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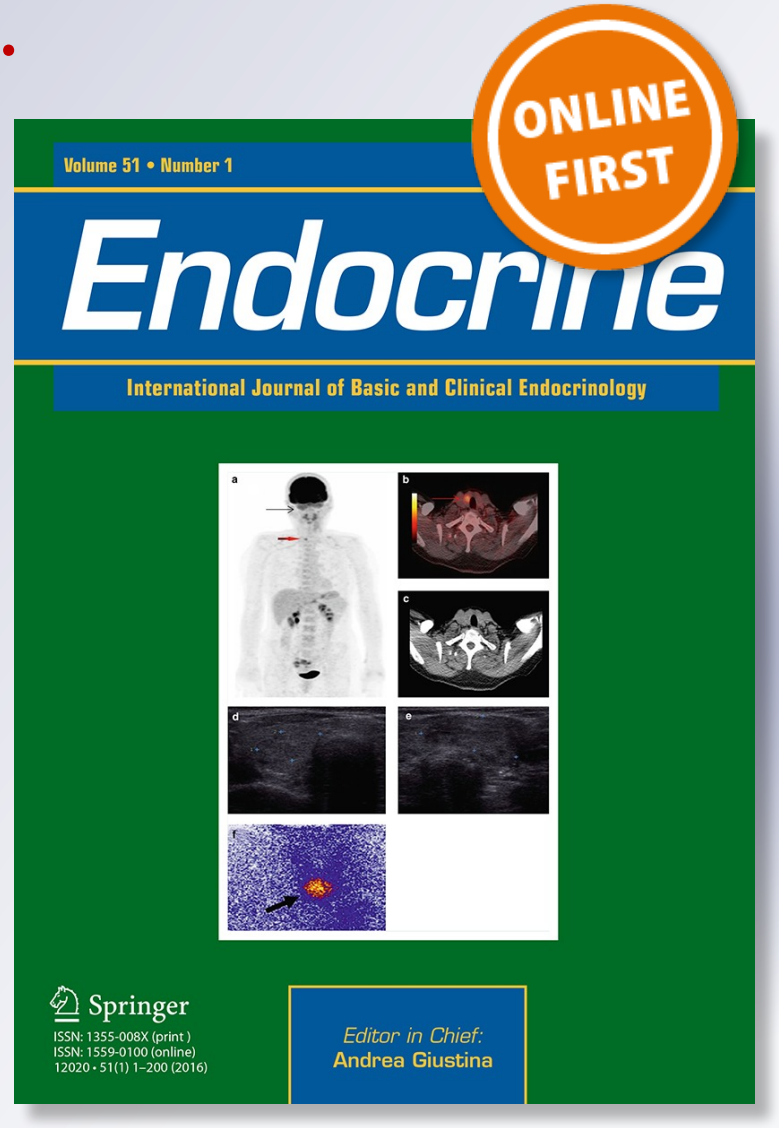

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ENDOCRINE METHODS AND TECHNIQUES

Assessment of trabecular bone score (TBS) in overweight/obese men: effect of metabolic and anthropometric factors

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Abstract The "trabecular bone score" (TBS) indirectly explores bone quality, independently of bone mineral density (BMD). We investigated the effects of anthropometric and metabolic parameters on TBS in 87 overweight/obese men. We assessed BMD and TBS by DXA, and some parameters of glucose metabolism, sex-and calciotropic hormone levels. Regression models were adjusted for either age and BMI, or age and waist circumference, or age and waist/hip ratio, also considering BMI >35 (y/n) and metabolic syndrome (MS) (y/n). Correlations between TBS and parameters studied were higher when correcting for waist circumference, although not significant in subjects with BMI >35. The analysis of covariance showed that the same model always had a higher adjusted *r*-square index. BMD at lumbar spine and total hip, fasting glucose, bioavailable testosterone, and sex hormone-binding globulin are the only covariates having a significant effect ($p < 0.05$) on the variations of TBS. The presence of MS negatively affected only the association between TBS and BMD at total hip. We did not find any significant effect of BMI >35 on TBS values or significant interaction terms between each covariate and either BMI >35 or the presence of MS. Obesity negatively affected TBS, despite unchanged BMD. Alterations of glucose homeostasis and sex hormone levels seem to influence this relationship, while calciotropic hormones have no role. The effect of waist circumference on TBS is more pronounced than that of BMI.

