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Original Article

Significant association factors of bone mineral density in Taiwan adults

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Abstract

Objective: To examine the biofactors associated with bone mineral density (BMD) in southern Taiwanese adults. **Materials and Methods:** The medical records of 3242 adults who underwent health examinations between June 2014 and February 2018 at a regional hospital in southern Taiwan were reviewed. The data collected included health history, anthropomorphic characteristics, clinical laboratory results, biochemical parameters, and BMD. The data were used to identify the biofactors associated with BMD/T-scores at the lumbar spine and femoral neck by multivariate linear regression analysis with the stepwise method. **Results:** The mean age of the patients was 58.1 years, and 71.4% were male. Factors positively correlated with BMD and the T-score included body mass index (BMI), male gender, calcium, and creatinine. Age, alkaline phosphatase (ALP), triiodothyronine, serum thyroxine, low-density lipoprotein cholesterol, and a history of hyperlipidemia were negatively correlated with BMD and the T-score. **Conclusion:** The associated biofactors reported here were similar to and had similar relationships as the biofactors identified in previous literature reports. Not all of the sites examined for BMD were influenced by the same association factors, except for BMI, male gender, age, and ALP, implying that the bone remodeling processes that shape BMD involve a complex regulatory network and demonstrating that our extracted factors are the most useful for clinical practice.

Keywords: *Bone mineral density, Factors, Health examination, Taiwan, T-score*

Introduction

Osteoporosis is accompanied by an imbalance between bone resorption and bone formation, which are two facets of the bone turnover process [1]. The loss of bone mass is linked to the development of fractures and subsequent disability and is an important cause of morbidity and mortality [2,3]. To develop interventions to increase the bone mineral density (BMD) and to reduce and prevent fractures, it is important to elucidate the variables predicting these factors.

Several variables, including aging, menopause status, metabolic and endocrine diseases, inadequate physical activity, body mass index (BMI), smoking, Vitamin D deficiency, thyroid function, serum ferritin levels, and a family history of osteoporosis, have been proposed to be associated with BMD changes in elderly subjects [2,4-6]. In our study, we expanded the age range to include south Taiwanese adults and included the clinical histories and laboratory data from health examinations as variability biofactors.

Our aim was to determine how demographic, biochemical, and clinical features are related to BMD at specific sites, including the bilateral femoral neck and lumbar spine.

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Materials and methods

Subjects

A retrospective study was conducted on all the adults who underwent health examinations between June 2014 and February 2018 at the preventive medical center of a regional teaching hospital in southern Taiwan. Subjects who previously had thyroid disease or underwent internal fixation or total hip replacement at the sites where BMD was measured were excluded. Medical records included (1) history regarding disease, such as hypertension, diabetes mellitus, hyperlipidemia, kidney disease, hepatitis B, and cardiovascular disease; (2) history regarding habits, such as smoking and drinking; and (3) anthropomorphic characteristics (age, sex, height, weight, and BMI). This retrospective study was approved by the Institutional Review Board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (No. B10601012), and the waiver of informed consent from each patient was also approved.

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Laboratory data

The clinical laboratory findings collected during the health examination included total cholesterol (TCH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose level before meal, alkaline phosphatase (ALP), calcium, systolic blood pressure (SBP), diastolic blood pressure (DBP), triiodothyronine (T3), serum thyroxine (T4), thyroid-stimulating hormone (TSH), blood urea nitrogen (BUN), creatinine (Cre), and hemoglobin (Hb).

Bone mineral density

BMD was assessed by dual-energy X-ray absorptiometry (DXA) using a Discovery Wi DXA system (Hologic Inc.). Absolute BMD values and T-scores (number of standard deviations below the BMD of a young normal reference group, Asia database) were calculated for all patients. The measured areas included the lumbar spine and the femoral neck regions of the hips bilaterally. The same densitometer was used for all patients to ensure accurate comparisons. For comparison, we divided the study participants into three groups: normal (the lowest T-score −1 or greater at any site), osteopenia (the lowest T-score between −1 and −2.5 at any site), and osteoporosis (the lowest T-score −2.5 or less at any site).

