

ORIGINAL STUDY

Association between osteoporosis and menopause in relation to SOX6 rs297325 variant in Taiwanese women

Tzu-Liang Hsu, MD,^{1,2} Disline Manli Tantoh, PhD,^{1,3} Ying-Hsiang Chou, MD,^{4,5,6}
Shu-Yi Hsu, MSc,¹ Chien-Chang Ho, PhD,⁷ Chia-Chi Lung, PhD,¹ Cheng-Feng Jan, MEd,⁸
Lee Wang, PhD,¹ and Yung-Po Liaw, PhD^{1,3}

Abstract

Objective: Osteoporosis, the most prevalent bone disorder in humans, is a global public health issue and its relationship with menopause is well-established. The interaction between menopause and genes on osteoporosis risk is, however, yet to be fully elucidated. We assessed the association between menopause and osteoporosis in relation to the SOX6 rs297325 variant in Taiwanese women.

Methods: There were 7,581 female participants, aged 30 to 70 years old. Information on SOX6 rs297325 and menopause were obtained from the Taiwan Biobank Database while that on osteoporosis was obtained from the National Health Insurance Research Database.

Results: Menopause but not SOX6 rs297325 was significantly associated with a higher risk of osteoporosis (odds ratio [OR] = 1.48; 95% confidence interval [CI] = 1.04-2.10). The interaction between menopause and rs297325 on osteoporosis was significant ($P = 0.0216$). After stratification by rs297325 genotypes, the risk of osteoporosis was significantly higher in menopausal women having the TT + CC genotype (OR = 2.02; 95% CI = 1.21-3.38). After stratification by menopausal status and rs297325 genotypes, the OR; 95% CI was 0.62; 0.38 to 0.99 in premenopausal women with the TC + CC genotype and 1.24; 0.82 to 1.88 in menopausal women with the TC + CC genotype.

Conclusion: SOX6 rs297325 was not significantly associated with osteoporosis but might have modulated the association between menopause and osteoporosis. The risk of osteoporosis was higher in menopausal women with the TC + CC genotype but lower in premenopausal women with the TC + CC genotype.

Key Words: Menopause – Osteoporosis – rs297325 – SOX6 – Taiwan Biobank.

Osteoporosis is a progressive skeletal disorder whereby the bone strength (bone density and quality) is compromised thereby predisposing an individual to an increased risk of fractures which could occur spontaneously or after minor injuries.^{1,2} It is associated with low bone mineral density (BMD) and loss of structural and biomechanical properties that are vital for the maintenance of bone homeostasis.¹ Osteoporosis is the most prevalent bone disorder in humans and

is a major global public health issue.³ Osteoporotic fractures are associated with increased mortality.³⁻⁵ In addition, fractures are associated with increased disability, reduced physical functions, and poor quality of life besides an increased financial burden.³⁻⁵ Globally, approximately 9 million new and 56 million prevalent cases of osteoporotic fractures were estimated in the year 2000.⁵ In Taiwan, the prevalence of osteoporosis between 2001 and 2011 increased by about 7.6%.⁶

Received November 5, 2019; revised and accepted January 9, 2020.

From the ¹Department of Public Health and Institute of Public Health, Chung Shan Medical University, Taichung City, Taiwan; ²Department of Orthopedic Surgery, Tungs' Taichung Metroharbor Hospital, Taichung City, Taiwan; ³Department of Medical Imaging, Chung Shan Medical University Hospital, Taichung City, Taiwan; ⁴Department of Radiation Oncology, Chung Shan Medical University Hospital, Taichung City, Taiwan; ⁵School of Medical Imaging and Radiological Sciences, Chung Shan Medical University, Taichung City, Taiwan; ⁶Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; ⁷Department of Physical Education, Fu Jen Catholic University, New Taipei City, Taiwan; and ⁸Office of Physical Education, Chung Yuan Christian University, Taoyuan City, Taiwan.