Keywords TBS · Bone quality · Obesity · Metabolic syndrome · Men

Introduction

The "trabecular bone score" (TBS) is a recently introduced simple and non-invasive tool able to explore factors influencing bone strength and fracture risk, other than bone mineral density (BMD) [1, 2]. The geometry of bone, micro-architecture, as well as bone micro-damage and bone mineralization strongly correlate to bone properties, but each of them is difficult to assess in routine clinical practice, so that the measurement of BMD still remains the cornerstone of bone evaluation. The TBS has been reported to indirectly reflect bone micro-architecture. It is a texture parameter seemingly recording pixel gray-level variations in DXA images. The software can be easily installed on DXA machines, and the value of TBS can be calculated retrospectively. Higher scores reflect stronger and more fracture-resistant micro-architecture, whereas lower scores indicate poor bone quality and greater susceptibility to fracture [3].

Several studies so far explored the clinical added value of TBS over BMD to assess the risk of fragility fractures [4, 5]. Recently, this tool has also been shown to predict fracture, independent of probabilities using the FRAX

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algorithm [6]. Moreover, in fractured patients with secondary causes of osteoporosis TBS values are significantly lower than in patients without fractures [7–9]. In addition, TBS change following different bone treatments [10, 11].

However, the larger body of literature focused on women [4, 5], whereas data on TBS in men are still limited. Two recent papers showed that, consistently with the results obtained in postmenopausal women, men with fractures had lower TBS values than men without fractures [12, 13]. Moreover, TBS and prevalent radiographic vertebral fracture are associated with incident major osteoporotic fractures in older men independent of each other and FRAX 10-year fracture risks [14].

To our knowledge, clinical factors influencing TBS have not been adequately explored in men. In particular, the effect of obesity could differ between sexes, due to the different pattern of fat distribution. Therefore, we investigated the role of overweight and obesity, as of some related hormonal and metabolic parameters on TBS, in a sample of men with a wide range of age and BMI.

Methods

In this retrospective cross-sectional study, 141 overweight/obese men admitted to the day-hospital of our department from January to September 2014, were initially examined. They had been consecutively recruited as a part of an ongoing study aimed to evaluate metabolic and hormonal profile in male relatives of patients with obesity, insulin resistance and/or type 2 diabetes mellitus. The study was approved by the local Ethics Committee, and all participants gave informed consent. All men underwent complete medical history and physical examination. From the whole sample, 18 subjects were excluded because of an history of spinal surgery, or two or more lumbar vertebrae not observable on DXA images, or scoliosis of lumbar spine, 10 because they were taking for more than one-year drugs commonly influencing bone metabolism, 21 because of a diagnosis of type 2 diabetes mellitus, five because of a secondary cause of bone loss (endogenous hypercortisolism in two subjects, primary hyperparathyroidism in one subject, suppressed TSH levels in two subjects). A sample of 87 men (mean age 53.42 ± 11.89 years, range 25–76 years) was finally evaluated. The presence of metabolic syndrome (MS) was diagnosed according to standard criteria [15]. Anthropometric measurements included weight, height, waist and hip circumference. Such circumferences (to the nearest 0.5 cm) were measured using a plastic tape meter at the level of the umbilicus and of the greater trochanters, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist to hip ratio (W/H) was also calculated. On a fasting blood sample routine biochemical parameters, glucose (FPG), insulin, HbA1c, total testosterone, estradiol (only in 35 subjects), sex hormone binding globulin (SHBG), parathyroid hormone (PTH), and 25-hydroxyvitamin D (25OHD) were measured according to standard laboratory methods at "Policlinico Umberto I" University Hospital of Rome. Free and bioavailable testosterone were calculated from SHBG, albumin and total testosterone, by the widely employed formula by Vermeulen et al. [16] (http://www.issam.ch/freetesto.htm). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting plasma insulin and glucose levels using the formula: insulin × glucose/22.5 (mU/L × mmol/L).

