Men with low normal TSH levels are more likely than usual to have lower bone mineral density

Kim BJ, Lee SH, Bae SJ, Kim HK, Choe JW, Kim HY, Koh JM, Kim GS. The association between serum thyrotropin (TSH) levels and bone mineral density in healthy euthyroid men. Clin Endocrinol (Oxf) 2010;73:396-403. doi.1111/j.1365-2265.2010.03818.x

SUMMARY

BACKGROUND

Although osteoporosis is mainly a disease of postmenopausal women, men account for up to 35% of all femoral fractures and approximately 50% of all vertebral fractures. In addition, the mortality rates are twofold to threefold greater in men with osteoporosis as compared with women with osteoporosis. The causes of osteoporosis in men are wide, including a number of diseases such as Cushing's disease, renal disease, hypogonadism, and hyperthyroidism, all of which have been linked to osteoporosis. Because thyroid hormone has a profound effect on bone metabolism, the question raised by Kim et al. is whether there is an association of bone metabolism and thyroid function in euthyroid men.

Methods and Study Subjects

The study population comprised 2000 Korean participants in a routine health screening program at the Health Promotion Center of the Asan Medical Center (AMC) in Seoul, South Korea. The study subjects were screened from January 1 through December 31, 2006; all the subjects were interviewed and examined by physicians in the health-promotion center, who elicited information on medication and a history of previous medical or surgical diseases. The height (in cm), weight (in kg) and body-mass index (the weight in kilograms divided by the square of the height in meters; BMI) was measured in each man. Smoking and drinking habits were categorized into three levels: never, past, or current smokers, and alcohol drinkers labelled as none, or moderate, 2 to 3 times per week or heavy, ≥4 times per week.

Subjects Excluded from the Study

Excluded from the study were men with abnormal serum thyrotropin (TSH) (>5.0 mIU/L) with or without free thyroxine (FT_4; <0.10.3 or >2.5 pmol/L), and those with a history of thyroid surgery or the use of thyroid hormone or antithyroid drugs. Also excluded were men who did not have blood taken in the fasting state or for whom anthropometric measurements were not taken; those who had any diseases that might affect bone metabolism, such as diabetes mellitus, cancer, hyperparathyroidism, or rheumatoid arthritis; and those who had a stroke or dementia (the last was because of concern about their limited physical activity). Also excluded were subjects with any abnormal results on liver- or renal-function tests, which might have caused thyroid hormone assay results or changes in bone metabolism. After these exclusions, 1478 men were eligible for the study.

Blood Measurements

After overnight fasting, early morning blood samples were analyzed at a central laboratory at AMC. Serum FT_4 concentrations were measured by radioimmunoassay. The intraassay and interassay coefficients of variation (CVs) were ≤8.3% and ≤7.5%, respectively, and the lower limit of detection was 0.5 pmol/L.

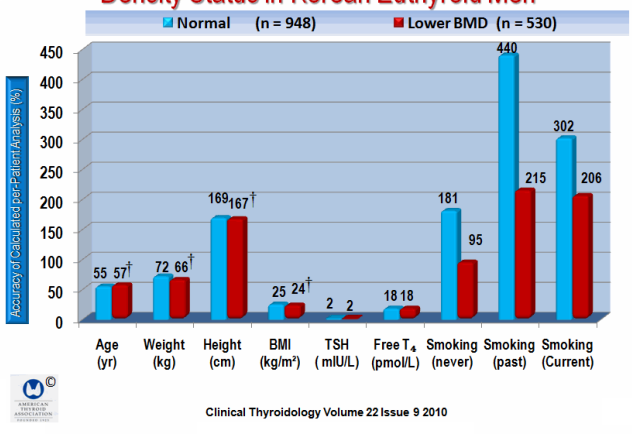

Figure 1. This figure shows baseline characteristics of the euthyroid Korean men by bone mineral density status. The values are means (±SD) . BMI = body-mass index (weight in kilograms divided by the square of the height in meters). The data for Figure 1 are derived from Table 1 of Kim et al.

