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Identification of Predictive factor for Bone Loss in Healthy Korean Adults

건강한 한국 성인에서 골소실 예측인자발굴

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Identification of Predictive factor for Bone Loss in Healthy Korean Adults

by

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A thesis submitted to the Department of Clinical Medical Sciences Graduate School in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Abstract

Introduction: There are several studies for predictive factors for osteoporotic fracture, while the risk factor for bone loss *per se* has not been well established. In the present study, I performed a study to evaluate the rate of bone loss at various skeletal sites and investigate the factors predictingaccelerated bone loss in Korean healthy adults.

Methods: The study population consisted of 547 male and 2,371 female (postmenopausal status 1,146) who had undergone bone mineral density (BMD) measurement at least twice between January 2003 and June 2011 in Seoul National University Hospital healthcare system Gangnam center. The BMD was measured with dual-energy X-ray absorptiometry at the multiple skeletal sites (at the lumbar spine, femur neck and total hip). Self-reported questionnaire, anthropometric and biochemical variables were obtained.

Results: The mean annual rate of BMD change at the lumbar spine, femur neck, and total hip were -0.56 %/year, -0.55 %/year, and -0.03 %/year, respectively (in male), -0.87 %/year, -0.91 %/year, and -0.40 %/year(in premenopausal female), -1.58 %/year, -1.38 %/year, and -0.96 %/year (in postmenopausal female), respectively. Total cholesterol and LDL cholesterol had positive effect on BMD at the lumbar spine in male (p=0.017 and p=0.002), whereas triglyceride was negative effect on BMD at the total hip in postmenopausal female (p=0.046) after adjustment for age, baseline BMD, and weight. Waist circumference and systolic blood pressure were positively associated with annual rate of BMD change at the femur neck in male (β=0.025, p=0.002 and 0.008, p=0.044, respectively). In addition, glycated hemoglobin seemed to accelerate bone loss at the femur neck in postmenopausal female (-0.215 ± 0.093, β ± SE, p=0.021).

To determine the effect of metabolic syndrome in the change of BMD, Icompared annual BMD changes in subjects with and without metabolic syndrome adjusted for age, baseline BMD, and weight. The rate of bone loss at the total hip was accelerated in male with metabolic syndrome

compared those without metabolic syndrome (-0.20% *Vs*. 0.01%, *p*=0.041).

Conclusion: Dyslipidemia, waist circumference, and blood pressure were associated with the rate of bone loss at the various skeletal sites. Mixed effects of these components for bone loss were not well established. Further study will be needed to evaluate the mechanism of association between metabolic syndrome and bone loss.

Keywords: Predictive factor, bone loss, metabolic syndrome

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Introduction

Osteoporotic fracture is amajor public health problem. The low bone mineral density (BMD) is known as a predictive factor for osteoporotic fractures[1]. Several clinical risk factors, such as age, low body-mass index, history of fragility fractures, a family history of fractures, taking glucocorticoids, and active cigarette smoking have been known be considered. [2].

Several demographic studies have been reported in Korea. A recent Korean cohort study (Ansung cohort) reported that prevalence of osteoporosis in adults living in the rural area was 13.1% for men and 24.3% for women[3].A previous study using the Forth Korea National Health and Nutrition Examination Survey (KNHANES IV) suggested that since early adult period, there was an accelerated phase of the bone loss at the femur in both gender and 60% or more of bone loss occurred before 50s[4]. In addition, a study based on the Korean Health Insurance Review Agency (HIRA) demonstrated a distinct increasing trend in medical burden of osteoporosis[5].Hence, the osteoporosis has become a major medical and socioeconomic problem in Korea.

The WHO Fracture Risk Assessment Tool (FRAX®) has been used to identify people at high risk of osteoporotic fractures. FRAX® is the easily accessible web-based calculator via algorithm using clinical risk factors following: age, sex, low body mass index, previous fragility fracture, parental history of hip fracture, current cigarette smoking, long term use of glucocorticoids over physiologic dose, rheumatoid arthritis, daily alcohol consumption over 3 units per day, and secondary osteoporosis[6, 7].

There are many studies about the predictive factors for fracture, while the risk factor for bone loss per se has not been well established. The bone loss over time in a repeated measured BMD will be an important factor to predict the fracture.The Study of Osteoporotic Fractures (SOF) suggested that there were "maintained", "expected", and "accelerated" bone loss groups in elderly women[8]. There were lower risk of fractures and mortality rates compared to those

which accelerate the loss of BMD in elderly women maintained BMD. The factors associated with accelerated bone loss were older age, more weight loss, diabetes mellitus, current smoking, and not taking of estrogen.

