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Predictors of Change of Trabecular Bone Score (TBS) in Older Men: results from the Osteoporotic Fractures in Men (MrOS) Study

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Abstract

Summary—Among older men, characteristics that predict longitudinal changes in Trabecular Bone Score (TBS) are different from characteristics that predict changes in bone mineral density (BMD). Most notably, weight loss is strongly associated with concomitant loss in BMD but with concomitant increases in TBS, when measured on Hologic densitometers.

Introduction—Our objective was to compare and contrast predictors of changes in Trabecular Bone Score (TBS), total hip BMD, and lumbar spine BMD.

Methods—Our study population was 3,969 Osteoporotic Fractures in Men (MrOS) cohort participants (mean age 72.8 years) with repeat measures of TBS, lumbar spine and total hip BMD; body mass index (BMI) less than 37 kg/m^2; and no use of bisphosphonate or glucocorticoid medications. TBS was scored (Med-Imaps Software version 2.1) and BMD measured on Hologic densitometers.

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Conflicts of Interest Disclosure

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Results—1444 men had a TBS decrease > 0.04 units (estimated least significant change for TBS), 795 men had a TBS increase > 0.04 units, and 1730 men had TBS change ≤ 0.04 units over mean follow-up of 4.6 years. Older age was not associated with TBS change, but was associated with greater decline in lumbar spine and total hip BMD. Compared to stable weight, >10% weight loss was strongly associated with an increase in TBS [effect size =1.24 (95% CI: 1.12, 1.36), and strongly associated with a *decrease in* total hip BMD [−1.16 (95% CI: −1.19, −1.03). Other predictors discordant for longitudinal changes of TBS and BMD included baseline BMI, walk speed, and ACE inhibitor use.

Conclusions—Predictors of changes in TBS are different from predictors of changes in lumbar spine and total hip BMD. At least when assessed on Hologic densitometers, weight loss is associated with subsequent declines in spine and total hip BMD but subsequent increase in TBS. Faster walk speed may protect against loss of hip BMD, but is not associated with longitudinal changes of TBS.

Keywords

Trabecular Bone Score; TBS; Bone Mineral Density; BMD; longitudinal change; weight loss

Introduction

Trabecular Bone Score (TBS) is a grey scale textural analysis of pixel-by-pixel differences in bone mineral density on AP spine DXA scans that is postulated to reflect the microarchitecture (specifically distribution and connectivity) of trabecular bone.[1, 2] Prospective studies in MrOS[3] and other cohorts[4, 5] have shown that TBS is associated with incident major osteoporotic and hip fractures, and in some cohorts with incident vertebral fractures.[6, 7] Hence there is interest in what individual characteristics are associated with TBS and subsequent changes in TBS over time.

Two prospective studies have estimated the annualized rate of change in TBS among older women in the absence of pharmacologic fracture prevention therapy to be −0.31%[8] and −0.16%[9] per year, respectively. In the Manitoba Bone Densitometry Database, the TBS annual rate of change (−0.31%) was similar to annualized changes in lumbar spine bone mineral density (BMD, −0.36%).[8] However, no study published to date has determined patient characteristics that predict change of TBS over time.

In contrast, several studies have identified predictors of changes in total hip and lumbar spine bone mineral density (BMD). The rate of hip bone loss has been shown in older men to be associated with weight loss,[10, 11] stressful life events,[12] Parkinson’s disease,[13] self-reported use of angiotensin converting enzyme (ACE) inhibitor therapy,[14] renal insufficiency,[15] and sex hormone deficiency alone[16]or combined with low vitamin D levels.[17, 18] Lumbar spine BMD tends to increase over time in older men, probably because of progression of degenerative disc disease and facet joint arthritis. Nonetheless, a prior study found that the same predictors of bone loss at the total hip were associated with lower rates of increase in lumbar spine BMD in older men.[19]

Whether or not any of these characteristics also predict changes in TBS over time is unknown. Our objective was to identify individual characteristics that predict longitudinal change in TBS in older men, and compare and contrast predictors of change in TBS, total hip BMD, and lumbar spine BMD.