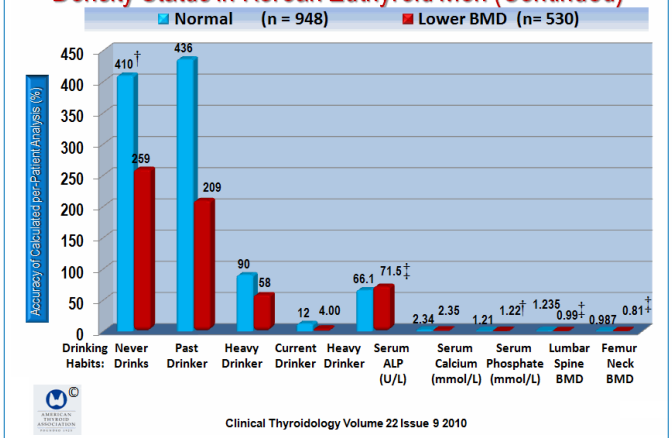

Figure 2. This is a continuation of Figure 1. The number of subjects with osteoporosis (n = 63) was too small for a separate analysis. As a consequence, subjects who met the criteria for at least osteopenia (T-score less than –1.0) at either the lumbar spine or femoral neck were classified as "lower BMD").

Serum TSH was measured by an immunoradiometric assay with a sensitivity of 0.04 mIU/L. Reference ranges for serum FT_4 were 10.3 to 24.5 pmol/L and for serum TSH 0.4 to 5.0 mIU/L. Euthyroidism was defined as a normal serum TSH while not taking thyroid hormone or antithyroid drugs. Serum calcium was measured by an autoanalyzer with intraassay and interassay CVs of 1.24% and 2.06%, respectively, and the reference range was 2.07 to 2.5 mmol/L after correction for serum albumin levels. The intraassay and interassay CVs for serum phosphate were 1.28% and 2.54%, respectively, and for serum alkaline phosphatase (ALP) concentrations 0.7% and 1.3%, respectively; the reference range was 40 to 120 U/L.

Bone Mineral Density (BMD) Measurements

BMD (g/cm2) at the lumbar spine (L2 to L4) and femoral neck was measured by dual-energy x-ray absorptiometry in 910 men using Hologic equipment. In the other 568 men, BMD was estimated using Lunar equipment. The intraassay and interassay CVs were 0.85% and 0.82% for the lumbar spine and 1.20% and 1.12% for the femoral neck, respectively. These values were obtained by scanning 17 volunteers who were not participating in the study, each of which had five scans on the same day, getting on and off the table between examinations to determine the cross-calibrations.

BMD measurements provided absolute values for each anatomic site and were then compared with those of healthy young Korean men (T-score). The reference populations were 245 and 274 men age 20 to 39 years for the Hologic and Lunar equipment, respectively. According to the World Health Organization definition, osteoporosis was diagnosed at a T-score of –25 SD or less at either the lumbar spine or femoral neck. Cutoff values of calibrated BMDs corresponding to osteopenia and osteoporosis were 1.068 and 0.879 g/cm2 for the lumbar spine, respectively, and 0.854 and 0.662 g/cm2 for the femoral neck, in the Korean population. Men who met the criteria for at least osteopenia (T-score less then –1.0) at either site were classified as having lower BMD.

RESULTS

Baseline Characteristics of Study Subjects (Figures 1 and 2)

The mean (±SD) ages of subjects with normal and lower BMD were 55±8.9 years (range, 22 to 84) and 57.2 ±9.2 years (range, 26 to 85), respectively. Weight, height, BMI, and serum TSH concentrations were significantly higher in normal men as compared with men who had lower BMD levels *(Figure 1)*. There were no significant differences in serum FT_4, calcium, and phosphate between the two groups. The serum ALP level was significantly higher in men with lower BMD *(Figure 2)*. About 32% of normal men and 39% with lower BMD levels were current smokers. The percentage of heavy drinkers was slightly higher in men with lower BMD (10.9%) as compared with normal men *(Figure 2)*.

Univariate Analysis (Figure 3)

Using BMD values as a continuous variable, weight and height were positively correlated with both lumber spine and femoral neck BMD, whereas age was only inversely related with the femoral neck BMD. Lumbar spine and femoral neck BMD were both significantly different according to smoking and drinking status. Univariate analysis by Pearson correlation analysis showed that age (P<0.001), weight (P<0.001), height (P<0.001), smoking (P = 0.041, and drinking habits (P = 0.005) were all statistically significant variables *(Figure 3)*.

Multivariate Analysis (Figure 4)

Multivariate analysis examined the independent effect of each variable on BMD. Weight was independently related to BMD at both the lumbar spine and femoral neck. Although current smoking showed an inverse relationship with BMD at both sites, past smoking was associated with only lumbar spine BMD *(Figure 4)*.

