REVIEW

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Body mass index inversely associated with bone microarchitecture quality: a systematic review and meta-analysis

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ABSTRACT

Introduction: The rising prevalence of obesity forces the orthopedist to consider it in fracture risk assessment. Multiple studies have consistently demonstrated that people with obesity have increased bone mineral density (BMD). Although it appears other factors in bone strength may influence the fracture risk, including bone microarchitecture, which recently can be measured by trabecular bone score (TBS). The complex associations between TBS and BMI remain unclear, and some studies show inconsistent findings. This systematic review and meta-analysis aimed to understand whether increased BMI is associated with lower TBS by indirectly pooling all the available evidence from the published literature.

Methods: A literature search was carried out using PubMed, Cochrane Library, Google Scholar and other popular journal databases using the terms "trabecular bone score", "body mass index" and the possible synonyms. We extracted the total sample, mean and standard deviation of TBS for patients within each BMI category from the selected literature. A meta-analysis was conducted using a random-effects model and inverse variant methods to synthesize the pooled effect size (mean difference) for each gender subgroup.

Results: After an initial search and screening of 2399 studies, seven reports published between 2016-2019 were included (five cross-sectional, one cohort, and one randomized clinical trial). These include 2872 samples which were mostly women (2286). One thousand thirty-one samples were with normal BMI, 1124 samples were with overweight BMI, and 717 samples were with obesity. The included studies varied by age group and gender. The between-study heterogeneity with I^2 index ranging 0%-76% studies in man showed higher heterogeneity. Compared with normal individuals, those with overweight and obesity had lower TBS with a mean difference of -0.02 (95% CI -0.03 to -0.01) and -0.07 (95% CI, -0.09 to -0.05), respectively. The differences were consistent across gender, although larger differences were found in men.

Conclusion: Individuals with higher BMI have a lower TBS than individuals with normal BMI in a stepwise manner. It suggests that the inclusion of TBS can improve the assessment of fracture risk in obese individuals.

Keywords: Trabecular bone score, Obesity, Body mass index.
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INTRODUCTION

Bone is a living tissue with various metabolic functions. The size and shape of bones change over a lifetime to ensure skeletal structure integrity. During bone remodeling, there is a coordination between bone cells such as osteocytes, osteoblasts (bone-forming cells), osteoclasts (bone-degrading cells), in maintaining the dynamic coupling of bone metabolism. However, many metabolic conditions disturb the equilibrium, including osteoporosis, systemic inflammation, bone tumor, and inflammatory arthritis. Overweight and obesity are identified as abnormal or excessive fat accumulation, leading to health impairment. Obesity and other metabolic diseases could also inflict a low-grade inflammation.[1,2] Body mass index (BMI) is a ratio of height to weight used to distinguish between normal, overweight, or obese adults. The WHO defines overweight as having a BMI of 25 – 30 kg/m^2 and obesity as a BMI of > 30 kg/m^2.[3] Bodyweight is a well-known environmental determinant of the overall bone condition, especially at the age of peak bone mass.[4,5]

According to numerous clinical studies, body weight correlates positively with bone mineral density (BMD). It correlates negatively with fracture risk, as BMI is positively associated with BMD assessed by dual X-ray absorptiometry (DXA). However, recent data show an increase in falls and a higher risk of some fractures with obesity.[6,7] In the U.S, according to BMD criteria, there are 53.6 million Americans who are at risk for fracture, including 10.2 million adults with osteoporosis and 43.4 million adults

with osteopenia and low bone mass. Since more than half of fragility fractures occur in individuals who have low bone mass but are not osteoporosis by DXA, other factors must influence bone strength and fracture risk.[6] Several other factors influenced bone strength, including bone geometry, cortical porosity, and bone microarchitecture. Among the three, bone microarchitecture may get less attention as it is difficult to quantify. A relatively recent measure, the trabecular bone score (TBS), has gained some interest in this regard.[8]

The trabecular bone score is a texture parameter inferred from recording gray pixel variations in DXA images. Higher scores mean stronger microarchitecture, more resilient to fracture and vice versa.[9] Several studies have shown that TBS predicts osteoporotic fractures independently of BMD, and it has been included in the Fracture Risk Assessment Tool (FRAX).[10] Some human studies have shown a negative correlation between BMI and TBS, whereas a positive association between BMI and BMD has been established.[11] The complex associations between TBS and BMI remain unclear, and some studies show inconsistent findings. Therefore, we performed this study to evaluate the correlation between BMI and TBS in adults.