Methods

From 2000 to 2002, 5994 community-dwelling men ≥65 years old were enrolled into the prospective MrOS study in six regions of the United States, described in previous publications.[20, 21] The study population for these analyses of longitudinal TBS change included 3,969 men who attended both the first and second MrOS study visits; had valid measures of TBS, lumbar spine BMD, and total hip BMD; had body mass index (BMI) less than 37 kg/m^2; and did not self-report use of bisphosphonate or glucocorticoid medications at either visit (figure 1). Men with BMI ≥ 37 kg/m^2 at either visit were excluded because TBS is not considered to be valid above this threshold.[22]

Measurement of TBS and BMD

TBS was scored on AP spine DXA scans obtained at the first and second MrOS visits using Med-Imaps Software (version 2.1) for the lumbar vertebrae L1 to L4 that had not been excluded in the AP spine BMD measurement. Participant weight and height are taken into account in this version of the TBS scoring algorithm. BMD was measured at the femoral neck and lumbar spine with QDR-4500 fan-beam densitometers (Hologic, Bedford, MA, USA), at the baseline and visit 2 MrOS visit. Central training of densitometry technologists and cross-calibration of densitometers across study centers with both BMD and TBS phantoms was done to ensure consistency and quality of bone mass measurement.[23]

Ascertainment of Predictor Covariates

Candidate predictor variables were those that in other studies have been shown to be significantly associated with TBS in cross-sectional studies[6, 24] or to predict changes in BMD at the lumbar spine[19] or total hip[25]. At both MrOS visits 1 and 2, participants' height was measured with a Harpenden stadiometer, weight recorded with a balance beam or electronic scale, and BMI calculated as weight (kg) divided by height squared (m^2) Weight change was categorized as ≥ 5% increase of body weight, no change (<5%) of body weight, ≥ 5% and <10% decrease of body weight, and ≥ 10% decrease of body weight. At the first MrOS visit, participants self-reported any prior fractures they experienced after age 50, whether or not either parent had a hip fracture, whether they were current smokers, and whether they were currently using systemic glucocorticoid or bisphosphonate medication. Self-reported physical activity was assessed with the Physical Activity Scale for Elderly (PASE) questionnaire.[26] Concurrent stressful life events were captured by mailed survey between MrOS visits 1 and 2.[12] Walk speed (meters per second) at usual pace was measured over a 6 meter distance and averaged. The ability and time to complete 5 chair stands was also assessed at the first visit.[27]

Statistical Analysis

We initially expressed change in TBS in three categories; increased TBS (increase > 0.04 units), decreased TBS (decrease >0.04 units), or no change in TBS (change in either direction ≤ 0.04 units). The cutpoint of 0.04 units was chosen as a reasonable approximation of the least significant change, based on prior studies of the test-retest reliability of TBS on Hologic densitometers[7, 28, 29]. Differences in continuous variables across the three TBS categories were tested with one-way analysis of variance for normally distributed variables and with the Kruskal-Wallis test for variables with a non-normal distribution. For categorical predictor variables, chi-square statistics were used to test significance of differences of predictor category frequencies across TBS change levels.

Since changes in TBS, lumbar spine BMD, and total hip BMD were all normally distributed, we used linear regression models to estimate the multivariable-adjusted associations of predictor variables with each dependent variable. Initial predictors in the models were those with an unadjusted p-value of association <0.1 with either TBS change, lumbar spine BMD change, or total hip BMD change. The variables in the final models for the comparison of predictors of TBS change versus those of lumbar spine (total hip) BMD change were those with a multivariable adjusted p-value of association of <0.1 with either TBS or lumbar spine (total hip) BMD change. Parameter coefficients were expressed as per standard deviation change in TBS or BMD change so that the strength of associations for TBS change and BMD change would be directly comparable. Models were tested for heteroscedasticity, for omitted variable bias with the Ramsey Powers test, and for model mis-specification with Pregibon's link test.[30] The null hypotheses that the standardized effect size of the association of predictor variables with TBS change were the same as those of the association with BMD change was tested with a modified Hausmann test, using the *suest* command of Stata (version 14.0, College Station, TX).[31] Because we compared parameter coefficients across two different sets of regression models, we considered p-values of <0.025 for the Hausman tests to be significant.

Three sets of secondary analysis were done. First, we examined whether or not the associations of weight changes with longitudinal changes of TBS and total hip BMD were modified by baseline BMI, by estimating these associations by BMI subgroup (normal BMI [18.5 to 24.9 kg/m^2], overweight BMI [25.0 to 29.9 kg/m^2], and obese BMI [≥ 30 kg/m^2]). Second, we repeated the primary analyses substituting changes of android mass, a whole body DXA direct measure of abdominal soft tissue mass through which x-rays need to penetrate to reach the lumbar spine, for changes in body weight. The inferior boundary of the android region of interest was a line across the lower abdomen between the right and left iliac crests, and the superior boundary was a horizontal line 20% of the distance between the inferior boundary and the chin. Third, we also examined whether or not the association of body weight changes with longitudinal TBS changes was altered by further adjusting for baseline TBS.