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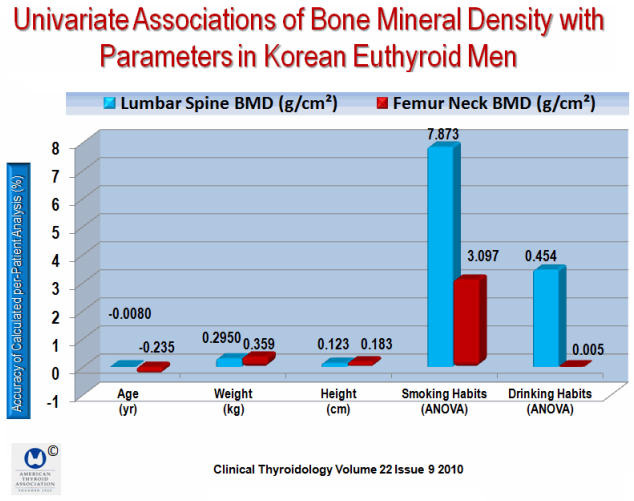

Figure 3. This figure shows the univariate associations of bone mineral density with parameters in Korean euthyroid men. ANOVA = analysis of variance. The data for this figure are derived from Table 2 of Kim et al.

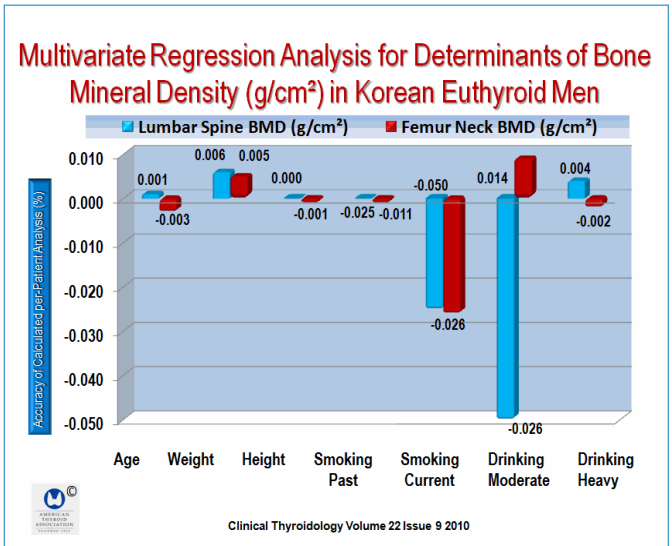

Figure 4. This figure shows the results of multiple regression analysis for determinant of bone mineral density (g/cm2) in Korean euthyroid men. This figure is derived from Table 3 of Kim et al.

inversely associated with femoral neck BMD after considering other independent variables, but it bore no relationship to lumbar spine BMD *(Figure 4)*.

Bone Mineral Density According to TSH Quintile Categories (Figure 5)

Pearson correlation analysis for continuous variables (age, weight, and height) and analysis of variance for categorical variables (smoking and drinking habits) showed mild associations of serum TSH concentration as a continuous variable with BMD values at the lumbar spine and femoral neck. To assess whether the relationships of TSH levels with BMD might have a threshold, subjects were categorized into five groups according to the serum TSH concentration *(Figure 5)*.

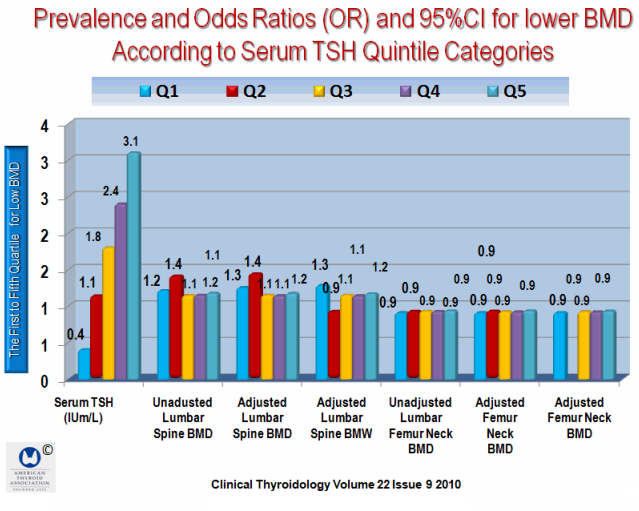

Figure 5. This figure shows bone mineral density according to TSH and the first to fifth quintile category before and after adjustment for confounding variables. The data shown are mean 95% CIs. For lumbar spine and femoral neck BMD according to serum quintile categories estimated by analysis of covariance. BMD = bone mineral density; CI = confidence interval; OR = odds ratio. These data are derived from Table 5 in Kim et al.