Recently, this has focused attention on the relationship of osteoporosis and cardiovascular disease. Further, the interest about metabolic syndrome characterized by several risk factors of cardiovascular disease has been increased[9-12].A recent study conducted in the USA reported that the metabolic syndrome was not an accelerating factor for BMD loss at the femur neck when stratified by BMI[9]. However, the Rancho Bernardo study demonstrated that there was a higher incidence of osteoporotic fractures in subjects with metabolic syndrome[10].The cross-sectional study in Korea reported that the lumbar spine BMD was significantly lower in women with metabolic syndrome than without metabolic syndrome[11]. On the other hand, a recent retrospective longitudinal study conducted in Korea suggested that metabolic syndrome could be a positive effects on bone mineral density by higher mechanical loading[13].

Acceleration of loss of BMD is associated with osteoporotic fracture. The aim of this study was to provide baseline rate of bone loss at different anatomical sites on repeated measures of BMD and to investigate the predictive factors on faster bone loss at the multiple skeletal sites in Korean healthy adults.

Subjects and Methods

Study population

This was a 8-year longitudinal health care center-based study. The study population consisted of 547 male and 2,371 female (postmenopausal status 1,146) who aged 40 years or older(Figure 1). All study population underwent BMD measurement at least twice for a health check-up between January 2003 and June 2011 in SeoulNational University Hospital healthcare system Gangnam center.

Exclusion criteria

Subjects who (1) did not complete the self-questionnaire, (2) currently being treated with anticancer drug or being diagnosed with cancer, (3) any medication for osteoporosis or hormonal replacement therapy (estrogen, selective estrogen-receptor modulators, bisphosphonate or calcitonin), (4) obscure information on menopausal status, (5) history of chronic renal failure, liver cirrhosis or thyroid disease, (6) being treated with medications known to effect on bone loss (anticonvulsants, steroids, thyroid hormone, anticoagulants), (7) had metabolic disorders known to affect bone mineral density were excluded.

Anthropometric measurements

All the subjects underwent anthropometric and blood pressure measurements. Waist circumference (cm), body weight (kg) and height (cm) were measured using standardized protocols. Body mass index (BMI, kg/m^2) was calculated as the ratio of weight (kg) to height square (m^2). Systolic and diastolic blood pressure (mmHg) weremeasured.

Clinical parameters

I checked for medical and medication history, lifestyle information and socioeconomic status (exercise duration, cigarette smoking, alcohol intake, income, education) using a standardized questionnaire. The following information was included in the questionnaire; parturition, time of menopause, hormonal replacement status. In addition, a gynecologist investigated again.

Biochemical parameters

Blood samples were collected after an overnight fast (≥12 hours). Complete blood count (with differential count) was measured using automated blood analysis equipment from Sysmex XE-2100. Serum Erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (hsCRP) were measured using the quantitative capillary photometry method (TEST-1) and the high sensitive latex coagulation method, respectively. Serum calcium was measured using an indirect ion-selective electrode method. Serum phosphorus was measured by molybdatereuction. Serum protein (Biuret method), serum albumin (bromcresol green assay), total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase/alanine aminotransferase (AST/ALT) were measured using Karmen method. Plasma gamma-glutamyltranspeptidase (GGT) was measured using γ-glutamyl-p-nitroanilide as substrate. Serum blood urea nitrogen (BUN, urease-GLDH method), creatinine (Jaffe method), total cholesterol (TC, cholesterol oxidase-peroxidase method), triglyceride (TG, GPO-PAP method), high density lipoprotein (HDL-C, homogeneous enzymatic assay), plasma glucose (Oxidase method), glycated hemoglobin (HbA1c, immunoturbidometry assay), thyroid-stimulating hormone (TSH, immunoradiometricassay), thyroxine (free T4) were measured in every subjects. For most female, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol were also measured. In some female, osteocalcin, 25-hydroxy vitamin D3 (25(OH) Vitamin D3) were measured using radioimmunoassay method and C-terminal telopeptide (CTX) was measured by

chemiluminescence immunoassay.