Results

Over the mean follow-up time of 4.6 years (SD 0.4 years), the mean (SD) change of TBS was −0.02 (0.08), or −0.25% (1.4%) per year. One thousand four hundred forty four (1444,

36%) men had a decrease of TBS > 0.04 units, 795 (20%) men had an increase of TBS >0.04 units, and 1730 (44%) men had a change of TBS ≤ 0.04 units (Table 1). Men whose TBS decreased between visits were slightly younger and were more likely to have gained weight between visits 1 and 2. In contrast, men whose TBS increased were slightly older, were more likely to have a body mass index ≥ 30 kg/m^2, walked slower, had slightly fewer chair stands per second, and were more likely to have lost weight between visits 1 and 2. Baseline TBS was higher in men who subsequently had a decrease of TBS, and was lower in men who subsequently had an increase of TBS. Longitudinal change in TBS was positively associated with longitudinal change of lumbar spine BMD, but negatively with longitudinal change of total hip BMD (Table 1).

In multivariable adjusted models, the association of a given predictor with change in TBS differed from the associations of this predictor with changes in lumbar spine and total hip BMD. Most striking, weight loss between visits 1 and 2 was strongly associated with *increases* in TBS with a large effect size (Tables 2 and 3), whereas, weight loss was weakly associated with a decline in lumbar spine BMD (Table 2), and strongly associated with a *decrease* in total hip BMD (table 3). In contrast, obesity at the first visit was weakly associated with a subsequent increase in TBS and more strongly associated with an increase in lumbar spine BMD (p-value for difference in strength of association with TBS change vs spine BMD change <0.001), whereas there was no association of baseline weight with subsequent change in total hip BMD.

Older age was associated with greater loss in total hip and spine BMD over the follow-up period, but was not associated with change in TBS. Faster walk speed at the first visit was weakly associated with an increase in total hip BMD, but not with change in TBS (p-value=0.001 for difference in association with hip BMD change vs TBS change, table 3) nor with changes in lumbar spine BMD. In contrast, self-reported physical activity at the first visit was not associated with change in TBS or change in BMD at either the lumbar spine or total hip. Self-reported use of an ACE inhibitor at the first visit was also moderately associated with subsequent loss of total hip BMD, but not with change in TBS (p-value<0.001 for difference in association with total hip BMD change vs. TBS change, table 3) nor with change in lumbar spine BMD.

No significant differences were noted in the strength of associations of chair stand speed, smoking status, or prevalent radiographic vertebral fracture with TBS change vs lumbar spine BMD change, or with TBS change vs total hip BMD change.

Within all subsets of BMI, body weight change was negatively associated with longitudinal TBS change, but this association became substantially stronger with higher levels of BMI category (table 4). In contrast, the strong positive association of weight change with longitudinal change of total hip BMD was not significantly different across baseline BMI categories (table 5). Changes of android mass were also negatively associated with longitudinal changes of TBS and positively with longitudinal changes of total hip BMD, albeit not as strongly as were changes of body weight (table 6). Adding baseline TBS as a predictor did not change the association of body weight changes with longitudinal changes of TBS (data not shown).

Discussion

Among community-dwelling older men, our results suggest that the set of characteristics that are associated with longitudinal changes in TBS are different from the set of characteristics associated with longitudinal changes in lumbar spine or total hip BMD, when TBS and BMD are measured using Hologic densitometers. Most strikingly, weight loss is associated with concurrent decline in BMD (particularly at the total hip), but is strongly associated with an increase in TBS. Moreover, the negative association of weight change with longitudinal TBS change is most pronounced among individuals with higher baseline BMI. Prior cross-sectional studies have noted that BMI and TBS are negatively correlated, and the present study confirms that this negative correlation extends to longitudinal change. The rate of change of TBS in these older men (−0.25% per year) was similar to the yearly rate of TBS longitudinal change (−0.31% and −0.16%) previously reported among older postmenopausal women.[8, 9]