METHODS

Search strategy and study inclusion

An electronic search of the literature was carried out using PubMed, Cochrane Library, EuropePMC, Google Scholar, Lens.org, Dimensions (1990 until June 2021) to identify studies relating to trabecular bone score and body mass index. The initial keywords used for the search included "trabecular bone score", "TBS", "Bone Microarchitecture", "Obesity", "Overweight", "BMI" and "Body Mass Index". In addition, we manually searched review articles and checked reference lists of original articles to identify studies that might have been missed from the electronic search. The inclusion criteria were (a) original studies published in English, reporting data on the trabecular bone score and body mass index; (b) observational studies; (c) using TBS Insight™ software on lumbar spine dual-energy X-ray absorptiometry scan technology; and (d) human studies on individuals aged 20+ years. We excluded case-control and case series or case reports, studies on children and adolescents, and animal studies. The meta-analysis was conducted and reported based on Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[12]

Two reviewers (KK and KAW) independently identified suitable articles according to the above criteria. The opinion disparity regarding whether the studies should be included or not was resolved by discussion and input from the third reviewers.

Data extraction and synthesis

Data extraction was done independently by two reviewers. We extracted data relating to study characteristics, specifically authors, journal, year of publication, study design, age group, gender, number of participants, and trabecular bone score in each BMI category. BMI category include normal (18.5 - 24.9 kg/m^2), overweight (25 - 29.9 kg/m^2) and obese (≥ 30 kg/m^2). If more than one paper with the same data or results from a similar study were identified, only the one that accommodated the original and definitive data was included.

This study utilized the mean difference (MD) as the primary effect measure. TBS was measured from an L1-L4 DXA image using specialized software and was quantified by similar methods on a similar scale. As for the meta-analysis, a random effect model was utilized to find the pooled mean difference across two groups (obese vs normal, obese vs overweight and overweight vs normal).

Not all studies directly present the TBS for each BMI group. The first attempt was to contact the corresponding author to provide the data for us kindly. The second measure was to calculate from the available data in published papers. If the studies provide the mean and confidence interval (CI), we convert the CI to standard deviation (SD) through standard error using methods provided by the Cochrane handbook. If the study provides data based on various groups of age or split data for a BMI group, we conducted a basic statistical calculation to combine mean and SD as outlined in the Cochrane handbook.[13]

Data preparation and analysis were conducted in R v4.1.1 and Rstudio v.14 on Ubuntu Linux Server (v21.04).[14,15] Meta-analysis specific calculation using the inverse variant method and forest and funnel plot generation conducted with Meta package.[16] PRISMA 2020 chart created with PRISMA2020 package.[17]

RESULTS

Characteristics of studies

A preliminary search returned 2399 articles written in English about TBS and body mass index. However, after eliminating duplicates and articles that did not fulfill the inclusion criteria, we found seven suitable studies published between 2015 and 2019.[6,8,9,18–21] The PRISMA flow diagram during study selection is presented in Figure 1. The studies included five cross-sectional studies, a clinical trial, and a cohort study. These seven studies involved a total of 2872 samples. Studies

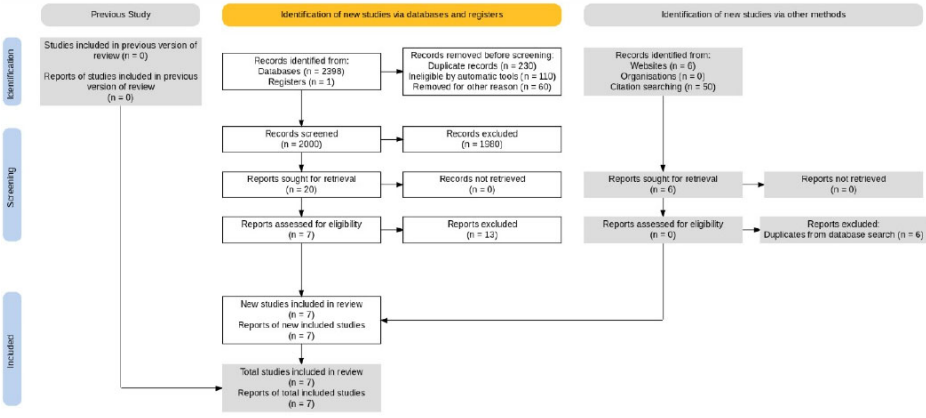

Figure 1. PRISMA flow diagrams summarizing the literature search from various sources.