Bone densitometry

The bone mineral density (BMD) (g/cm^2) of the lumbar spine (L1-L4), femoral neck and total hip was measured by dual energy X-ray absorptiometry (DXA) using the Prodigy Advance (Lunar, General Electric, Madison, WI, USA). I used standard positioning and calibrated machine everyday as recommended by the manufacturer. The coefficient of variation (CV) of measurements were within 1%. All values were measured from the same machine and analyzed by the same software.

Definition of metabolic syndrome

The metabolic syndrome was defined by the Third Report on the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)[13]. Clinical diagnosis of metabolic syndrome was determined by combination of the following five components: (1) Hypertension (blood pressure ≥130/≥85 mmHg or taking antihypertensive medication); (2) high blood glucose level (fasting glucose level ≥100 mg/dL or drug treatment for diabetes mellitus); (3) abdominal obesity (waist circumference ≥90 cm for men and ≥80cm for women); (4) triglycerides ≥150 mg/dL; (5) high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women. The criteria of abdominal obesity were determined as the cutoff value by the Asia-Pacific region proposed from the International Diabetes Federation (IDF). Subjects who had three or more components were considered as having metabolic syndrome.

Statistical analysis

Summary statistics are presented as frequencies and percentages for categorical variables and as the mean ± standard deviation (SD) for continuous variables. Baseline characteristics were compared using Student's *t*-tests and Fisher's exact-test. For comparison between groups of sex, analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables was used.I calculated percent change in BMD (%/year BMD) as the difference between baseline and follow-up BMD, divided by baseline BMD, and multiplied by 100[14]. Low density lipoprotein cholesterol (LDL-C) was calculated as Freidewald formula: LDL = TC – HDL – TG/5 (mg/dL)[15].To investigate the relationship between annual rate of BMD change in the lumbar spine, femur neck, and total hip, univariate and multivariate linear regression analyses were performed.I comparedleast-square mean annual BMD changes in subjects with and without metabolic syndrome adjusted for age, baseline BMD, and weight.Two-sided *p*-values less than 0.05 were considered statistically significant. The results were analyzed with SPSS Statistics 20 (SPSS Inc., Armonk, NY).

Ethics statement

The study was approved by the institutional review board of Seoul National University Hospital (IRB number: H 1304 092 481).

Results

The baseline characteristics of 547 male, 1,225 premenopausal female and 1,146 postmenopausal female are shown in Table 1. The means for duration of follow-up of male, premenopausal female, and postmenopausal female were 29.3, 34.2 and 34.8months, respectively. The mean agefor male, premenopausal and postmenopausal female were 59.3, 47.4 and 57.8years old, respectively.

Figure 2 showed the annual rate of BMD change with aging at lumbar spine, femur neck and total hip of male, premenopausal and postmenopausal female.

The mean baseline BMD for male were 1.190 g/cm^2 at the lumbar spine, 0.923g/cm^2 at the femur neck, and 0.994g/cm^2 at the total hip, respectively (Table 2). Average annual percent BMD change for male were 0.56% loss per year at the lumbar spine, 0.55% loss per year at the femur neck, and 0.03% loss per year at the total hip, respectively. For premenopausal female, the mean baseline lumbar BMD, femur neck, and total hip BMD were higher than those of male, 1.194 g/cm2 at the lumbar spine, 0.925g/cm^2 at the femur neck, and 0.971g/cm^2 at the total hip, respectively. For postmenopausal female, the mean baseline BMD was lower than those of male and premenopausal female. For postmenopausal female, the mean annual percent BMDs loss were more than those of male and premenopausal female at lumbar spine, femur neck and total hip site.

Multivariate linear regression analyses were performed to determine which biochemical and metabolic parameters were associated with the annual rate of lumbar spine (Table 3). Age, baseline BMD, weight were adjusted as confounding factors. Serum creatinine was associated with accelerated bone loss at the lumbar spine (p=0.033), while total cholesterol and LDL cholesterol showed protective effects against bone loss at the lumbar spine(p=0.017 and p=0.002, respectively) in male. Annual change of height, ESR, serum creatinine, albumin and ALP were associated with accelerated bone loss at the lumbar spine in premenopausal female

(p=0.006, p<0.001, p=0.019, p=0.003, respectively). In postmenopausal female, annual change of weight had a protective effect against bone loss at the lumbar spine(p=0.001). Serum glucose showed positive effect on annual BMD change(p=0.033). ESR and serum creatininehad negative effects on annual rate of BMD at the lumbar spine in postmenopausal female as well as in premenopausal female(p=0.016 and p<0.001, respectively).