BMD was measured by DXA (QDR Discovery Acclaim, Hologic Inc., Waltham, MA) at the lumbar spine in posterior-anterior projection (L1–L4) (LS-BMD) and at total hip (TH-BMD) in all subjects. The coefficients of variations were 1.0 % at lumbar spine and 1.7 % at total hip. TBS was evaluated in the same regions used for LS-BMD (L1-L4) using the latest version of TBS iNsight® (version 2.1.2, Med-Imaps, Pessac, France) proved also for men. TBS was calculated as the mean value of the individual measurements for vertebrae L1–L4. The coefficient of variation for TBS was 1 %, and it did not vary among the measured vertebrae.

Statistical analysis

Data are expressed as mean ± standard deviation or *n* (%). One-way analysis of variance (ANOVA) was used to test differences among groups. Simple correlation coefficients were computed for all the variables. Kendall's correlation was computed either controlling for age and BMI (model 1), or controlling for age and waist circumference (model 2), or for age and waist/hip ratio (model 3), to assess the association between TBS and the other variables. Kendall's thau was used due to its robustness as a measure of correlation and to the possibility to use it in a non-parametric framework to test for absence of correlation. Correlation matrices were computed on the whole sample and in subjects with a BMI lower or greater than 35. Such a conservative cut-off level of BMI was chosen because it has been claimed that above this value the effect of obesity may potentially degrade the reliability of TBS measurement [2].

To analyze the effect of several covariates on TBS, analysis of covariance models was applied to the three models considered (model 1, 2, and 3). In all the models, interaction terms between the covariate and the dummy variables BMI >35 (yes, no) and metabolic syndrome (yes, no) have been considered. All the covariates, in turn, were considered one by one, fitting as many models as the number of covariates. The goodness of fit of each model

was assessed via the adjusted r-square index. Hypothesis of normality of the errors was visually assessed on the residuals.

In all the analysis a p value of 0.05 was used as a statistical threshold to indicate a statistically significant effect. All the analyses have been carried out using R version 3.0.2.

Results

Table 1 summarizes the characteristics of the study subjects, both in the whole sample and in subjects subdivided according to BMI values: 25.3 % of men were normal/overweight (BMI Kg/m^2 ≤29.9), 34.5 % were moderately obese (BMI between 30 and 35) and 40.2 % were severely obese (BMI ≥35). Mean TBS values significantly decreased to the increase of BMI ($p < 0.001$ by one-way ANOVA), while age and LS-BMD did not differ among the three groups.

In the whole sample, TBS values negatively correlated with age ($r = -0.235$, $p < 0.05$), BMI ($r = -0.452$, $p < 0.0001$), waist ($r = -0.578$, $p < 0.0001$), and W/H ($r = -0.403$, $p < 0.001$). TBS positively associated to LS-BMD ($r = 0.367$, $p < 0.001$) but not with TH-BMD. Moreover, TBS negatively correlated with FPG ($r = -0.325$, $p < 0.01$), fasting insulin ($r = -0.228$, $p < 0.05$), HbA1c ($r = -0.302$, $p < 0.01$), and HOMA-IR ($r = -0.246$, $p < 0.05$). TBS also showed a significant positive correlation with total ($r = 0.265$, $p < 0.05$), free ($r = 0.371$, $p < 0.001$), and bioavailable testosterone ($r = 0.428$, $p < 0.001$), whereas it negatively correlated with SHBG ($r = -0.241$, $p < 0.05$). TBS did not correlate with estrogen, nor with 25(OH)D and PTH serum levels.