Funding/support: We are grateful to the Ministry of Science and Technology (MOST), Taiwan for partially funding this work (MOST 107-2627-M-040-002 and 108-2621-M-040-001).

Financial disclosures/conflicts of interest: None reported.

Ethics approval and consent to participate: The ethics approval for this study was obtained from the Chung Shan Medical University Institutional Review Board (CS2-17070).

Address correspondence to: Yung-Po Liaw, PhD; Lee Wang, PhD, Department of Public Health and Institute of Public Health, Chung Shan Medical University, No. 110, Sec. 1, Jianguo N. Rd, Taichung City 40201, Taiwan. E-mail: Liawyp@csmu.edu.tw; wl@csmu.edu.tw

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

MATERIALS AND METHODS

BMD is a valuable clinical diagnostic index for osteoporosis and the best tool for osteoporotic fracture prediction.⁷⁻¹⁰ Osteoporosis is associated with several genetic and nongenetic factors,^{1,3} some of which include age,^{1,11-14} sex,¹⁻³ menopausal status,^{1-3,15} educational level,^{11,12,14,16} coffee drinking,¹¹ smoking,^{1,2,12} exercise,^{1,2,12} alcohol consumption,^{1,2,12} diet,^{1,2,17} and body mass index (BMI).^{1,11,13,14,18}

Sex is a well-established nonmodifiable factor for osteoporosis.¹⁹ The risk of osteoporosis is greater in women than in men.¹⁻³ For instance, using data from the National Nutrition and Health Survey in Taiwan (2005-2008), the estimated prevalence of osteoporosis was 23.9% and 38.3% in men and women, respectively.²⁰ One major reason for sex differences in osteoporosis prevalence is menopause.¹⁹ Menopausal women are estrogen deficient and more likely to have bone loss, osteoporosis, and fractures than premenopausal women.^{1-3,15,19}

Like sex, genetic traits are nonmodifiable factors for osteoporosis¹⁹ and approximately 75% of osteoporosis is heritable.²¹ Moreover, BMD, an essential biomarker for osteoporosis and osteoporotic fracture prediction is a highly heritable quantitative trait.^{7,10,22} It is evident that approximately 50% to 82% of variations in BMD are of genetic origin.^{23,24} These genetic variations are also believed to be associated with menopausal status.^{25,26} For instance, the total genetic percentage of spine BMD variance in premenopausal and postmenopausal women was 88% and 77%, respectively.²⁵

Several genes are associated with BMD and osteoporosis,^{7,27-30} one of which is SOX6.²⁷⁻³⁰ SOX6 is a chondrogenic transcription factor that influences BMD and is differentially expressed during osteoblast development.³¹⁻³⁴ It affects osteoporosis by regulating endochondral bone formation^{32,34} and enhances fracture healing by activating and maintaining chondrogenesis.³⁵

SOX6 has been suggested as a new potential determinant gene for osteoporosis estimation,^{27,29} owing to its significant genome-wide association with BMD in addition to its essential role in cartilage formation.²⁸ More studies to confirm the association between the SOX6 rs297325 variant and osteoporosis are, however, warranted. Available literature shows inconsistent associations between SOX6 rs297325 and BMD. For instance, in a genome-wide association study (G-WAS) on a White population with a subsequent replication in a Chinese population, the SOX6 rs297325 variant was not significantly associated with wrist BMD.²⁸ In another G-WAS, significant bivariate associations of BMD and BMI with SOX6 rs297325 were, however, observed in white men.³⁰

Despite the well-established relationship between menopause and osteoporosis,^{1-3,15} more is yet to be known about the interaction between menopause and genes on the risk of osteoporosis.²⁵ We, therefore, conducted this study to assess the association between menopause and osteoporosis in relation to SOX6 rs297325 single nucleotide polymorphism (SNP) in Taiwanese women.