I performed the analysis for the annual rate of bone loss at the femur neck in male, premenopausal and postmenopausal female (Table 4). Waist circumference and systolic blood pressure were positively associated with the change of BMD at the femur neck in male (p=0.002 and p=0.044, respectively). Initial height and annual weight change rate showed a protective effect on annual rate of BMD change at the femur neck in postmenopausal female (p=0.030 and p=0.036, respectively). In postmenopausal female, annual height change and HbA1c were associated with bone loss at femur neck (p<0.001 and p=0.021, respectively). BUN was negativelyassociated with annual rate of femoral neck BMD in premenopausal female (p=0.045).

Table 5 showed that annual rate of BMD at the total hip were associated with multiple metabolic parameters. Initial height, serum phosphorus level and serum creatinine were associated with accelerated bone loss at total hip in male (p=0.002, p=0.018 and p=0.001, respectively). In premenopausal female, the serum calcium and BUN level had a negative impact on the annual rate of BMD at the total hip (p=0.014 and p=0.011, respectively). Annual weight change was a protective effect on annual rate of BMD at the total hip though triglyceride level was a negative effect in postmenopausal female (p<0.001 and p=0.046, respectively).

There was a significant association between annual rate of BMD at multiple skeletal sites and metabolic component such as TG, cholesterol, HbA1c, waist circumference and systolic blood pressure. Metabolic syndrome was based on the NCEP-ATP III definition (2005 revision). Baseline BMD at the lumbar spine, femur neck and total hip were lower in subjects with metabolic syndrome than those without metabolic syndrome(Table 6). Both in premenopausal female and postmenopausal female, baseline BMD at the femur neck was significantly lower in

subjects with metabolic syndrome than without metabolic syndrome.

Following adjustment for age, baseline BMD, weight, male subjects with metabolic syndrome showed 19% more bone loss at the total hip compared with those without metabolic syndrome (Table 7). For premenopausal female and postmenopausal female, annual rate of BMD at various sites were not associated with metabolic syndrome.

Discussion

The present study was to assess the predictive factorsfor bone loss at the multiple skeletal sites in healthy Korean adults.I found that the associations of annual rates of bone loss with serum total cholesterol, LDL cholesterol, creatinine and metabolic syndrome.

The baseline BMD at the lumbar spine was higher than other skeletal sites. Femoral bone loss was reliable for evaluate the risk for osteoporotic fracture of elderly person[16]. Because BMD at the spine may reflect degenerative changes such as osteoarthritis, osteophytes, sclerosis, aortic calcification, longitudinal studies for the rate of BMD change that had performed only at the lumbar spine could be error[18-20].

This study demonstrated that metabolic syndrome was at increased risk for rate of bone loss at the total hip in male after adjusted by age, weight and baseline BMD. Several clinical studies have been carried out for the correlation between metabolic syndrome and BMD[9-11, 21-23].

There are also controversy about the relationship between cardiovascular diseases and BMD. Von Muhlen D *et al*. suggested the metabolic syndrome affected on lower BMD at the femoral neck in men, but not in women (p=0.05)[10]. Similarly, Kim HY *et al*. demonstrated that femoral neck BMD was significantly lower in subjects with metabolic syndrome in men[22]. Result of the present study showed lower BMD at the total hip only in male with metabolic syndrome. When combined, these findings suggested that the men with metabolic syndrome may be a negative effect on BMD. However, these findings are in contrast to the results of Hwang DK *et al*[11]. These data suggested that vertebral BMD were lower in women with metabolic syndrome. Interestingly, the relationship between BMD and metabolic syndrome have been reported differently according to sex, menopausal status, or sites. As previously reported, gender has been proposed the effect on BMD[36]. It might be explained that fat mass and its distribution in the body have different association with BMD depending on the gender and age[24].

The mechanism for the association between the metabolic syndrome and bone metabolism could be described in relation to fat and bone. There are several studies that reported adiponectin from adipose tissue appeared to induce pro-inflammatory cytokines such as interleukin 1 and 6 in renal epithelial cells[25, 26]. In addition, adiponectin could activate nuclear factor-kappaB (NF-κB) [27]. Central obesity of metabolic syndrome may influence on the bone loss via adipokine and inflammation.