Statistical analysis

The results were expressed as the means ± standard deviations or numbers (percentages), as appropriate. Differences in means or frequencies were tested by the Chi-square test or *t*-test, as appropriate. Multiple linear regression analysis was performed with the BMD and T-score values of each measured site as the dependent variable. The final regression models were developed using stepwise variable selection procedure. All variables listed in Table 1 (except height and weight) were included as independent variables in the initial regression models for evaluation. All statistical analyses were performed using the PASW Statistics, Version 18 program (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

In total, the medical records of 3242 adults were included, and their demographic and clinical characteristics are presented in Table 1. The study population was predominantly male (71.4%), with a mean age of 58.1 ± 11.0 years. Analysis of clinical characteristics indicated that 27.0% of patients had hypertension, 9.6% were diabetic, 6.9% had hyperlipidemia, 1.7% presented kidney disease, 13.7% had hepatitis B, 18.9%

Table 1: Characteristics of the normal bone mineral density, osteopenia, and osteoporosis subgroup participants

	Normal	Osteopenia	Osteoporosis	*P*
n	921	1811	510	
Male (%)	785 (85.2)	1336 (73.8)	193 (37.8)	<0.001*
Smoking (%)	74 (8.0)	88 (4.9)	7 (1.4)	<0.001*
Drinking (%)	190 (20.6)	272 (15.0)	40 (7.8)	<0.001*
Hypertension (%)	246 (26.7)	480 (26.5)	149 (29.2)	0.464
Diabetes mellitus (%)	83 (9.0)	183 (10.1)	45 (8.8)	0.534
Hyperlipidemia (%)	59 (6.4)	129 (7.1)	37 (7.3)	0.749
Renal disease (%)	17 (1.8)	29 (1.6)	9 (1.8)	0.889
Hepatitis B (%)	133 (14.4)	247 (13.6)	63 (12.4)	0.545
Cardiovascular disease (%)	130 (14.1)	327 (18.1)	156 (30.6)	<0.001*
Age (years)	54.2±11.5	58.6±10.6	63.2±9.0	<0.001*
Height (cm)	168.0±7.1	163.8±7.2	158.3±7.1	<0.001*
Weight (kg)	73.0±12.2	65.0±10.0	56.5±8.6	<0.001*
BMI (kg/m^2)	25.8±3.5	24.1±3.1	22.6±3.1	<0.001*
TCH (mg/dL)	178.4±35.1	181.8±38.3	182.2±35.8	0.052
LDL-C (mg/dL)	116.3±29.8	118.3±33.0	115.7±30.9	0.132
HDL-C (mg/dL)	43.3±11.9	45.7±13.6	51.7±15.6	<0.001*
Triglycerides (mg/dL)	134.3±81.4	125.1±74.0	109.2±65.4	<0.001*
Glucose (mg/dL)	107.6±24.3	107.0±21.7	105.8±21.1	0.333
ALP (IU/L)	79.9±23.5	85.5±23.9	95.6±39.0	<0.001*
Calcium (mmol/L)	2.25±0.10	2.24±0.10	2.24±0.10	0.082
SBP (mmHg)	130.7±19.1	129.4±19.9	127.7±20.6	0.028*
DBP (mmHg)	78.0±11.3	76.7±11.4	73.3±11.6	<0.001*
T3 (ng/mL)	0.99±0.18	1.0±0.18	1.0±0.3	0.488
T4 (μg/dL)	8.1±1.6	8.2±1.6	8.6±1.6	<0.001*
TSH (μIU/mL)	2.20±1.40	2.56±6.12	2.43±1.92	0.158
BUN (mg/dL)	11.6±3.7	11.6±3.7	11.8±5.6	0.681
Cre (mg/dL)	1.04±0.30	1.00±0.28	0.92±0.40	<0.001*
Hb (g/dL)	15.1±1.5	14.8±1.5	14.0±1.3	<0.001*