Data sources

Data were retrieved from the Taiwan Biobank Database and the National Health Insurance Research Database. These data sources were linked using personal identification numbers of participants which were encrypted for privacy reasons. Data on SOX6 rs297325 genotypes, menopausal status, educational level, cigarette smoking, alcohol drinking, exercise, height, weight, and age were obtained from the Taiwan Biobank Database (2008-2015) while information on osteoporosis was obtained from the National Health Insurance Research Database (1998-2015).

Definition of variables

Cases of osteoporosis were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification code 733.0 and were included in the study if they had at least two outpatient visits or one inpatient visit before enrolling into the biobank project. Menopausal status, educational level, cigarette smoking, alcohol drinking, exercise, and age were self-reported. The SOX6 rs297325 genotypes were determined using biochemical examinations while the BMI was derived from height and weight which were determined by physical examination.

Natural menopause was defined as the complete absence of menstrual periods for 12 consecutive months in women without a history of hysterectomy. Participants were categorized as alcohol drinkers or nondrinkers. Drinkers were those who reported having or have ever had a habit of drinking at least 150 cm³ of alcohol per week for 6 months continuously. Nondrinkers were those who did not drink at all or occasionally drank alcohol (<150 cm³/wk for 6 months continuously). Regular exercise was defined as taking exercise (not including manual labor, agriculture, and housework) that lasted for 30 minutes or more at least three times per week. Activities like hiking, swimming, gymnastics, strolling, rope jumping, hula hoop, "Taijiquan," aerobic dance, biking, "Qigong," jogging, weight training, Chinese martial arts, yoga, badminton, tennis, table tennis, soccer, golf, basketball, and other ball games, among others were considered as exercise. Smokers were those who continuously smoked cigarettes for more than 6 months. BMI (in kg/m²) was calculated as weight (in kg) divided by height (in m²). Genotypes were determined using the custom Taiwan Biobank chips and run on the Axiom Genome-Wide Array Plate System (Affymetrix, Santa Clara, CA). Quality control measures for SNPs in the Taiwan Biobank include the exclusion of SNPs whose Hardy-Weinberg equilibrium *P* values were less than 1.0×10^{-3} , call rate was low (<95%), and whose minor allele frequency was less than 0.05.

A total of 10,089 women (30-70 years old), enrolled in the Taiwan Biobank were initially recruited for the current study. Those with incomplete data ($n = 1,150$) and those on hormone therapy or who underwent hysterectomy ($n = 1,358$) were, however, excluded. The final study participants included 7,581 women comprising 726 osteoporosis patients and 6,855 controls.

TABLE 1. Descriptive data of the study participants by rs297325 genotypes in SOX6

Variables	rs297325 (TT) (n = 3,683)	rs297325 (TC + CC) (n = 3,898)	P
Osteoporosis			0.600
No	3,337 (90.61%)	3,518 (90.25%)	
Yes	346 (9.39%)	380 (9.75%)	
Menopausal status			0.942
Premenopause	2,315 (62.86%)	2,447 (62.78%)	
Menopause	1,368 (37.14%)	1,451 (37.22%)	
Age, y	47.31 ± 10.81	47.50 ± 10.75	0.434
Educational level			0.168
Elementary school	256 (6.95%)	233 (5.98%)	
Junior and senior high school	1,535 (41.68%)	1,675 (42.97%)	
University above	1,892 (51.37%)	1,990 (51.05%)	
Cigarette smoking			0.049
No	3,465 (94.08%)	3,707 (95.10%)	
Yes	218 (5.92%)	191 (4.90%)	
Alcohol drinking			0.852
No	3,591 (97.50%)	3,798 (97.43%)	
Yes	92 (2.50%)	100 (2.57%)	
Exercise			0.075
No	2,334 (63.37%)	2,393 (61.39%)	
Yes	1,349 (36.63%)	1,505 (38.61%)	
BMI, kg/m ²			0.766
BMI <18.5 (underweight)	181 (4.91%)	184 (4.72%)	
18.5 ≤ BMI <24 (normal weight)	2,167 (58.84%)	2,324 (59.62%)	
24 ≤ BMI <27 (overweight)	792 (21.50%)	804 (20.63%)	
BMI ≥27 (obesity)	543 (14.74%)	586 (15.03%)	
Age at menarche, y	13.38 ± 1.55	13.40 ± 1.50	0.523

Categorical and continuous variables are presented as percentages (%) and mean ± SD, respectively. BMI, body mass index; SD, standard deviation.

