecture, which may be also involved in general loss of bone strength, in some cases producing augmented skeletal fragility *per sé*, independent of BMD status. In an interesting manner, Garnero et al. showed in EPIDOS study, women with increased bone formation and resorption were at greater risk of hip fracture if compared with healthy premenopausal subjects (21). Furthermore, according to different Authors like Siris et al. (22), even if fracture risk proportionally increases in association with BMD and corresponding T-score levels reduction, the condition of osteopenia (-1<T score>-2.5) does not exclude the possibility to present fragility fractures. This fact confirmed post menopausal women affected by initial bone loss may show critical decrease of bone structure regardless of BMD (22).

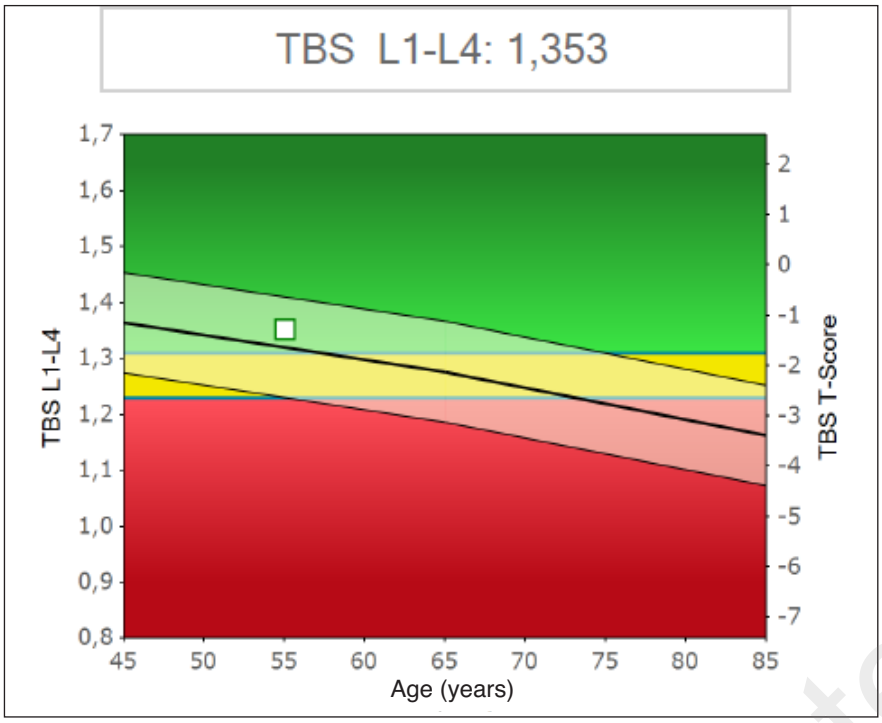

Figure 1 - Patient n.1 TBS at baseline.

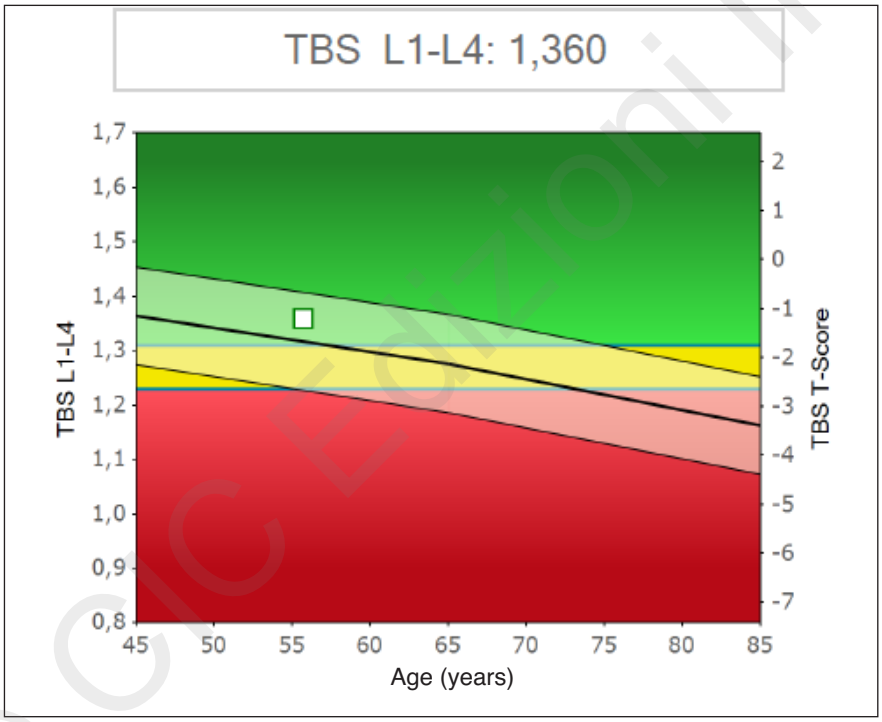

Figure 2 - Patient n.1. TBS after 6 months of treatment.