*P<0.05. BMI: Body mass index, TCH: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ALP: Alkaline phosphatase, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, T3: Triiodothyronine, T4: Serum thyroxine, TSH: Thyroid-stimulating hormone, BUN: Blood urea nitrogen, Cre: Creatinine, Hb: Hemoglobin

had cardiovascular disease, 5.2% were smokers, and 15.5% drank alcohol. There were significant differences between male and female subjects with regard to smoking, drinking, hepatitis B, cardiovascular disease, height, weight, BMI, TCH, HDL-C, TG, ALP, calcium, SBP, DBP, T3, T4, TSH, BUN, Cre, and Hb.

Bone mineral density

Mean lumbar spine T-scores on DXA were −0.43 ± 1.30 for men, −1.31 ± 1.32 for women, and −0.68 ± 1.36 for all patients. There were significant differences between male and female subjects in the BMD for the lumbar spine and the femoral neck region of the bilateral hips. Spine and femoral neck T-scores were also significantly different between males and females. There was a higher rate of osteoporosis in the female subjects [Table 2].

Subgroup characteristics

There were significant differences among the normal, osteopenia, and osteoporosis subgroups in their percentage of males, smoking, drinking, and cardiovascular disease. Subjects in the osteoporosis subgroup were older and had lower height, lower weight, lower BMI, higher HDL-C, lower TG, higher ALP, lower SBP and DBP, higher T4, lower Cre, and lower Hb [Table 1].

Multiple linear regressions

In the analysis of the factors associated with BMD, multivariate linear regression showed that BMD, or the T-score, in some regions was positively correlated with some of the factors, including BMI, male sex, calcium, and Cre, and negatively correlated with other factors, including age, ALP, T3, T4, LDL-C, and hyperlipidemia [Table 3]. Among them, BMI