These TBS findings may be artefactual and not attributable to actual changes in bone properties, since the negative associations are discordant with the BMD findings. DXA superimposes overlying soft tissue (as well as posterior vertebral elements) onto a 2-dimensional projection of the lumbar vertebral bodies. Higher BMI is correlated with greater trunk fat and lean mass, and this increased soft tissue may introduce additional noise into the TBS measurement, and this increased measurement noise has been shown to bias TBS measurements downward.[32]

After the inverse association of BMI with TBS was originally reported in 2013,[33] revisions were made to the Med-Imaps software, adjusting TBS values for weight and height in order to remove this apparent downward bias. However, a recent report from the Canadian Multicenter Osteoporosis Study (CaMos) showed that while there was no association between TBS (measured with a later version [Med-Imaps version 2.1]) and BMI at study centers that used GE-Lunar densitometers, an inverse association between TBS and BMI persisted at study centers that used Hologic densitometers.[34] Similarly, in the National Health and Nutrition Examination Survey (NHANES) study, TBS measured on Hologic densitometers with Med-Imaps version 2.1 also is negatively correlated with body weight and other body size variables such as trunk fat and lean mass, waist circumference, and total body fat mass.[35] Hence, the association between TBS change and weight change may be specific to the version of TBS that is used and the type of densitometer on which it is installed.

Our findings extend those prior studies by showing that clinicians need to compare current with prior TBS values only in conjunction with changes (if any) of body weight. These findings are also relevant because of prior and ongoing studies investigating changes in TBS with medication therapies for fracture prevention that are testing the hypothesis that improvement of TBS with drug treatment may represent improvements of trabecular microarchitecture.[36] Results of previous studies examining TBS change with pharmacotherapy have reported smaller changes in TBS than with BMD. Changes in TBS thus far have appeared to be significant only with use of agents that also have a marked effect on bone mass, such as denosumab [36, 37] and teriparatide [29, 36, 38]. However,

investigations of longitudinal changes of TBS with drug treatment for fracture prevention may be biased if effects of weight change on TBS are not considered. In the FREEDOM, and FIT randomized clinical trials, therapy with denosumab and alendronate, respectively, were associated with small weight gain compared to placebo.[39] Even if the *mean* weight change of treated subjects does not differ from that in the placebo group, change in weight among individual participants will create additional variation and artefactual noise in the measurements of TBS change. This could bias estimates of the effect of drug treatment on TBS change toward the null. This bias will be magnified in populations with higher BMI. Clearly, further adjustments to the TBS software to ensure that TBS values are consistent across the spectrum of BMI would be very helpful for clinicians and clinical researchers. Finally, our findings reinforce that pooling TBS values from densitometers made by different manufacturers should not be done.

There were other characteristics that had different associations with TBS change vs BMD change that are worthy of mention. While older age is associated with faster rates of hip BMD loss, the rate of longitudinal change of TBS is not associated with age. A faster baseline walk speed was associated with a gain in total hip BMD over the subsequent 4.6 year follow-up period, even after adjustment for baseline BMI and concomitant changes of body weight. In contrast, walk speed was not associated with subsequent changes in TBS or lumbar spine BMD. To our knowledge, the association of walk speed with subsequent changes in hip BMD has not been reported previously. The reason(s) for this finding are not clear. Higher walk speed may be associated increased loads on the total hip as well as with maintenance of muscle mass and physical activity levels, and therefore maintenance of bone mass (especially cortical bone).

Obesity was also moderately associated with subsequent gains in lumbar spine BMD, but only weakly associated with subsequent increases in TBS. Lumbar spine BMD increases with increasing age in older men,[19] and this has been attributed to progression of lumbar spine osteoarthritis,[40, 41] which in turn may be related to obesity.[42] In contrast, TBS values are not affected by lumbar spine osteoarthritis.[40, 41] However, the association of weight gain with lumbar spine BMD loss (table 2) is inconsistent with this hypothesis, and additional studies are required to further test this theory.

As reported previously in the MrOS population,[14] baseline self-reported use of ACE inhibitor medication was associated with subsequent decline in total hip BMD, but was not associated with change in TBS. The reason(s) for these findings remain unclear.

The primary strength of our study is that it is the largest single study of TBS in older men in existence. However, this study has important limitations. Most importantly, this study is only applicable to TBS measurement obtained with Hologic bone densitometers and not to others such as those manufactured by GE-Lunar or Norland. Our findings may not be applicable to women or those younger than 65 years. While 10% of the MrOS study population at the baseline visit was non-white, our findings may not be generalizable to non-white populations. Our estimate of TBS least significant change (0.04 units) was derived from other studies, and not from the MrOS study population.