My results corresponded with the results of previous studies which reported that renal impairments affect the bone loss[28-30]. The surrogate marker for renal function, serum creatinine showed negative effects on the annual rate of BMD at lumbar spine and total hip in male and at lumbar spine in premenopausal and postmenopausal female. Although, chronic renal failure was excluded, my results demonstrated that renal function represented by the serum creatinine was associated with acceleration of bone loss.

In this study, waist circumference, as well as systolic blood pressure showed the protective effect on BMD at the femur neck in male. In postmenopausal female, higher HbA1c had a negative effect on BMD at the femur neck. As above, metabolic parameters such as serum total cholesterol, waist circumference, blood pressure, HbA1c showed the influence on the rate of change of BMD, thus, I performed a further analysis about the relevance of the metabolic syndrome and BMD change.

The present study suggested that total cholesterol and LDL cholesterol were a positive effect on BMD at the lumbar spine in male, while triglyceride level was associated with acceleration of bone loss at the total hip in postmenopausal female. Not been established for the effect of hyperlipidemia on bone mineral density. The clinical studies have been performed for the association between hypercholesterolemia and BMD [31-37]. Some suggested an association of hypercholesterolemia with accelerated bone loss[31-33], and others found a relationship between hypercholesterolemia and higher bone densities[34]. And there was an experimental evidence to support my results at the cellular level. Parhami F. *et al* suggested that the process

of cholesterol synthesis is a significant role in the differentiation of bone marrow stromal cells to osteoblasts[38]. This study may explain that the higher total cholesterol and LDL cholesterol was associated with the higher bone mass in lumbar spine in my results. On the other hand, others proposed that there was little association between hypercholesterolemia and change of BMD[35-37]. The association of hypercholesterolemia and bone loss remains in the hypothesis, further research for mechanism is needed.

This present study has some strengths. First, my study is 8-year longitudinal study, the longest follow-up period in Korea. This study is superior to several cross-sectional studies. Second, I examined annual rate of BMD change at various skeletal sites by gender and menstrual status. So, I found the differences according to gender and skeletal sites of the annual rate of BMD change and determined the predictive factors for accelerated bone loss.

Also, there are a few limitations in the present study. First, because the study population enrolled from health promotion center, there may have selection bias. These subjects might have more higher socioeconomic statuses and be more healthier than general population. Second, lifestyles and medical histories about chronic diseases depends on self-reported questionnaire, so, recall bias can be considered.

In summary, I described the annual rate of BMD at the various skeletal sites for healthy adults during 8 year observed period. The results obtained in the present study suggested that metabolic syndrome could facilitate the bone loss at total hip in male.

Since metabolic syndrome is a heterogeneous group of abdominal obesity, dyslipidemia, diabetes mellitus, hypertension, further study will be needed to trace the mechanisms.

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초록

서론: 골다공성 골절의 예측인자에 대한 여러 연구는 있으나 골소실 그 자체에 대한 위험인자는 잘 정립되어 있지 않다. 본 연구는 한국의 건강한 성인에서 빠른 골소실의 예측인자를 발굴하고자 여러 골격근의 골소실율을 조사한 연구이다.

방법: 서울대학교 병원 강남 건강검진센터에서 2003년 1월부터 2011년 6월까지 적어도 2회 이상 골밀도를 측정한 547명의 남성과 2,371명의 여성 (폐경한 여성 1,146명)에 대해 분석을 시행하였다. 골밀도는 이중 에너지 방사선 흡수계측법 (dual energy X-ray absorptiometry)으로 요추, 대퇴경부, 고관절에서 측정하였다. 음주, 흡연, 운동 등에 대한 자가설문조사와 신장, 체중, 혈압 등에 대한 인체 측정학적 정보 및 생화학적인 검사 정보를 이용하였다.