Table 2: Demographic and clinical characteristics of study participants

	All	Male	Female	*P*
n	3242	2314	928	
Age (range) (years)	58.1±11.0 (22-89)	58.0±11.2 (22-89)	58.4±10.6 (22-88)	0.315
Smoking (%)	169 (5.2)	165 (7.1)	4 (0.4)	<0.001*
Drinking (%)	502 (15.5)	475 (20.5)	27 (2.9)	<0.001*
Hypertension (%)	875 (27.0)	633 (27.4)	242 (26.1)	0.459
Diabetes mellitus (%)	311 (9.6)	229 (9.9)	82 (8.8)	0.354
Hyperlipidemia (%)	225 (6.9)	160 (6.9)	65 (7.0)	0.927
Kidney disease (%)	55 (1.7)	41 (1.8)	14 (1.5)	0.600
Hepatitis B (%)	443 (13.7)	349 (15.1)	94 (10.1)	<0.001*
Cardiovascular disease (%)	613 (18.9)	233 (10.1)	380 (40.9)	<0.001*
Height (cm)	164.1±7.8	167.3±6.2	156.3±5.4	<0.001*
Weight (kg)	65.9±11.7	69.3±11.0	57.5±8.9	<0.001*
BMI (kg/m^2)	24.4±3.4	24.7±3.3	23.5±3.5	<0.001*
TCH (mg/dL)	180.9±37.0	178.1±36.8	187.8±36.7	<0.001*
LDL-C (mg/dL)	117.3±31.8	116.7±31.7	119.0±32.2	0.055
HDL-C (mg/dL)	46.0±13.8	43.4±12.4	52.3±14.9	<0.001*
Triglycerides (mg/dL)	125.2±75.1	130.2±79.1	112.8±62.5	<0.001*
Glucose (mg/dL)	107.0±22.4	107.4±22.8	105.9±21.3	0.089
ALP (IU/L)	85.5±27.2	84.2±24.2	88.7±33.4	<0.001*
Calcium (mmol/L)	2.24±0.10	2.24±0.10	2.25±0.10	0.023*
SBP (mmHg)	129.5±19.8	131.6±19.2	124.3±20.4	<0.001*
DBP (mmHg)	76.4±11.5	78.8±10.9	70.7±10.9	<0.001*
T3 (ng/mL)	1.00±0.19	1.01±0.18	0.98±0.22	0.011*
T4 (μg/dL)	8.2±1.6	8.1±1.6	8.5±1.6	<0.001*
TSH (μIU/mL)	2.44±4.70	2.29±3.12	2.81±7.25	0.034*
BUN (mg/dL)	11.6±4.1	12.1±3.8	10.5±4.5	<0.001*
Cre (mg/dL)	1.00±0.31	1.07±0.29	0.82±0.29	<0.001*
Hb (g/dL)	14.7±1.5	15.3±1.3	13.4±1.3	<0.001*
L-spine BMD (g/cm^2)	0.957±0.156	0.988±0.148	0.878±0.146	<0.001*
L-spine T-score	−0.68±1.36	−0.43±1.30	−1.31±1.32	<0.001*
Right hip neck BMD (g/cm^2)	0.710±0.126	0.736±0.122	0.647±0.112	<0.001*
Right hip neck T-score	−1.19±1.04	−1.01±0.98	−1.63±1.04	<0.001*
Left hip neck BMD (g/cm^2)	0.710±0.126	0.735±0.122	0.646±0.112	<0.001*
Left hip neck T-score	−1.19±1.05	−1.00±0.99	−1.64±1.04	<0.001*
BMD category				
Normal	921 (28.4)	785 (33.9)	136 (14.7)	<0.001*
Osteopenia	1811 (55.9)	1336 (57.7)	475 (51.2)	<0.001*
Osteoporosis	510 (15.7)	193 (8.3)	317 (34.2)	<0.001*

*P<0.05 BMI: Body mass index, TCH: Total cholesterol, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ALP: Alkaline phosphatase, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, T3: Triiodothyronine, T4: Serum thyroxine, TSH: Thyroid-stimulating hormone, BUN: Blood urea nitrogen, Cre: Creatinine, Hb: Hemoglobin, BMD: Bone mineral density

Table 3: Multiple linear regression for the data analysis: Correlation between parameters and regional bone mineral density or *T*-score by multiple regression analysis using the stepwise method

	Spine				Right hip neck				Left hip neck			
	BMD		*T* score		BMD		*T* score		BMD		*T* score	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
BMI (kg/m^2)	0.278	<0.001	0.284	<0.001	0.280	<0.001	0.295	<0.001	0.287	<0.001	0.291	<0.001
Sex (male:female=1:0)	0.255	<0.001	0.221	<0.001	0.262	<0.001	0.211	<0.001	0.267	<0.001	0.209	<0.001
Calcium (mmol/L)									0.033	0.024	0.041	0.007
Cre (mg/dL)	0.039	0.020	0.044	0.010								
Age (years)	−0.105	<0.001	−0.079	<0.001	−0.313	<0.001	−0.288	<0.001	−0.307	<0.001	−0.278	<0.001
ALP (IU/L)	−0.142	<0.001	−0.176	<0.001	−0.131	<0.001	−0.168	<0.001	−0.131	<0.001	−0.170	<0.001
T3 (ng/mL)	−0.060	<0.001	−0.053	0.001	−0.033	0.024	−0.031	0.042	−0.039	0.009		
T4 (μg/dL)											−0.046	0.003
LDL-C (mg/dL)							−0.036	0.016				
Hyperlipidemia					−0.043	0.004	−0.042	0.005	−0.034	0.020	−0.035	0.021