In conclusion, predictors of change in TBS are different from predictors of changes in lumbar spine and total hip BMD. Most notably weight loss is associated with subsequent loss in spine and total hip areal BMD, but subsequent gain in TBS when TBS and BMD are measured using Hologic densitometers. Future cohort studies and randomized trials evaluating the effects of pharmacologic fracture prevention therapies on TBS need to consider the effect of change in body weight over the treatment period, particularly if TBS is measured using a Hologic densitometer.

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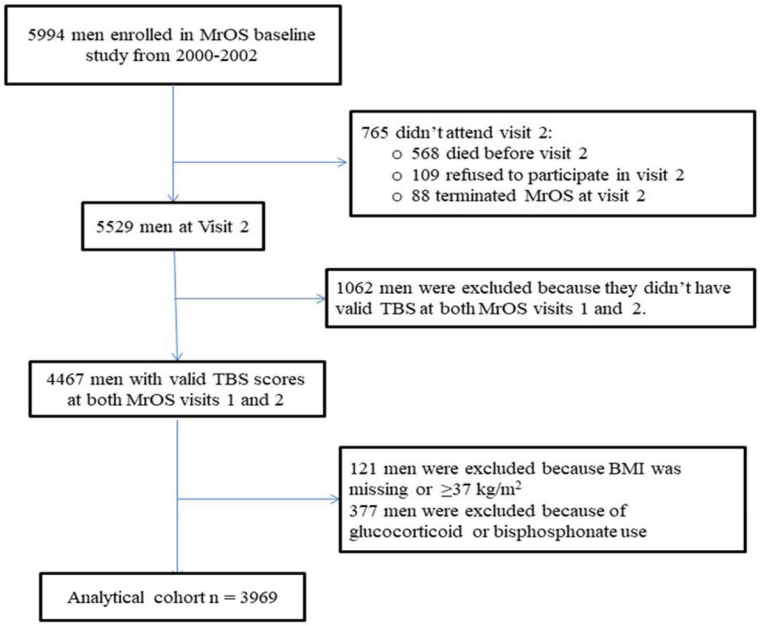

Figure 1.
Flow Diagram of Men Included in Analysis Cohort

Table 1

Characteristics of Patients according to TBS Change Category (N=3969)

Predictor	Decrease TBS (>0.04) Range: (−0.42 : −0.04) N=1444	No Change of TBS Range: (−0.04 : 0.04) N=1730	Increase of TBS (>0.04) Range: (0.04:0.42) N=795	P-value for difference
Age (mean, sd)	72.4(5.3)	73.0(5.5)	73.3(5.3)	<0.001
Baseline TBS (mean,sd)	1.28(0.11)	1.25(0.11)	1.17(0.12)	<0.001
Total hip BMD (mean, sd)	0.97(0.13)	0.97(0.13)	0.98(0.13)	0.14
Change in total hip BMD (mean, sd)	−0.013(0.036)	−0.016(0.034)	−0.025(0.040)	<0.001
Lumbar Spine BMD (mean,sd)	1.08(0.18)	1.08(0.18)	1.09(0.19)	0.62
Change in LS BMD, (mean, sd)	0.017(0.051)	0.029(0.049)	0.046(0.057)	<0.001
Body Mass Index category				
< 25 kg/m^2	410(28.4%)	538(31.1%)	113(14.2%)	<0.001
25–29.9 kg/m^2	753(52.1%)	949(54.9%)	420(52.8%)	
≥ 30 kg/m^2	281(19.5%)	243(14.0%)	262(33.0%)	
Self-reported Prior Clinical Fracture, %	215(14.9%)	272(15.7%)	131(16.5%)	0.59
Prevalent Radiographic Vertebral Fracture %	76(5.3%)	102(5.9%)	59(7.5%)	0.11
Parental History of Hip Fracture %	192(13.3%)	229(13.2%)	93(11.7%)	0.50
Smoking status				0.12
Never	579(40.1%)	704(40.7%)	281(35.3%)	
Past	821(56.9%)	973(56.2%)	491(61.8%)	
Current	43(3.0%)	53(3.1%)	23(2.9%)	
Use of ACE Inhibitor therapy %	251(18.3%)	282(17.0%)	154(20.0%)	0.19
PASE Score	154.8(68.0)	155.3(66.3)	145.3(64.4)	0.001
Walk Speed (mean, sd)	1.25(0.21)	1.24(0.20)	1.19(0.22)	<0.001
Number of stands per second	0.50(0.13)	0.50(0.13)	0.49(0.13)	0.03
One or More Stressful Life Events %	1065(73.8%)	1261(74.0%)	609(76.6%)	0.29
Change in Weight V2 minus V1				<0.001
No change	1073(74.3%)	1271(74.6%)	376(47.3%)	
≥ 5% increase	263(18.2%)	73(4.2%)	13(1.6%)	
≥ 5 to < 10% decrease	89(6.2%)	293(16.9%)	263(33.1%)	
≥ 10% decrease	19(1.3%)	73(4.2%)	143(18.0%)	