There were no differences in height and drinking habits among the groups; however, current smoking and serum ALP concentration showed inverse associations with serum TSH quintile categories, while age and weight increased linearly. BMD values at both the lumbar spine and the femoral neck also increased in a dose-response fashion across increasing TSH quintile categories, before adjustment for age, weight, and height *(Figure 5)*. However, in contrast to results for lumbar spine BMD, the trend for femoral neck BMD was no longer statistically significant after additional control for smoking and drinking habits. Lastly, when ALP concentration was added as a confounding variable, the relationship between lumbar spinal BMD and TSH quintile categories was still significant (P for trend = 0.016). Especially as compared with those in the highest TSH quintile category (Q5), men in the lowest TSH quintile category (Q1) had significantly lower lumbar spine BMD both before and after adjustment for confounding factors *(Figure 5)*.

The overall proportion of subjects in the first Quintile1 and fifth Quintile who met the criteria for osteopenia and osteoporosis were 31.6% and 4.3%, respectively. The prevalence of lower BMD among subjects in Q1 was 42.1%, while only 31.5% of subjects in Q5 met criteria for osteopenia or osteoporosis. After adjusting for age, weight, and height, the odds of lower BMD was 55% higher among subjects in Q1 than it was among subjects in Q5, and the odds ratio (OR) remained statistically significant after additional adjustment for smoking and drinking habits (Table 6 of the article by Kim et al.) When the serum ALP was added as a confounding variable in this model, statistical significant persisted (OR, 1.45 , 95% confidence interval, 1.02 to 2.10) *(Figure 5)*.

CONCLUSION

There is an increased likelihood of lower bone mineral density in men with low normal TSH levels.

COMMENTARY

This study shows that serum TSH concentrations were positively associated with lumbar spine BMD but not femoral neck BMD in healthy euthyroid men after adjusting for several potentially confounding factors. The main finding was that men with low-normal serum TSH concentrations had significantly greater odds of having a lower BMD as compared with men with high-normal TSH concentrations. The authors suggest that these findings are consistent with findings previously reported in women (1;2). The study by Morris et al. (1) also found that low-normal TSH levels were associated with low bone mineral density and an increased risk for osteoporosis in healthy postmenopausal women, even in the euthyroid state. Morris et al. also found that American women with low-normal TSH were levels were 3.4- to 2.2-fold as likely to have osteoporosis and osteopenia, as compared with women with high-normal TSH levels.

Kim et al. identified only one study of BMD in healthy men; Grimnes et al. (3) evaluated the relationship between TSH and BMD in healthy men. The Grimnes study comprised 993 postmenopausal women and 968 men with valid BMD measurements at the hip and forearm in the fifth Tromsø study conducted in 2001. The study subjects were divided into six groups based on the 2.5th and 97.5th percentiles of serum TSH and the quartiles between them. Multiple linear regression analyses adjusting for age, weight, height, and smoking status and for physical activity level and the use of hormone-replacement therapy in women was used in the analyses. After multivariate adjustment, 28 men and 18 women with serum TSH levels less than the 2.5th percentile had significantly lower BMD at the ultradistal forearm (women) and the distal forearm (both men and women), as compared with 921 men and 950 women with serum TSH in the normal range. Also, the 25 postmenopausal women with a serum TSH

above the 97.5th percentile had significantly higher BMD at the femoral neck as compared with women who had a serum TSH level in the normal range. Across the normal range of serum TSH, there was no association between TSH and BMD, and serum TSH as a continuous variable had no effect on BMD in the multiple linear regression model. The authors concluded that TSH within the normal range was not associated with BMD. The small groups of men and women with serum TSH consistent with hyperthyroidism had lower BMD at the forearm than those with serum TSH in the normal range.

In summary, Kim et al. found that serum TSH concentrations within the reference range showed a clear trend of increasing lumbar spine BMD with increasing TSH levels after multivariate adjustment. They also found a lower BMD in association with low-normal TSH, as compared with high-normal TSH concentrations. The authors suggest that longitudinal studies are necessary to document that low-normal serum TSH concentrations are associated with accelerated bone loss, and more importantly, increased risk for fracture.

— Ernest L. Mazzaferri, MD, MACP

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3. Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jorde R.The relationship between serum TSH and bone mineral density in men and postmenopausal women: the Tromso study. Thyroid 2008;18:1147-55.