Statistical analysis

Categorical variables included rs297325 genotypes, menopausal status, educational level, cigarette smoking, alcohol drinking, exercise, and BMI, whereas continuous variables included age and age at menarche. Chi-square test and *t* test were used to compare the differences between categorical and continuous variables, respectively. Results of chi-square tests were presented as percentages (%) and those of *t* tests were presented as mean ± standard deviation. Logistic regression was used to determine the association of menopause and SOX6 rs297325 variant with osteoporosis and the results were presented as odds ratios (ORs) at 95% confidence intervals (CIs). Moreover, logistic regression was used to test the interaction (*) between menopause and SOX6 rs297325. Statistical analyses were performed using the Statistical Analysis System (SAS) software 9.4 (SAS Institute, Cary, NC) and PLINK.

RESULTS

Table 1 shows the descriptive characteristics of the study participants stratified by rs297325 genotypes. Overall, there were 7,581 participants comprising 726 osteoporosis cases and 6,855 controls. Among these participants, 4,762 were in the premenopausal stage, whereas 2,819 were in the menopausal stage (Table 1).

The association of rs297325 and menopause with osteoporosis is illustrated in Table 2. With TT as the reference genotype, TC + CC was not significantly associated with the risk of osteoporosis. Menopause was, however, significantly associated with a higher risk of osteoporosis

(OR = 1.48; 95% CI = 1.04-2.10). Age was also significantly associated with a higher risk of osteoporosis (OR = 1.17; 95% CI = 1.15-1.19). That is, each yearly increase in age was associated with a 17% increase in the odds of osteoporosis. A borderline significant association was observed between overweight and lower risk of osteoporosis (OR = 0.81; 95% CI = 0.66-1.00). Obesity was significantly associated with a lower risk of osteoporosis (OR at 95% CI = 0.61; 0.46-0.80; Table 2).

TABLE 2. Association of rs297325 in SOX6 and menopause with osteoporosis

Variables	OR	95% CI
Menopausal status (ref: premenopause)		
Menopause	1.48	1.04-2.10
rs297325 (ref: TT)		
TC + CC	1.04	0.87-1.24
Age	1.17	1.15-1.19
Educational level (ref: elementary school)		
Junior and Senior high school	0.87	0.67-1.12
University above	0.79	0.60-1.05
Cigarette smoking (ref: no)		
Yes	0.87	0.51-1.49
Alcohol drinking (ref: no)		
Yes	0.68	0.31-1.48
Exercise (ref: no)		
Yes	1.08	0.90-1.30
BMI (ref: 18.5 ≤ BMI < 24)		
BMI <18.5	1.12	0.69-1.80
24 ≤ BMI <27	0.81	0.66-1.00
BMI ≥27	0.61	0.46-0.80
Age at menarche	1.04	0.98-1.10

BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref, reference.

TABLE 3. Association between osteoporosis and menopause stratified by rs297325 genotypes in SOX6

	rs297325 (TT)		rs297325 (TC + CC)	
	n = 3,683		n = 3,898	
	OR	95% CI	OR	95% CI
Menopausal status (ref: premenopause)				
Menopause	1.10	0.67-1.79	2.02	1.21-3.38
Age	1.17	1.14-1.20	1.17	1.14-1.20
Educational level (ref: elementary school)				
Junior and senior high school	0.85	0.60-1.22	0.87	0.60-1.26
University above	0.88	0.60-1.30	0.70	0.46-1.05
Smoke (ref: no)				
Yes	0.73	0.33-1.62	1.03	0.50-2.12
Alcohol drink (ref: no)				
Yes	0.77	0.26-2.31	0.60	0.20-1.81
Physical activity (ref: no)				
Yes	1.16	0.90-1.50	1.01	0.78-1.31
BMI (ref: 18.5 ≤ BMI <24)				
BMI <18.5	1.75	0.93-3.28	0.66	0.31-1.40
24 ≤ BMI <27	0.97	0.72-1.31	0.68	0.50-0.92
BMI ≥27	0.71	0.48-1.05	0.52	0.36-0.76
Age at menarche	1.05	0.97-1.14	1.02	0.94-1.11
Menopause*rs297325				
			<i>P</i> value = 0.0216	

BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref, reference.