Trabecular Bone Score is a bone parameter calculated with a specific software associated with DXA (23). It was been recently proposed as a complementary analysis which can complete standard areal BMD study reflecting bone microarchitecture, as an additional index of bone texture can be promptly obtained (24). TBS tool is based on some complex variograms of 2D projection images – generally get from DXA at lumbar level-, quantifying variation in grey-level texture from one pixel to the adjacent pixels. Resulted measurements are related to 3D bone characteristics such as trabecular number and separation and the connectivity density (considered parameters of bone quality) (24). For example, an elevated TBS usually corresponds to strong, fracture-resistant microarchitecture, while a low TBS value usually reflects weak, fracture-prone microarchitecture (25). It is largely recognized TBS may promote risk stratification in bone

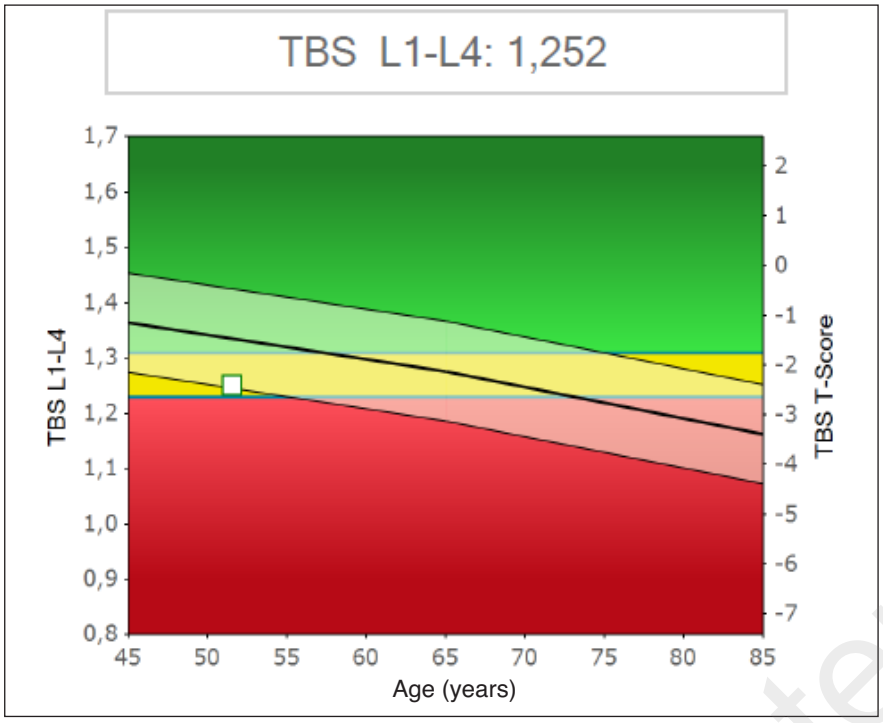

Figure 3 - Patient n. 2 TBS at baseline.

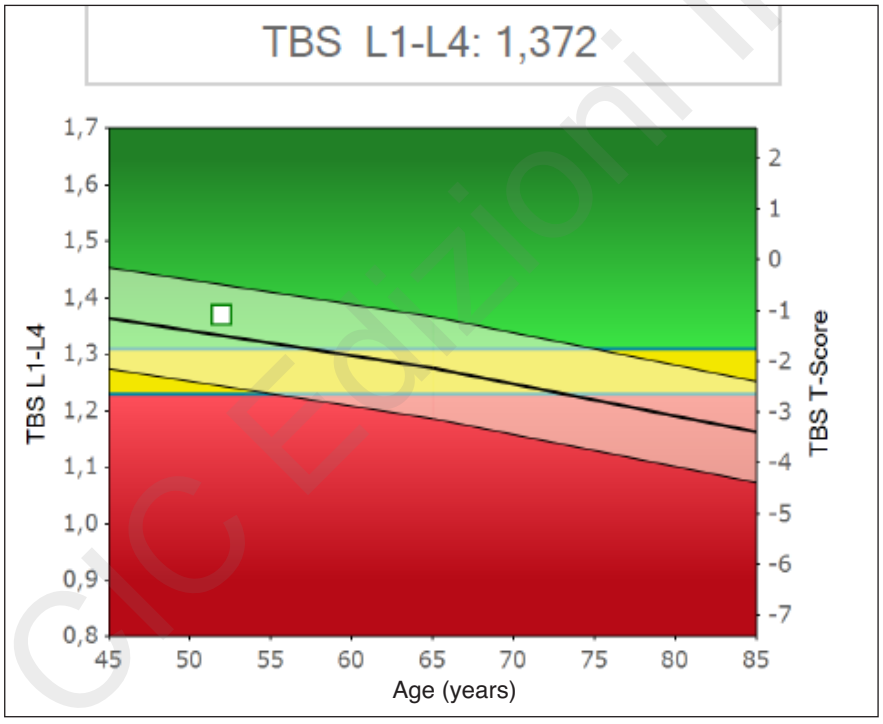

Figure 4 - Patient n. 2 TBS after 6 months of treatment.