Table 1. The summary of included studies.

Author (year)	Study Design	Gender	Age*	Normal		Overweight		Obese	
				N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Romagnoly (2016)	Cross-sectional	Man	53.42 ± 11.89 (25–76)			22	1.310 (0.100)	30**	1.250 (0.120)*
								35***	1.160 (0.140)**
Ayoub (2016)	Cross-sectional	Man		23	1.401 (0.084)	32	1.348 (0.080)	12	1.367 (0.112)
Berro (2018)	Cross-sectional	Women	(18 - 32)	42	1.430 (0.080)	14	1.380 (0.120)		
Goldman (2018)	Randomized Clinical Trial	Man	63.5 ± 6.0 (50 - 84)	74	1.390 (0.129)	206	1.350 (0.150)	88	1.280 (0.123)
		Woman		113	1.310 (0.193)	104	1.280 (0.185)	83	1.240 (0.150)
Messina (2019)	Cross-sectional	Woman	66 ± 10	30	1.328 (0.085)	30	1.300 (0.081)	30	1.259 (0.077)
Rajaei (2019)	Cross-sectional	General	57.26 ± 14.06 (20 - 90)	170	1.350 (0.110)	203	1.310 (0.120)	169	1.270 (0.118)
Shevroja (2019)****	Cohort	Woman	64.4 ± 7.5	579	1.350 (0.090)	513	1.330 (0.100)	270	1.290 (0.110)

*Mean ± SD or (Range) or both
**30-34.9 kg/m^2
***≥ 35 kg/m^2
****TBS iNsight version 3.03

were mostly in women (2286) than men (586). Samples from individual studies vary widely (min-max) with median X. Most of the studies were conducted in the European population. X studies involved women only, Y studies involved men only, and Z involved both men and women. Among the studies, only X studies include data on all the BMI categories (normal, overweight and obese). X studies only compare normal and overweight-obese categories and y studies compared normal and obese. The study summary was presented in Table 1.

We also analyzed the possibility of publication bias and small study influence, as we utilized the random effect model. The funnel plot of the included study was shown in Figure 2. The standard error over mean difference showed that studies with higher power and lower power were all distributed equally on each side of the mean difference.

Association of BMI and TBS

Five studies included data regarding the TBS score among subjects with Obese and normal BMI. Overall random effects model showed a lower TBS score among obese subject by 0,07 (95% CI 0,05 - 0,09) points. The effects were consistent across studies, except in Ayoub et al (2017) studies. The overall heterogeneity was moderate (I^2 = 37%, p = 0,17). The effects were slightly larger in men than women, although the calculation involved a lower number of overall subjects and higher subgroup heterogeneity, thus resulting in a larger confidence interval (Figure 3).

Overall random-effects model of data from six studies showed a lower TBS score among obese subject by 0,05 (95% CI 0,03 - 0,07) points compared to the overweight. The effects were less consistent across studies as data from three studies. The overall heterogeneity was borderline high (I^2 = 55%, p = 0,05). The effect was slightly larger in men than women, although subgroup analysis showed non-significant effects and heterogenous results in men. Subgroup analysis in women showed consistent and homogenous results (Figure 4).

The random-effects model comparing overweight and normal BMI subjects showed relatively homogenous results.

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The effects were consistent across six studies. The effect was twice larger and more consistent in men than women. Subgroup analysis in women showed less consistent results. Due to the significantly larger sample size from Shevroja et al,, the subgroup random effects model showed significant results (Figure 5).