Despite the absence of a relationship between rs297325 and osteoporosis, the interaction between menopause and rs297325 on osteoporosis was significant ($P = 0.0216$; Table 3). After stratification by rs297325 genotypes, menopause remained associated with a higher risk of osteoporosis. Significant results were, however, observed only in menopausal women having the TT + CC genotype (OR = 2.02; 95% CI = 1.21-3.38). Age remained significantly associated with a higher risk of osteoporosis. The OR; 95% CI was 1.17; 1.14 to 1.20 for both the TT and TC + CC genotypes. Nonetheless, overweight and obesity were associated with a lower risk of osteoporosis only in those with the TC + CC genotype. The ORs; 95% CIs were 0.68; 0.50 to 0.92 and 0.52; 0.36 to 0.76 for overweight and obesity, respectively (Table 3).

After further stratification by menopausal status and rs297325 genotypes using premenopause and TT as the

TABLE 4. Odds ratios (95% confidence interval) for osteoporosis after combining menopausal status and rs297325 genotypes in SOX6

	OR	95% CI
Menopausal status and rs297325 (ref: premenopause and TT)		
Premenopause and TC + CC	0.62	0.38-0.99
Menopause and TT	1.10	0.72-1.67
Menopause and TC + CC	1.24	0.82-1.88
Age	1.17	1.15-1.19
Educational level (ref: elementary school)		
Junior and senior high school	0.86	0.67-1.12
University above	0.79	0.59-1.04
Smoke (ref: no)		
Yes	0.87	0.51-1.49
Alcohol drink (ref: no)		
Yes	0.68	0.31-1.49
Physical activity (ref: no)		
Yes	1.08	0.90-1.30
BMI (ref: 18.5 ≤ BMI <24)		
BMI <18.5	1.12	0.69-1.81
24 ≤ BMI <27	0.81	0.66-1.00
BMI ≥27	0.61	0.46-0.80
Age at menarche	1.04	0.98-1.10

BMI, body mass index; CI, confidence interval; OR, odds ratio; Ref, reference.

reference (Table 4), the risk of osteoporosis was significantly lower in premenopausal women with the TC + CC genotype (OR; 95% CI = 0.62; 0.38-0.99). Age remained significantly associated with a higher risk of osteoporosis (1.17; 95% CI = 1.15-1.19). A borderline significant association was observed between overweight and lower risk of osteoporosis (OR = 0.81; 95% CI = 0.66-1.00). Obesity was significantly associated with a lower risk of osteoporosis (OR at 95% CI = 0.61; 0.46-0.80; Table 4).

DISCUSSION

In the current study, we aimed to broaden our knowledge of the relationship between osteoporosis and menopause with regard to SOX6 rs297325 SNP. The SOX6 rs297325 variant was not directly associated with osteoporosis. It, however, appeared to modulate the association between menopause and osteoporosis. That is, the risk of osteoporosis was higher in menopausal women with the TC + CC genotype but lower in premenopausal women with the TC + CC genotype. As far as we know, this is the first study to show a relationship between osteoporosis and menopause in relation to the SOX6 rs297325 variant. Nonetheless, determining the potential mechanistic link underlying the relationship between SOX6, menopausal status, and osteoporosis was beyond the scope of the current study.