frail patients, indipendent of areal BMD assessment (24, 25). According to recent evidence, its value should effectively improve after different treatments of bone loss, confirming its growing role on clinical practice in follow-up of osteopenia/osteoporosis (26). Interestingly, Di Gregorio et al. enrolled 390 patients (men: 72; women: 318; age>40 years; mean follow-up of 20 months and BMI<37 kg/m) divided into 4 groups according to treatment: Naive of treatment (Naive, n=67), Calcium and Vitamin D (CaVitD, n=87), Testosterone (Te, n=36), Alendronate (AL, n=88), Risedronate (Ri, n=39), Denosumab (Dmb, n=43) and Teriparatide (PTH, n=30). Relevant increase ($p<0.05$) was observed in both TBS and areal BMD for Te, AL, Ri, Dmb and PTH groups while only for TBS in the CaVitD group if compared to the Naive group. In fact, in Naive subjects TBS decreased by 3.1% ($p<0.05$) whereas a non-significant increase was observed for spine aBMD

(Δ=+0.5%). The Authors concluded TBS naturally decreased with age in Naive patients while bone stucture preservation, considering TBS as a surrogate of bone quality, should be ensured by antiosteoporotic treatments, even by the simple association between calcium and vitamin D (26).

Interestingly, both our patients showed normal values at baseline about DXA, but TBS revealed a significant reduction counteracted by TSEC therapy after only 6 months of administration. These results may suggest the predictive role of TBS in monitoring not only major antiosteoporotic drugs, but also hormonal menopausal therapy, particularly the new option TSEC (27).

The most important randomized controlled trials published on menopause, especially heart and estrogen/progestin replacement study (HERS) and Women's Health Initiative (WHI), demonstrated HRT at standard dose had positive effects on bone mass with more intensity at trabecular level (28, 29). However, beneficial consequences of HRT on bone only persists during the treatment and is usually rapidly lose after the interruption of therapy (27, 30).

BMD and markers of bone turnover were typically the main parameters investigated to prove HRT efficacy. In particular, precocious beneficial impact on bone health of HRT had been traditionally demonstrated by the rapid even small reduction of bone turnover markers, as perimenopausal higher turnover rate owing to the hormonal milieu makes bone more responsive to hormonal replacement, particularly if started in early post-menopause (31, 32).

On the basis of the short-term follow-up of our patient, we should suggest TBS may represent a valid and reliable method to highlight at an early stage the positive effects of TSEC on bone. The protective activity on skeleton of this new pharmacological association composed by conjugated estrogens (CE), 0.45 mg and 20 mg bazedoxifene (BZA) was reported in clinical trials SMART-1 and SMART-5 (12, 13). TSEC resulted effective in increasing BMD and reducing markers of bone turnover. In SMART-1 trial, changes in bone metabolism parameters (osteocalcin as bone formation marker and C-telopeptide as serum resorption marker) appeared significant following treatment with BZA/CE compared with placebo ($p<0001$). These data were confirmed by the one-year, double-blind, randomized, placebo-controlled SMART-5 clinical trial, which enrolled 1886 women (mean age: 53 years; range: 40 to 60 years) in postmenopause for 1-5 years, with at least one additional osteoporosis risk factor. Both BZA/CE doses evaluated in that study enhanced lumbar spine and total hip BMD after 12 months, with significant differences reported at 6 and 12 months ($p<005$) *versus* placebo. Besides, TSEC induced a more significant reduction from baseline of C-telopeptide and procollagen I N-terminal propeptide ($p<001$), suggesting a protective effect on bone metabolism as well as on BMD (13).

According to our results, we could assume TSEC may preserve bone strength from microarchitectural deterioration even in early postmenopausal women without significant initial BMD loss. Sometimes, in that period, the real effects of hormonal deficiency on bone densitometry should not be yet noticeable. TBS may partially reflect bone status and sustain clinical approach in order to better classify our patients and monitor antiosteoporotic preventive pharmacological and non pharmacological interventions.

However, its sole use in osteoporotic patients management produces intriguing but insufficient informations: in fact, TBS need to be still associated with an accurate densitometric and clinical evaluation, considering all clinical fracture risks, eventually assessed with other specific tools (FRAX, DeFRAcalc) (23).

At the same time, the relationship between change in TBS and magnitude of fracture risk reduction, the main objective of all anti-osteoporotic drugs, remains to be clarified.

Our case report underlines the potential role of TBS tool to analyse the effect of TSEC on bone mineral quality, introducing an additional indicator of bone resistance independent from BMD. On the other hand, TSEC confirms its ability to preserve bone strength, as showed by the improvement of TBS in our clinical cases, even if after a short-term therapy. At our knowledge, this is the first report about this positive effect of TSEC on TBS. That innovative evidence needs to be further investigated to eventually confirm our results in larger future studies.

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