Blue color: Positive correlation, Red color: Negative correlation. BMI: Body mass index, LDL-C: Low-density lipoprotein cholesterol, ALP: Alkaline phosphatase, T3: Triiodothyronine, T4: Serum thyroxine, Cre: Creatinine, BMD: Bone mineral density

and male sex were positively correlated with BMD and the T-score at all measured sites, and age and ALP were negatively correlated with BMD and the T-score at all measured sites. T3 was negatively associated with BMD and the T-score at nearly all the measured sites except for the left femoral neck T-score, which showed a negative association with T4. Not all anatomic sites had the same association factors, but their positive or negative correlation was consistent. The parameters and association tendencies were also similar to the ones described in the literature [7-15].

Discussion

Traditional risk factors for low BMD include advanced age, female sex, low BMI, smoking, Caucasian race, and glucocorticoids [7]. We confirm that male patients had higher BMD and consistently in all measured sites. A Korean study suggested that aging, waist circumference, BMI, weight training, hypercholesterolemia, hypertriglyceridemia, and diabetes were site specifically associated with BMD in adult men [8]. We expand the population to adults of both sexes; a higher BMI is generally with higher BMD and the T-score at the lumbar and hip sites. The beneficial effect of obesity on BMD has been attributed to the mechanical loading effect of the weight on bone [16]. Increasing calcium intake from dietary sources or taking calcium supplements were found to be significantly associated with increased BMD [17,18]. BMD scores were significantly higher in postmenopausal women, as shown by their T-scores along with increased serum calcium levels [19]. Postmenopausal women, compared to premenopausal women, had a significant reduction in Vitamin D and serum calcium levels, and all of them had low BMD [20]. Low serum calcium and Vitamin D levels were found to be major risk factors associated with osteopenia and osteoporosis among postmenopausal women from slum areas in Ahmedabad [9].

Serum Cre can serve as a marker of muscle mass [10]. Independent of age, a strong positive correlation exists between Cre clearance and bone mass in healthy elderly women [21]. There was a significant linear association between Cre clearance, as measured by the Cockcroft–Gault equation, or glomerular filtration rate, as measured by the Modification of Diet in Renal Disease equation, and hip BMD; however, this association was not observed between serum Cre and BMD [22]. Low serum Cre was independently associated with low BMD in an older population with normal kidney function [10]. Our result showed that both calcium and Cre are positive factors of BMD in our population, which includes Taiwanese adults ranging from 21 to 90 years old.

Bone mass decreases with aging and results in osteoporosis in elderly subjects [2]. ALP is a ubiquitous enzyme that plays an important role in osteoid formation and bone mineralization. It is secreted during osteogenesis and is commonly used to assess osteoblastic activity [23]. An increase in ALP activity in women is associated with more severe osteoporosis [11,24]. Osteocalcin and ALP are valid biomarkers to diagnose low BMD in postmenopausal women [23]. In a group of 3149 healthy Korean men, a negative correlation was found between BMD and ALP [12]. A more specific marker, bone alkaline phosphatase (BAP), was negatively correlated with BMD in Japanese postmenopausal osteoporotic women during denosumab treatment [25]. We confirmed that age and ALP are important negative factors, both generally and consistently in all measured sites, in our population of both men and women.

Thyrotoxicosis accelerates bone remodeling and is one of the known risk factors for osteoporosis [13,26,27]. Subjects with a history of thyroid disease were excluded from our study, because their disease status would have influenced T3, T4, and TSH levels. It was previously shown that thyrotoxicosis causes a remarkable loss of bone mineral mass, which cannot be compensated for after 1 year of successful treatment [28]. Studies of BMD in euthyroid populations indicate that thyroid hormone also regulates bone turnover, and low BMD in a euthyroid population of postmenopausal women was associated with free T4 and free T3 levels but not with TSH [29]. Higher free T4 levels within the physiological reference range, but not low TSH, are independently correlated with low BMD in perimenopausal women [30]. Prolonged treatment with T4 and T3 can directly increase bone resorption in cultured fetal rat long bones [31]. Our study suggested that, even in healthy adults, thyroid function still affects BMD,

especially T3, which is much more potent than T4, in nearly all sites (except left femoral neck T-score) and that there is no relationship between TSH levels and BMD.