Low BMD and subsequent bone loss, osteoporosis, and fractures are more common in postmenopausal women^{1-3,15,19,36-38} due to higher osteoclastic activities and gonadal deficiency.^{15,39} Bone mass is maintained by the balance between osteoclasts (bone resorbing cells) and osteoblasts (bone-forming cells).³⁹ Increases in both bone formation and resorption could, however, still result in bone loss because bone formation takes longer than bone resorption.³⁹ From an epidemiological viewpoint, estrogen is the main reason for the differences in the prevalence of osteoporosis between postmenopausal and premenopausal women.³⁸⁻⁴¹ During

menopause, estrogen levels fall sharply leading to increased bone resorption.^{42,43}

In line with our findings, the SOX6 rs297325 variant was not significantly associated with wrist BMD²⁸ in a G-WAS on a White population (both men and women) with a subsequent replication in a Chinese population (both men and women). In another G-WAS on White men and women, rs297325 was not univariately associated with BMD but was bivariately associated with BMD and BMI in men.³⁰

Age is an evident nonmodifiable primary risk factor for osteoporosis.^{1,11-14} This was proven in this study as it remained significantly associated with an increased risk of osteoporosis regardless of the genotype. The capacity of the bone tissue to synthesize bone decreases as age increases.¹⁴ Several combined factors including hormonal, biochemical, genetic, and environmental factors trigger bone loss attributed to age.⁴⁴

Overweight and obesity were associated with a lower risk of osteoporosis in several studies.^{1,11,13,45-48} Similar results were observed in our study. After stratification by the SOX6 rs297325 genotypes, these factors, however, remained significantly associated with osteoporosis only among those with the TC + CC genotype. Therefore, the association between BMI and osteoporosis might be prominent only in women having the TC + CC genotype. Higher mechanical loading on the skeleton, in addition to the capability of fat cells, to convert androgens to 17 β -estradiol are some of the reasons behind the decreased risk of osteoporosis in overweight and obese individuals.⁴⁵⁻⁴⁷

The limitation of the current study is that the findings were not compatible with any prior hypotheses and could be due to chance. Appropriate interpretations of apparent interactions require replication of findings in other studies. Our findings were, however, not replicated and should be interpreted cautiously until further research is conducted to replicate the results.

CONCLUSIONS

SOX6 rs297325 was not significantly associated with osteoporosis. It, however, might have modulated the association between menopause and osteoporosis. The risk of osteoporosis was higher in menopausal women with the TC + CC genotype but lower in premenopausal women with the TC + CC genotype. In the stratified analysis, age was significantly associated with a higher risk of osteoporosis regardless of the genotype, whereas overweight and obesity were associated with osteoporosis only among individuals with the TC + TT genotype. Our findings could provide molecular insights into preventing, predicting, diagnosing, and developing personalized treatments for osteoporosis in menopausal women. Further studies with regard to SOX6 rs297325, menopause, and osteoporosis are, however, recommended.

REFERENCES

1. Ivanova S, Vasileva L, Ivanova S, Peikova L, Obreshkova D. Osteoporosis: therapeutic options. *Folia Med (Plovdiv)* 2015;57:181-190.

2. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;285:785-795.
3. Sözen T, Özişik L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol* 2017;4:46.
4. Cauley JA. Public health impact of osteoporosis. *J Gerontol* 2013;68:1243-1251.
5. Johnell O, Kanis J. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726-1733.
6. Chen F-P, Huang T-S, Fu T-S, Sun C-C, Chao A-S, Tsai T-L. Secular trends in incidence of osteoporosis in Taiwan: a nationwide population-based study. *Biomed J* 2018;41:314-320.
7. Ioannidis JP, Ng MY, Sham PC, et al. Meta-analysis of genome-wide scans provides evidence for sex- and site-specific regulation of bone mass. *J Bone Miner Res* 2007;22:173-183.
8. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 2005;20:1185-1194.
9. Kanis J, Odén A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18:1033-1046.
10. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 2002;359:1929-1936.
11. Chang H-C, Hsieh C-F, Lin Y-C, et al. Does coffee drinking have beneficial effects on bone health of Taiwanese adults? A longitudinal study. *BMC Public Health* 2018;18:1273.
12. Khoo C, Woo J, Leung P, Kwok A, Kwok T. Determinants of bone mineral density in older postmenopausal Chinese women. *Climacteric* 2011;14:378-383.
13. Fawzy T, Muttappallymyalil J, Sreedharan J, et al. Association between body mass index and bone mineral density in patients referred for dual-energy X-ray absorptiometry scan in Ajman, UAE. *J Osteoporos* 2011;2011:876309.
14. Cristina de Sousa E Silva Araujo E, Pagotto V, Silveira EA. Bone mineral density in the noninstitutionalized elderly: influence of sociodemographic and anthropometric factors. *Curr Gerontol Geriatr Res* 2016;2016:4946593.
15. Mo D, Hsieh P, Yu H, et al. The relationship between osteoporosis and body composition in pre- and postmenopausal women from different ethnic groups in China. *Ethn Health* 2017;22:295-310.
16. Maddah M, Sharami SH, Karandish M. Educational difference in the prevalence of osteoporosis in postmenopausal women: a study in northern Iran. *BMC Public Health* 2011;11:845.
17. Langsetmo L, Hanley DA, Prior JC, et al. Dietary patterns and incident low-trauma fractures in postmenopausal women and men aged ≥ 50 y: a population-based cohort study. *Am J Clin Nutr* 2010;93:192-199.
18. Akhlaque U, Ayaz SB, Akhtar N, Ahmad N. Association of bone mineral density and body mass index in a cohort of Pakistanis: relation to gender, menopause and ethnicity. *Egypt Rheumatol* 2017;39:39-43.
19. Vijayakumar R, Büsselberg D. Osteoporosis: an under-recognized public health problem. *J Local Glob Health Sci* 2016;2016:2.
20. Lin Y-C, Pan W-H. Bone mineral density in adults in Taiwan: results of the Nutrition and Health Survey in Taiwan 2005-2008 (NAHSIT 2005-2008). *Asia Pac J Clin Nutr* 2011;20:283-291.
21. Mendoza N, Quereda F, Presa J, et al. Estrogen-related genes and postmenopausal osteoporosis risk. *Climacteric* 2012;15:587-593.
22. Chen Y, Xia RG. Screening and functional microarray analysis of differentially expressed genes related to osteoporosis. *Genet Mol Res* 2014;13:3228-3236.
23. Liu CT, Karasik D, Zhou Y, et al. Heritability of prevalent vertebral fracture and volumetric bone mineral density and geometry at the lumbar spine in three generations of the Framingham study. *J Bone Miner Res* 2012;27:954-958.
24. Howard GM, Nguyen TV, Harris M, Kelly PJ, Eisman JA. Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements: a twin study. *J Bone Miner Res* 1998;13:1318-1327.
25. Hunter DJ, De Lange M, Andrew T, Snieder H, MacGregor AJ, Spector TD. Genetic variation in bone mineral density and calcaneal ultrasound: a study of the influence of menopause using female twins. *Osteoporos Int* 2001;12:406-411.
26. Hunter D, De Lange M, Snieder H, et al. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. *J Bone Miner Res* 2001;16:371-378.