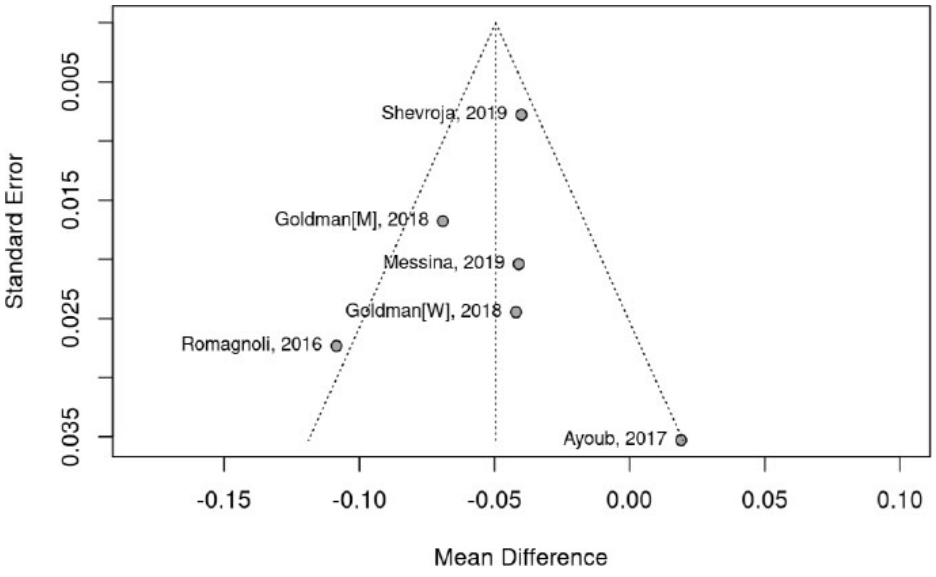

Figure 2. Funnel plot of the included studies.

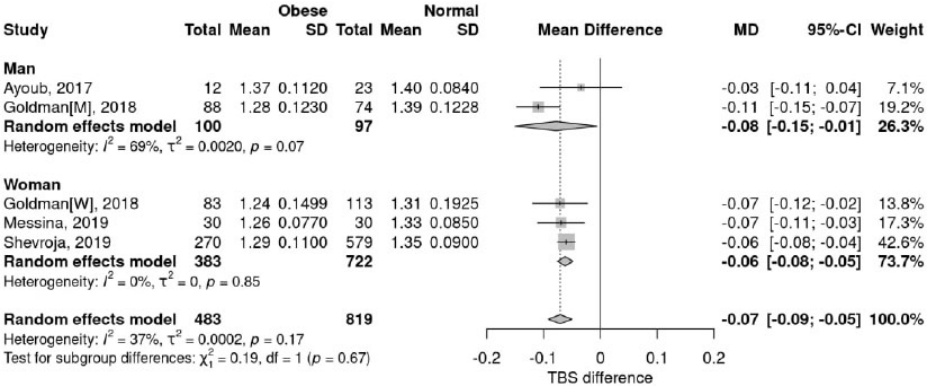

Figure 3. Forest plot summarizing the comparison of TBS between obese and normal BMI subject.

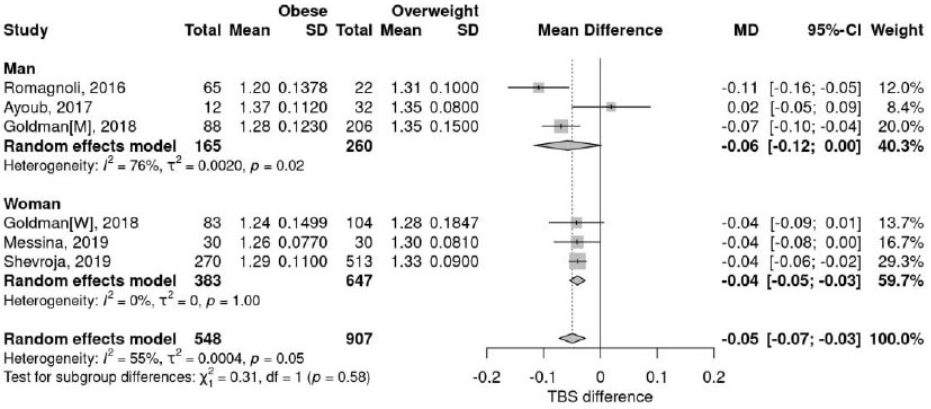

Figure 4. Forest plot summarizing the comparison of TBS between obese and overweight subject.

DISCUSSION

This study summarized the relationship between BMI and TBS. Overall, Obese patients had lower TBS than overweight and normal BMI patients. Similarly, overweight showed lower TBS than Normal BMI patients. The difference in TBS between each group was slightly larger in men than women, although it was not statistically significant. Men have shown a larger I index than women regarding the study heterogeneity, despite fewer studies included. The result of three comparisons showed consistency of decreased TBS in obese and overweight compared to normal BMI patients.

Before the TBS, BMD was considered the only main parameter of bone strength.[22] BMD itself has performed well in predicting a bone tendency to fracture in many clinical situations. It is not a perfect predictor, and thus there are caveats. For some clinical conditions, such as diabetes and obesity, BMD fails to perform as expected for fracture risk estimators.[23,24] It even showed a positive correlation with BMI, although higher BMI is associated with higher fracture risk. Researchers had turned to find another possible parameter of bone strength beyond mineral density, the microarchitecture. It is clearly difficult to quantify how good or bad a bone microarchitecture is. Recent attempts have invented the Trabecular Bone Score. A previous study showed that TBS has better properties in predicting fracture risk. It has been incorporated into the FRAX scoring systems and approved by the US FDA. This study was to answer part of the contested BMD vs TBS in various BMI, as we assume that BMI had correlated with fracture risk.