Hyperlipidemia increases the risk for generating lipid oxidation products, which accumulate in the subendothelial spaces of the vasculature and bone, impairing bone regeneration and its mechanical strength; thus, these oxidation products may be risk factors for osteoporosis [14,32]. There is an inverse relationship between lumbar spine and whole-body BMD and serum TCH and LDL-C levels in postmenopausal women and HDL-C in premenopausal women [15,33]. Serum lipids, especially low HDL-C and high LDL-C, influence BMD by acting on the long bones and affecting osteoporosis and osteopenia [34]. In a 2018 study of 2,347 male and female participants, TCH and LDL-C had a weak, but significant, negative correlation with the BMD at the sites of the femur and lumbar spine [35]. Plasma LDL-C and HDL-C levels were inversely and positively correlated, respectively, with BMD [36]. Other studies found no significant associations between serum lipid levels and BMD [37,38]. However, in a 2018 meta-analysis of postmenopausal women, the levels of HDL-C, LDL-C, and TCH were higher in the osteoporosis group than in the normal bone density group [39]. Statin use was associated with a significant increase in BMD [40].

The facts that the relationship between BMD changes and many associated factors varied across the different studies may be attributed to study design or to the characteristics of the study's subjects, such as ethnicity, lifestyle, and demographic features [5,41]. The other factors in our study were not identified as significant independent variables. Although smoking, diabetes, and Hb levels were identified in other studies as factors associated with osteoporosis, our study did not find them to be associated with BMD, probably due to the coexistence of one or more associated factors or due to the involvement of complex regulatory networks in bone modeling.

Our study has certain limitations. First, this is a cross-sectional study. Second, the effects of medications might not have been adequately evaluated by virtue of the study design. However, the parameters that we considered, which included not only the clinical histories but also the laboratory data, reflect the status of the subjects at the time when the study was conducted. Third, because a large number of independent variables were evaluated in the regression models, inflation of Type I error rates is possible. Nevertheless, most of our observed P values were at < 0.001 rather than near the 0.05 level. Fourth, some factors already known to be associated with BMD, such as iPTH, phosphate, serum 25-hydroxyvitamin D, osteocalcin, BAP, and free T4, were not included in the health examination data. Fifth, our study included both males and females, but the menopausal status was not evaluated. However, we included our population (both male and female and both younger and older adults) and factors (clinical characteristics, habit history, and laboratory data) as much as possible and used stepwise multiple linear regression; the factors significantly affecting BMD and the T-score are summarized in Table 3. In addition, the population size from the general health check is large enough (3242 subjects). In our study, the direction of association was the same across the BMD measurement sites. This study is considered clinically important because it reconfirms the potentially modifiable clinical characteristics for increased or decreased BMD and chooses the most crucial ones among the factors in the literature, thus making them considered most noticeable for use in clinical practice. A better understanding of the key risk factors for low BMD may help reduce the risk of osteoporosis.

Conclusion

We evaluate an expansive population and variables simultaneously using the stepwise method. The male patients had higher BMD; hip and L-spine BMD and T-scores were positively correlated with BMI, and some of them were positively correlated with serum calcium and Cre levels. Hip and L-spine BMD and T-scores were negatively associated with age and ALP, and some scores were inversely correlated with T3, T4, and LDL-C. Cases with hyperlipidemia also showed lower value in the hip BMD and T-score. These factors are part of complex regulatory networks that participate in bone modeling and shape BMD. The directions of their associations are consistent; thus, these identified factors can be considered the most significant for clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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