결과: 요추, 대퇴경부 및 고관절의 평균 연간 골밀도 변화율은 남성에서 각각 -0.56 %/년, -0.55 %/년, -0.03 %/년 이었고, 폐경 전 여성에서 -0.87 %/년, -0.91 %/년, -0.40 %/년이었으며, 폐경 후 여성에서는 -1.58 %/년, -1.38 %/년, -0.96 %/년이었다. 교란변수인 연령, 기저 골밀도, 체중을 보정하여 분석하였고, 중성 지방은 폐경 후 여성의 고관절 골밀도에는 부정적인 영향을 보이는 반면 (p=0.046), 총 콜레스테롤과 저밀도 지단백 콜레스테롤은 남성의 요추 골밀도에 긍정적인 영향을 보였다 (p=0.017 과p=0.002). 이상지질혈증 뿐 아니라 인체 측정학적 정보인 허리둘레, 수축기 혈압도 남성의 대퇴 경부 골밀도의 연간 변화율과 관련성이 있었다 (0.025 ± 0.002, β ± SE, p=0.002 and 0.008 ± 0.004, p=0.044). 당화 혈색소는 폐경 후 여성의 대퇴 경부의 골소실을 악화시키는 것으로 보였다 (-0.215 ± 0.093, β ± SE, p=0.021).

대사 질환과 관련된 인자가 골밀도와 관련성이 있어 대사증후군이 골밀도의 변화에 미치는 영향을 확인하기 위해 나이, 기저 골밀도, 체중을 보정한 후 공분산분석을 시행하였다. 대사증후군인 집단과 대사증후군이 없는 집단을 비교하였을 때, 대사증

후군인 남성에서 대퇴골의 골소실율이 높은 것을 확인하였다 (-0.20% *Vs.* 0.01%, p=0.041).

결론: 이상지혈증, 허리둘레, 혈압은 건강한 성인 남성과 여성의 골밀도 소실율에 영향을 주었다. 이러한 요인들의 골소실에 대한 혼합 효과는 정확히 밝히기가 힘들다. 대사증후군이 골소실에 영향을 주는 기전에 대한 추가적인 연구가 필요하겠다.

주요어: 예측인자, 골소실, 종단연구, 대사증후군

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Table 1. Clinical characteristics of the study population

	Male	Female	
		Premenopausal	Postmenopausal
Variables	(n =547)	(n=1,225)	(n=1,146)
Follow-up duration (months)	29.3 ± 16.8	34.2 ± 18.5	34.8 ± 18.4
Age (years)	59.3 ± 9.9	47.4 ± 3.4	57.8 ± 6.0
Height (cm)	169.0 ± 5.8	158.8 ± 4.8	156.9 ± 5.0
Weight (kg)	69.6 ± 8.3	55.1 ± 7.0	56.4 ± 6.7
BMI (kg/m^2)	23.0 ± 2.8	22.7 ± 3.0	22.8 ± 2.8
Waist circumference (cm)	83.5 ± 7.9	82.2 ± 8.1	81.6 ± 7.8
SBP (mmHg)	115.2 ± 15.8	114.5 ± 16.0	115.15 ± 16.2
DBP (mmHg)	73.9 ± 11.8	72.7 ± 11.8	73.0 ± 11.8
Δ Height/year	0.08 ± 0.56	0.06 ± 0.48	0.03 ± 0.48
Δ Weight/year	0.02 ± 1.44	0.05 ± 1.30	0.03 ± 1.24
Past medical history (n, (%))			
Diabetes mellitus	46 (8.4)	13 (1.1)	36 (3.1)
Hypertension	142 (26)	64 (5.2)	209 (18.2)
CAD	26 (4.8)	6 (0.5)	20 (1.7)
hypercholesterolemia	60 (11.0)	33 (2.7)	105 (9.2)
Osteoarthritis	15 (2.7)	26 (2.1)	60 (5.2)
Medication (n, %)			
Calcium	15 (2.7)	38 (3.1)	65 (5.7)
NSAIDs	12 (2.2)	11 (0.9)	22 (1.9)
Herbal medication	38 (6.9)	68 (5.6)	63 (5.5)
Regular exercise (n, %)	418 (76.4)	720 (58.8)	764 (66.7)
Alcohol (frequency/week)			