Table 2

Comparison of Multivariable Adjusted Associations (95% C.I.) of Predictors with Changes of TBS vs. Changes of Lumbar Spine BMD*^

Predictors	TBS Change** Effect Size (95% C.I.)	Lumbar Spine BMD Change** Effect Size (95% C.I.)	P-Value for Difference
Age (per 5 year increase)	0.00(−0.03 : 0.03)	−0.06(−0.09: −0.02)	0.002
Body Mass Index category			
< 25 kg/m^2	Reference	Reference	
25 to 29.9 kg/m^2	0.04 (−0.02: 0.11)	0.20 (0.13: 0.28)	0.001
≥ 30 kg/m^2	0.10 (0.02: 0.19)	0.43 (0.33: 0.52)	<0.001
Change in Weight V2 minus V1 category			
No change	Reference	Reference	
≥ 5% increase	−0.82(−0.92: −0.72)	−0.19 (−0.30: −0.08)	<0.001
≥ 5 to < 10% decrease	0.66 (0.59:0.74)	0.07 (−0.02: 0.16)	<0.001
≥ 10% decrease	1.22 (1.11: 1.34)	−0.17 (−0.30: −0.03)	<0.001
Prevalent Radiographic Vertebral Fracture (yes vs. no)	0.12 (0.00: 0.23)	−0.05 (−0.18: 0.08)	0.04
PASE Score (per SD increase, SD=66.6)	−0.03 (−0.06: 0.00)	−0.02 (−0.04: 0.02)	0.38
Walk Speed (per SD increase, SD=0.21m/s)	−0.02 (−0.05: 0.01)	0.02 (−0.02: 0.05)	0.15
Chair Stand Speed (per SD increase, SD=0.13stands/second)	0.04 (0.01: 0.07)	0.02 (−0.02: 0.05)	0.30
Smoking Status			
Never	Reference	Reference	
Former	−0.00 (−0.06: 0.05)	0.00 (−0.06: 0.07)	0.87
Current	−0.05 (−0.21: 0.11)	−0.06 (−0.25: 0.12)	0.91

*Global p-value <0.0001 that all predictors have the same association with TBS change as with lumbar spine BMD change (Tested with Modified Hausmann test [Suest command in Stata version 14])

^Number of TBS or Lumbar Spine BMD standard deviations change per SD change of continuous predictor, or with predictor category compared to reference

***Models also adjusted for study enrollment site

Table 3

Comparison of Multivariable Adjusted Associations (95% C.I.) of Predictors with Changes of TBS vs. Changes of Total Hip BMD[*,^]

Predictors	TBS Change[**] Effect Size (95% C.I.)	Total Hip BMD Change[**] Effect Size (95% C.I.)	P-Value for Difference
Age (per 5 year increase)	0.00 (−0.03: 0.03)	−0.14 (−0.17: −0.11)	<0.001
Body Mass Index category			
< 25 kg/m^2	Reference	Reference	
25 to 29.9 kg/m^2	0.05 (−0.02: 0.12)	0.06 (−0.01: 0.13)	0.78
≥ 30 kg/m^2	0.09 (0.00: 0.17)	0.07 (−0.02: 0.16)	0.81
Change in Weight V2 minus V1 category			
No change	Reference	Reference	
≥ 5% increase	−0.83 (−0.93: −0.73)	0.32 (0.21: 0.43)	<0.001
≥ 5 to < 10% decrease	0.67 (0.60: 0.75)	−0.44 (−0.52: −0.36)	<0.001
≥ 10% decrease	1.24 (1.12: 1.36)	−1.16 (−1.29: −1.03)	<0.001
Prevalent Radiographic Vertebral Fracture	0.11 (−0.01: 0.23)	−0.02 (−0.14: 0.11)	0.11
Pase Score (per SD increase, SD=66.6)	−0.02 (−0.05: 0.01)	−0.02 (−0.05: 0.01)	0.38
Walk Speed (per SD increase, SD=0.21m/s)	−0.02 (−0.05: 0.01)	0.06 (0.02: 0.09)	0.001
Chair Stand Speed (per SD increase, SD=0.13stands/second)	0.03 (−0.00: 0.06)	0.01 (−0.03: 0.04)	0.35
Smoking Status			
Never	Reference	Reference	
Former	−0.01 (−0.07: 0.05)	0.08 (0.01: 0.14)	0.03
Current	−0.04 (−0.21: 0.13)	−0.18 (−0.35: 0.00)	0.23
Baseline use of ACE Inhibitor Therapy (yes vs. no)	0.01 (−0.06: 0.09)	−0.21 (−0.28: −0.13)	<0.001
Parental History of Hip Fracture (yes vs. no)	−0.02 (−0.10: 0.06)	0.10 (0.01: 0.18)	0.04