Both in the whole sample, and in subjects grouped for BMI value (≤ or >35), the correlation analysis between TBS and the parameters studied corrected for age and BMI (model 1), for age and waist circumference (model 2) and for age and W/H (model 3) displayed higher values in model 2. So only the result concerning model 2 have

Table 1 Characteristics of study subjects

Parameters	Whole sample $n = 87$	BMI ≤29.9 $n = 22$	30 ≤ BMI < 35 $n = 30$	BMI ≥35 $n = 35$	p
Age (years)	53.42 ± 11.89	54.40 ± 11.58	52.70 ± 12.27	53.42 ± 12.04	ns
Waist circumference (cm)	114.03 ± 14.39	99.19 ± 8.63	110.55 ± 7.87	126.48 ± 11.10	<0.001
Waist/hip circumference ratio	1.010 ± 0.06	0.982 ± 0.06	1.003 ± 0.05	1.035 ± 0.06	<0.05
Body mass index (BMI)(Kg/m^2)	33.79 ± 5.66	26.52 ± 1.93	32.54 ± 1.20	39.43 ± 3.03	<0.001
TBS	1.23 ± 0.13	1.31 ± 0.10	1.25 ± 0.12	1.16 ± 0.14	<0.001
LS-BMD (g/cm^2)	1089 ± 0168	1017 ± 0.164	1101 ± 0148	1124 ± 0176	ns
TH-BMD (g/cm^2)	1064 ± 0163	0952 ± 0127	1049 ± 0147	1146 ± 0154	<0.001
Glucose (mmol/l)	5.89 ± 1.95	5.17 ± 0.68	6.08 ± 2.40	6.19 ± 2.00	ns
Insulin (pmol/l)	129.3 ± 99.18	70.67 ± 78	100.97 ± 68.22	188.94 ± 103.26	<0.001
HbA1c (%)	4.94 ± 1.16	4.28 ± 0.46	5.11 ± 1.20	5.23 ± 1.24	<0.01
HOMA-IR	6.10 ± 6.35	2.77 ± 3.07	4.43 ± 3.04	9.55 ± 8.14	<0.001
Total testosterone (nmol/l)	3.72 ± 1.34	4.09 ± 1.35	3.90 ± 1.34	3.30 ± 1.27	ns
Free testosterone (ng/dl)	7.26 ± 2.88	8.48 ± 3.2	7.40 ± 2.43	6.34 ± 2.83	<0.05
Bioavailable testosterone (ng/dl)	171.44 ± 67.18	199.21 ± 73.47	175.65 ± 59.06	149.32 ± 64.6	<0.05
Estradiol (pmol/l)[a]	99.85 ± 38.43	81.16 ± 33.4	97.46 ± 35.79	110.42 ± 41.04	ns
SHBG (nmol/l)	36.29 ± 12.73	33.58 ± 9.94	37.63 ± 14.95	36.82 ± 12.26	ns
25(OH)D (ng/ml)	21.02 ± 10.03	26.45 ± 11.96	20.39 ± 5.43	19.15 ± 11.52	<0.05
PTH (pg/ml)	39.98 ± 19.42	33.38 ± 16.93	41.88 ± 22.41	39.09 ± 16.58	ns

Variables are expressed as mean ± SD

BMI body mass index; *TBS* trabecular bone score; *LS-BMD* lumbar spine bone mineral density; *TH-BMD* total hip bone mineral density; *HOMA-IR* homeostasis model assessment insulin resistance; *SHBG* sex hormone binding globulin; *25(OH)D* 25-hydroxyvitamin D; *PTH* parathyroid hormone

The p values refer to significant differences among the three groups of males subdivided according to BMI range (≥29.9, between 30 and 35, ≤35)

[a] Measured in 35 out of 87 subject

Table 2 Correlation analysis between TBS and the investigated skeletal, metabolic, and hormonal parameters, corrected for age and waist circumference (model 2)

Parameter	Whole sample	BMI ≤35	BMI >35
LS-BMD	0.334***	0.358***	0.436**
TH-BMD	0.226**	0.321**	0.180
Fasting plasma glucose	−0.147	−0.276**	−0.02
Fasting insulin	−0.017	−0.027	0.014
HbA1c	−0.249**	−0.268*	−0.177
HOMA-IR	−0.050	−0.089	−0.006
Total testosterone	0.074	0.087	−0.014
Free testosterone	0.172*	0.147	0.082
Bioavailable testosterone	0.194*	0.169	0.124
SHBG	−0.209*	−0.164	−0.269
25[OH]D	−0.092	−0.111	−0.055
PTH	0.053	0.037	0.111