27. Villalobos-Comparán M, Jiménez-Ortega RF, Estrada K, et al. A pilot genome-wide association study in postmenopausal Mexican-Mestizo women implicates the RMND1/CCDC170 locus is associated with bone mineral density. *Int J Genomics* 2017;2017:5831020.
28. Tan L, Liu R, Lei S, et al. A genome-wide association analysis implicates SOX6 as a candidate gene for wrist bone mass. *Sci China Life Sci* 2010;53:1065-1072.
29. Park SE, Oh KW, Lee WY, et al. Association of osteoporosis susceptibility genes with bone mineral density and bone metabolism related markers in Koreans: the Chungju Metabolic Disease Cohort (CMC) study. *Endocr J* 2014;61:EJ14-0119.
30. Liu Y-Z, Pei Y-F, Liu J-F, et al. Powerful bivariate genome-wide association analyses suggest the SOX6 gene influencing both obesity and osteoporosis phenotypes in males. *PLoS One* 2009;4:e6827.
31. Hsu Y-H, Zillikens MC, Wilson SG, et al. An integration of genome-wide association study and gene expression profiling to prioritize the discovery of novel susceptibility Loci for osteoporosis-related traits. *PLoS Genet* 2010;6:e1000977.
32. Yang T-L, Guo Y, Liu Y-J, et al. Genetic variants in the SOX6 gene are associated with bone mineral density in both Caucasian and Chinese populations. *Osteoporos Int* 2012;23:781-787.
33. Lefebvre V, Behringer R, De Crombrughe B. L-Sox5, Sox6 and Sox9 control essential steps of the chondrocyte differentiation pathway. *Osteoarthritis Cartilage* 2001;9:S69-S75.
34. Smits P, Li P, Mandel J, et al. The transcription factors L-Sox5 and Sox6 are essential for cartilage formation. *Dev Cell* 2001;1:277-290.
35. Uusitalo H, Hiltunen A, Ahonen M, et al. Accelerated up-regulation of L-Sox5, Sox6, and Sox9 by BMP-2 gene transfer during murine fracture healing. *J Bone Miner Res* 2001;16:1837-1845.
36. Chowdhury S, Khatun S, Sarkar N. Comparison of bone mineral density between premenopausal and postmenopausal women in Bangladesh. *Bangladesh Med Res Counc Bull* 2001;27:48-54.
37. Jain V, Agrawal B, Varshney A, Biswas S. Prediction of bone mineral density by age, body mass index and menopausal status in middle socioeconomic status women of urban Kolar region of Bhopal. *JOSR J Dental Medical Sci* 2013;12:17-21.
38. Myong J-P, Kim H-R, Choi SE, Koo J-W. The effect of socioeconomic position on bone health among Koreans by gender and menopausal status. *Calcif Tissue Int* 2012;90:488-495.
39. Harada S, Rodan GA. Control of osteoblast function and regulation of bone mass. *Nature* 2003;423:349-355.
40. Järvinen TL, Kannus P, Sievänen H. Estrogen and bone—a reproductive and locomotive perspective. *J Bone Miner Res* 2003;18:1921-1931.
41. Fan J-Z, Yang L, Meng G-L, et al. Estrogen improves the proliferation and differentiation of hBMSCs derived from postmenopausal osteoporosis through notch signaling pathway. *Mol Cell Biochem* 2014;392:85-93.
42. Terauchi M. Bone and calcium metabolism in menopause transition [in Japanese]. *Clin Calcium* 2011;21:1353-1359.
43. Reginster J-Y, Neuprez A, Beaudart C, et al. Antiresorptive drugs beyond bisphosphonates and selective oestrogen receptor modulators for the management of postmenopausal osteoporosis. *Drugs Aging* 2014;31:413-424.
44. Demontiero O, Vidal C, Duque G. Aging and bone loss: new insights for the clinician. *Ther Adv Musculoskelet Dis* 2012;4:61-76.
45. Chin K-Y, Low N, Dewiputri W, Ima-Nirwana S. Factors associated with bone health in Malaysian middle-aged and elderly women assessed via quantitative ultrasound. *Int J Environ Res Public Health* 2017;14:736.
46. Wong SK, Chin K-Y, Suhaimi FH, Ahmad F, Ima-Nirwana S. The relationship between metabolic syndrome and osteoporosis: a review. *Nutrients* 2016;8:pii: E347.
47. Prabha V, Stanly AM. Effect of body mass index on bone mineral density. *Int J Community Med Public Health* 2017;2:380-383.
48. Barrera G, Bunout D, Gattás V, De la Maza MP, Leiva L, Hirsch S. A high body mass index protects against femoral neck osteoporosis in healthy elderly subjects. *Nutrition* 2004;20:769-771.