[*] Global p-value <0.0001 that all predictors have the same association with TBS change as with total hip BMD change (Tested with Modified Hausmann test [Suest command in Stata version 14])

[^] Number of TBS or Total Hip BMD standard deviations change per SD change of continuous predictor, or with predictor category compared to reference

[**] Models also adjusted for study enrollment site

Table 4

Comparison of Multivariable Adjusted Associations (95% C.I.) of Predictors with Changes of TBS by BMI category[^]

Predictors	TBS Change** Effect Size (95% C.I.)		
	BMI category		
	< 25 kg/m^2	25 to 29.9 kg/m^2	≥ 30 kg/m^2
Age (per 5 year increase)	0.01(−0.03:0.05)	0.01(−0.03:0.05)	0.00(−0.10:0.10)
Change in Weight V2 minus V1 category			
No change	Reference	Reference	Reference
≥ 5% increase	−0.49(−0.62: −0.35)	−0.89(−1.02: −0.76)	−1.34(−1.66: −1.02)
≥ 5 to < 10% decrease	0.42(0.30:0.54)	0.63(0.53:0.72)	1.10(0.88:1.31)
≥ 10% decrease	0.56(0.33:0.79)	0.97(0.82:1.13)	2.12(1.83:2.40)
Prevalent Radiographic Vertebral Fracture	0.11(−0.07:0.29)	0.05(−0.10:0.20)	0.27(−0.06:0.61)
Pase Score (per SD increase, SD=66.6)	0.01(−0.04:0.05)	−0.05(−0.08: −0.01)	0.05(−0.04:0.13)
Walk Speed (per SD increase, SD=0.21m/s)	−0.02(−0.06:0.03)	0.00(−0.04:0.05)	−0.08(−0.17:0.02)
Chair Stand Speed (per SD increase, SD=0.13stands/second)	0.01(−0.03:0.06)	0.02(−0.02:0.06)	0.05(−0.05:0.15)
Smoking Status			
Never	Reference	Reference	Reference
Former	0.02(−0.07:0.10)	0.00(−0.07:0.07)	0.00(−0.17:0.17)
Current	−0.26(−0.51: −0.02)	0.02(−0.19:0.22)	0.30(−0.30:0.89)
Baseline use of ACE Inhibitor Therapy (yes vs. no)	−0.12(−0.25:0.01)	0.02(−0.06:0.11)	0.15(−0.04:0.35)
Parental History of Hip Fracture (yes vs. no)	0.06(−0.05:0.18)	−0.04(−0.14:0.07)	−0.10(−0.36:0.15)

[^] Number of TBS standard deviation change per SD change of continuous predictor, or with predictor category compared to reference

** Models also adjusted for study enrollment site

Table 5

Comparison of Multivariable Adjusted Associations (95% C.I.) of Predictors with Changes of Total Hip BMD by BMI category[^]