Data are presented in the whole sample and in subjects subdivided according to BMI, lower or higher than 35

LS-BMD lumbar spine bone mineral density; *TH-BMD* total hip bone mineral density; *HOMA-IR* homeostasis model assessment insulin resistance; *SHBG* sex hormone binding globulin; *25(OH)D* 25-hydroxyvitamin D; *PTH* parathyroid hormone

* $p < 0.05$; ** $p < 0.01$;*** $p < 0.001$

presented (Table 2). In all groups a significant correlation was found between TBS and LS-BMD. TBS correlated with TH-BMD only in the whole sample and in subjects with BMI <35. In the same groups, TBS negatively correlated with HbA1c and FPG. Finally, TBS positively correlated with both free and bioavailable testosterone, and negatively with SHBG.

The analysis of covariance models shows that model 2 always had a better fitting (measured by the adjusted *r*-square index) than those obtained by either model 1 or model 3 (data not shown). Concerning the effect of each covariate on TBS, and its possible interaction effects with MS (y/n) and BMI >35, only LS-BMD, TH-BMD, FPG, bioavailable testosterone, and SHBG showed a significant effect ($p < 0.05$) on the variations of TBS. MS negatively affected only the association between TBS and TH-BMD. We did not find any significant effect of BMI >35 on TBS or significant interaction terms between each covariate and either BMI >35 or the presence of MS.

Discussion

We investigated the influence of some anthropometric, metabolic and hormonal parameters on TBS in a group of overweight/obese men with a wide range of age, BMI, and degree of insulin resistance, but without type 2 diabetes mellitus.

In men of similar mean age, with the increase of BMI, TBS significantly decreased; on the contrary, LS-BMD did not vary and TH-BMD progressively increased, so that in obese men, lower TBS values could reflect a bone quality deterioration.

Since age and anthropometric variables may strongly influence the correlations of TBS with all the parameters investigated, we set-up three different models adjusted for either age and BMI (model 1), or age and waist circumference (model 2) or age and W/H (model 3). The second model best fitted our data, showing that TBS significantly correlated with BMD, HbA1c, free and bioavailable testosterone, in the whole sample or in subjects with BMI <35. By the analysis of covariance, this model showed that at the increase of LS-BMD, TH-BMD and bioavailable testosterone, TBS values increased, while fasting, glucose and SHBG had a negative effect on TBS values. In subjects with MS, TBS was on average lower than in those without MS.

The contribution of TBS in determining bone properties has been scarcely investigated in men. Recently, two papers demonstrated that in men with fractures TBS values were reduced and predicted incident fractures in older men [12, 13]. Moreover, in diabetic patients of both genders, TBS negatively correlated with HbA1c, FPG, fasting insulin, and HOMA-IR also in men, suggesting that TBS could be a marker of skeletal deterioration in diabetes [17]. Our results show that TBS relates to metabolic risk factors also in men without diabetes but with different degree of insulin resistance. In particular, after adjustment for age and anthropometric variables, TBS negatively correlated with HbA1c levels and fasting glucose, implying impaired bone quality, possibly due to the accumulation of advanced glycosylation end-products in the organic bone matrix [18].

We also investigated the effect on TBS of metabolic syndrome. This is a very common condition in obese patients, whose abdominal fat and insulin resistance may affect bone. However, the effects of MS on bone health are still controversial, particularly in clinical studies assessing BMD, in which the protection afforded by increased body weight is balanced by the damage due to the inflammatory state, insulin resistance, hyperglycemia, and other factors [19, 20]. A recent meta-analysis suggested that MS is a risk factor for osteoporosis in men [21], probably because of impaired bone quality. No studies so far assessed the role of TBS to evaluate bone properties in patients with MS. At this regard, our results are mostly negative. We did not find any significant interaction terms between each covariate and the presence of MS, although it negatively affected the association between TBS and TH-BMD. In other words, subjects with MS showed on average a lower value of TBS.