The measurement of BMD has been shown as inadequate for assessing fracture risk in patients with metabolic conditions such as obesity. TBS may be able to predict the risk of fracture in people with obesity. Each decrease of standard deviation in TBS is associated with a 1.4 times increase in fracture risk.[25,26] Our findings showed that obesity had about 0.07 lower TBS value, equal to 0,63 SD lower than individuals with normal BMI. The results were higher

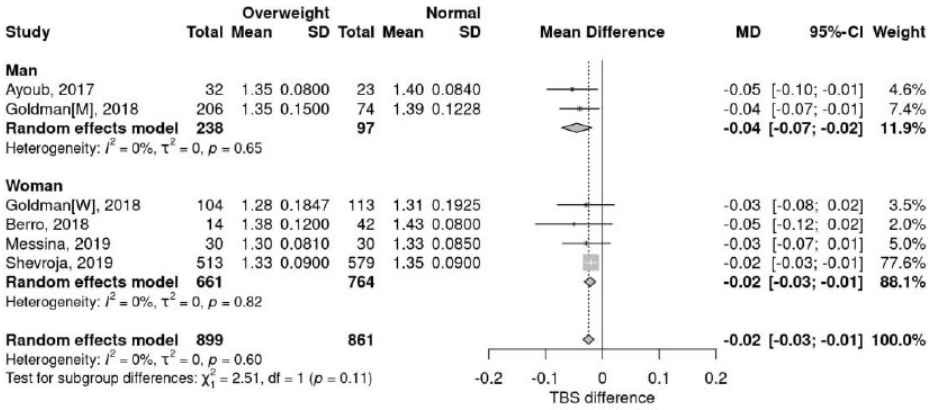

Figure 5. Forest plot summarizing the comparison of TBS between overweight and normal BMI Subjects.

than the impact of diabetes as it showed 0,31 SD lower than normal or equal to an 11% increased risk of vertebral fracture. This finding showed that our estimate fell between 11% to 40% increased the risk of vertebral fracture. Additionally, the increased difference in TBS was seen higher among obese than overweight compared to overweight than normal. This translates to a significant jump in estimated fracture risk when an individual has passed into the obesity group.

Obesity impacts negatively on optimal bone metabolism via various physiologic processes. Obesity may promote adipocyte differentiation and fat accumulation while lowering osteoblast differentiation and bone production because both adipocytes and osteoblasts are generated from multipotential mesenchymal stem cells.[27] Obesity has been associated with a period of prolonged low-grade inflammation. An increase in the rate of circulating and tissue proinflammatory cytokines is predicted to stimulate osteoclast activity and bone resorption by altering the receptor activator of the NF-κB (RANK)/RANK ligand/osteoprotegerin pathway.[28-30] Furthermore, with obesity, adipocytes' excessive secretion of leptin and/or decreased adiponectin synthesis may directly or indirectly impact bone formation through up-regulated pro-inflammatory cytokine production.[31–33] Finally, a high fat diet may interfere with intestinal calcium absorption, resulting in a reduction in calcium availability for bone production.[34–36]

Overall, this study showed that higher BMI had lower TBS, resulting in poorer bone microarchitecture quality. As far as we know, this metanalysis is the first to assess this relation. This study had some limitations. Due to limited funding, we could not access a wider range of paid databases, thus we might not pick up all the suitable studies. This study also only assessed the mean difference of TBS among BMI groups, thus it only drew an indirect conclusion regarding its relation with fracture risk. Nevertheless, this study could be the starting point for further investigation.

CONCLUSION

Individuals with increased BMI had lower TBS than those with normal BMI stepwise. It suggests that the inclusion of TBS can improve the assessment of fracture risk in obese individuals.

FUNDING

This study did not receive any third-party funding or support.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest.

AUTHOR CONTRIBUTION

KK, KAW, IMBS and SDTR contributed to the concept and design of the study. KK and KAW conducted the literature search and preliminary screening independently, IMBS resolved any differences. KK and KAW conducted the analysis and wrote the initial version of the manuscript. IMBS and SDTR provided corrections and advice. All authors had agreed on the final version for publication.

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