Predictors	Total Hip BMD Change[**] Effect Size (95% C.I.)		
	BMI category		
	< 25 kg/m^2	25 to 29.9 kg/m^2	≥ 30 kg/m^2
Age (per 5 year increase)	−0.13(−0.19: −0.07)	−0.13(−0.17: −0.09)	−0.19(−0.28: −0.10)
Change in Weight V2 minus V1 category			
No change	Reference	Reference	Reference
≥ 5% increase	0.26(0.08:0.43)	0.39(0.24:0.53)	0.24(−0.06:0.54)
≥ 5 to < 10% decrease	−0.47(−0.63: −0.31)	−0.44(−0.55: −0.33)	−0.40(−0.59: −0.20)
≥ 10% decrease	−1.27(−1.58: −0.96)	−1.08(−1.25: −0.91)	−1.23(−1.49: −0.96)
Prevalent Radiographic Vertebral Fracture	−0.01(−0.24:0.23)	−0.04(−0.20:0.13)	0.03(−0.27:0.33)
Pase Score (per SD increase, SD=66.6)	0.00(−0.05:0.06)	−0.02(−0.06:0.02)	−0.02(−0.10:0.06)
Walk Speed (per SD increase, SD=0.21m/s)	0.04(−0.02:0.10)	0.06(0.02:0.11)	0.05(−0.04:0.15)
Chair Stand Speed (per SD increase, SD=0.13stands/second)	−0.02(−0.08:0.03)	0.03(−0.01:0.07)	0.00(−0.10:0.09)
Smoking Status			
Never	Reference	Reference	Reference
Former	0.06(−0.06:0.17)	0.09(0.00:0.17)	0.06(−0.09:0.22)
Current	−0.12(−0.45:0.20)	−0.21(−0.44:0.01)	−0.13(−0.68:0.41)
Baseline use of ACE Inhibitor Therapy (yes vs. no)	−0.28(−0.45: −0.11)	−0.18(−0.28: −0.08)	−0.21(−0.39: −0.03)
Parental History of Hip Fracture (yes vs. no)	0.09(−0.07:0.24)	0.11(0.00:0.23)	0.08(−0.16:0.31)

[^] Number of total hip standard deviation change per SD increase of continuous predictor, or with predictor category compared to reference

[**] Models also adjusted for study enrollment site

Table 6

Comparison of Multivariable Adjusted Associations (95% C.I.) of Android Mass Change with Longitudinal Changes of TBS vs. Changes of Total Hip BMD[*,^]

Predictors	TBS Change[**] Effect Size (95% C.I.)	Total Hip BMD Change[**] Effect Size (95% C.I.)	P-Value for Difference
Age (per 5 year increase)	0.02(−0.01:0.05)	−0.15(−0.18: −0.11)	<0.001
Body Mass Index category			
< 25 kg/m^2	Reference	Reference	
25 to 29.9 kg/m^2	0.05(−0.01:0.12)	0.05(−0.02:0.12)	0.94
≥ 30 kg/m^2	0.10(0.01:0.19)	0.04(−0.05:0.14)	0.44
Change in Android Mass V2 minus V1 category			
No change	Reference	Reference	
≥ 5% increase	−0.59(−0.66: −0.52)	0.14(0.07:0.22)	<0.001
≥ 5 to < 10% decrease	0.40(0.31:0.49)	−0.22(−0.32: −0.13)	<0.001
≥ 10% decrease	0.65(0.56:0.73)	−0.49(−0.58: −0.40)	<0.001
Prevalent Radiographic Vertebral Fracture	0.12(0.00:0.23)	−0.03(−0.16:0.10)	0.08
Pase Score (per SD increase, SD=66.6)	−0.02(−0.05:0.00)	−0.01(−0.04:0.02)	0.47
Walk Speed (per SD increase, SD=0.21m/s)	−0.01(−0.04:0.02)	0.05(0.02:0.09)	0.01
Chair Stand Speed (per SD increase, SD=0.13stands/second)	0.03(0.00:0.06)	0.02(−0.02:0.05)	0.59
Smoking Status			
Never	Reference	Reference	
Former	0.04(−0.02:0.10)	0.03(−0.04:0.09)	0.78
Current	−0.02(−0.19:0.15)	−0.22(−0.40: −0.03)	0.14
Baseline use of ACE Inhibitor Therapy (yes vs. no)	−0.03(−0.10:0.05)	−0.18(−0.26: −0.10)	0.01
Parental History of Hip Fracture (yes vs. no)	−0.06(−0.15:0.02)	0.11(0.02:0.20)	<0.01

[*] Global p-value <0.0001 that all predictors have the same association with TBS change as with total hip BMD change (Tested with Modified Hausmann test [Suest command in Stata version 14])

[^] Number of TBS or Total Hip BMD standard deviations change per SD change of continuous predictor, or with predictor category compared to reference

[**] Models also adjusted for study enrollment site