In our study, we also attempted to evaluate the effect of obesity on TBS assessment. A very large amount of soft

tissue overlying ROI may potentially degrade image quality and affect texture analysis, reducing the TBS estimate in obese subjects. Therefore, it is claimed that the better performance of TBS is obtained when BMI ranges from 15 to 35 kg/m^2, and TBS assessment is not validated beyond these limits of BMI [2]. Actually, this manufacturer's recommendation for TBS software does not rely on published data. It cannot be excluded that TBS could capture alterations in bone structure of obese individuals, who may have higher fracture risk despite a higher BMD [22]. On the other hand, BMI can not adequately reflect central abdominal fat or distinguish it from adiposity at other sites. Moreover, due to the difference in fat tissue distribution and muscle weight, the adjustment for BMI could not work equally well in men and women. Actually, studies evaluating the influence of BMI on TBS provided discordant results. In older women, the negative correlation between TBS and BMI was attenuated after excluding obese individuals with BMI >30 kg/m^2 [23]. On the other hand, TBS was significantly lower in the diabetic than nondiabetic women, when stratifying results by obesity [24]. Therefore, we evaluated not only the influence on TBS of BMI >35 (the current cut-off for TBS reliability) but also that of waist circumference and W/H, two easy-to-perform measures of abdominal fat accumulation. This represents a relevant novel approach, since no studies hitherto considered the influence of abdominal fat on TBS values. Simple models showed better correlations between TBS and other parameters when controlling for age and waist circumference, in respect to models controlled for either age and BMI or age and W/H. Noteworthy, the results of covariance analysis showed that model 2 provided an adjusted r-square index always higher than the other models. This implies an increase in the explained variance of TBS when controlling for age and waist circumference. Collectively, our data indicate that TBS assessment does not provide reliable results in subjects with BMI >35, but below this BMI the model adjusting for waist circumference better fitted the data. Therefore, waist circumference, instead of BMI, should be probably taken into account when assessing TBS performance in obese men. Conceivably, central obesity, mirrored by waist circumference, may affect skeletal health more than general obesity reflected by BMI [25]. On the other hand, previous results on the association between waist circumference and BMD have been inconsistent. Gonnelli demonstrated that fat distribution differently affects BMD in men and women: android fat is positively associated with BMD at different skeletal sites in men, whereas in women BMD at the same skeletal sites is negatively associated with gynoid fat [26]. On the contrary, waist circumference was negatively and independently associated with lumbar spine and femoral neck BMD in men [27]. Differences in the populations studied, in the methods used to measure BMD and central adiposity, or in the number and type of covariates controlled for across studies may account for these divergent findings [28].

Besides, the association between TBS and sex hormones deserves interest. TBS significantly correlated with both free and bioavailable testosterone and negatively with SHBG. The analysis of covariance also showed a positive effect of bioavailable testosterone and a negative one of SHBG on TBS. The effects of sex steroids in male bone health are complex and incompletely known. Our results are in line with a recent study demonstrating that men with abdominal obesity have impaired bone micro-architecture and strength as measured by HR-pQCT at distal radius [25].

Our study has some limitations. Firstly, the cross-sectional design of the study allows investigating for association and not for causality. Secondly, sample size was relatively small. Moreover, the lack of comparison with women does not allow infer whether gender-related distribution of body fat differently affects TBS measurement in men and women [29]. Finally, due to the retrospective design of the study, not all confounding factors have been considered and sex hormone levels were measured by commercial assays which lack the reliability of newer liquid chromatography tandem mass spectrometry methods [30].

In conclusion, our data showed that abdominal fat accumulation could negatively affect TBS values in overweight/obese men, independent of LS-BMD. Parameters of glucose homeostasis and sex hormone levels seem to influence TBS, at least in this group. Moreover, for the first time, we also demonstrated that waist circumference did influence TBS values more than BMI, contrary to current beliefs. This latter finding could be relevant when investigating bone quality in obese men.

Compliance with ethical standards

Conflict of interest Elisabetta Romagnoli, Carla Lubrano, Vincenzo Carnevale, Daniela Costantini, Luciano Nieddu, Susanna Morano, Silvia Migliaccio, Lucio Gnessi, and Andrea Lenzi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent 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.

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