<1	102 (18.6)	207 (16.9)	144 (12.6)
1-2	154 (28.2)	242 (19.8)	159 (13.9)
3-4	51 (9.3)	19 (1.6)	49 (4.3)
≥5	32 (5.9)	11 (0.9)	10 (0.9)
Smoking status (n, %)			
Never smoker	133 (24.3)	1059 (86.4)	942 (82.2)
Ex-smoker	232 (42.4)	32 (2.6)	25 (2.2)
Current smoker	124 (22.7)	34 (2.8)	15 (1.3)
Education grade	3.97 ± 0.97	3.88 ± 0.76	3.45 ± 1.03
Income grade	4.14 ± 2.32	3.63 ± 2.19	3.34 ± 2.26
Parturition (n)	-	1.7 ± 0.9	2.0 ± 1.2
Laboratory data			
WBC ($x10^3/mm^3$)	5.8 ± 1.7	5.3 ± 1.4	5.1 ± 1.5
Hb (g/dL)	15.4 ± 1.1	12.8 ± 1.3	13.3 ± 0.9
Hct (%)	45.5 ± 3.2	39.0 ± 3.3	40.4 ± 2.7
Platelet ($x10^3/mm^3$)	225.0 ± 51.0	251.9 ± 55.9	242.2 ± 52.7
ESR (mm/hr)	7.7 ± 8.4	9.5 ± 9.0	12.9 ± 11.1
hs CRP (mg/L)	0.1 ± 0.4	0.1 ± 0.1	0.1 ± 0.2
Calcium (mg/dL)	9.3 ± 0.4	9.0 ± 0.4	9.3 ± 0.4
Phosphorus (mg/dL)	3.5 ± 0.5	3.7 ± 0.4	4.0 ± 0.5
Glucose (mg/dL)	103.5 ± 17.8	91.9 ± 11.8	95.8 ± 15.0
Hb A1c (%)	5.9 ± 0.7	5.6 ± 0.4	5.8 ± 0.5
Insulin (μIU/mL)	9.9 ± 4.6	8.5 ± 3.5	8.7 ± 4.2
BUN (mg/dL)	15.2 ± 3.3	12.2 ± 3.1	14.4 ± 3.5
Creatinine (mg/dL)	1.1 ± 0.1	0.9 ± 0.1	0.9 ±0.1
Total cholesterol (mg/dL)	195.8 ± 32.2	189.0 ± 30.8	207.8 ± 35.0

Triglyceride (mg/dL)	125.7 ± 77.5	84.0 ± 44.4	99.3 ± 52.6
LDL cholesterol (mg/dL)	124.3 ± 30.0	114.8 ± 28.1	132.0 ± 32.5
HDL cholesterol (mg/dL)	51.4 ± 13.1	60.8 ± 13.5	59.6 ± 14.2
Total protein (mg/dL)	7.2 ± 0.4	7.1 ± 0.4	7.2 ± 0.4
Albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.2	4.3 ± 0.2
Total bilirubin (mg/dL)	1.2 ± 0.4	0.9 ± 0.3	0.9 ± 0.4
ALP (IU/L)	62.5 ± 15.9	51.1 ± 13.1	68.9 ± 18.1
AST (IU/L)	26.5 ± 10.7	20.3 ± 8.0	24.2 ± 8.5
ALT (IU/L)	30.1 ± 19.2	17.4 ± 11.6	22.1 ± 11.9
GGT (IU/L)	44.8± 50.3	17.4 ± 12.5	22.9 ± 20.1
TSH (μIU/mL)	2.0 ± 1.7	2.1 ± 1.7	2.4 ± 4.1
Free T4 (ng/dL)	1.3 ± 0.3	1.2 ± 0.2	1.2 ± 0.3
LH(IU/L)	-	6.5 ± 5.4	25.2 ± 14.0
FSH(IU/L)	-	7.4 ± 7.6	58.6 ± 32.7
Estradiol (pg/mL)	-	116.5 ± 108.9	24.2 ± 48.0
25(OH) viatamin D3 (ng/mL)	-	19.5 ± 8.9	22.9 ± 8.3
CTX (ng/mL)	-	0.3 ± 0.1	0.5 ± 0.2
Osteocalcin (ng/mL)	-	14.0 ± 8.9	22.9 ± 8.3

Results expressed as mean ± standard deviation (SD) or frequency with percentage.

Table 2.Baseline and annual change in BMD for male and female.

	Male (n=547)	Female (n=2371)		
		Premenopausal (n=1,225)	Postmenopausal (n=1,146)	*p* value
Baseline BMD (g/cm2)				
Lumbar spine	1.190 ± 0.184	1.194 ± 0.152	1.081 ± 0.168	<0.001[a,c] 0.049[b]
Femur neck	0.923 ± 0.127	0.925 ± 0.109	0.864 ± 0.110	<0.001[b,c] 0.924[a]
Total hip	0.994 ± 0.134	0.971 ± 0.115	0.917 ± 0.116	<0.001[b,c] 0.001[a]
%Δ BMD/year				
Lumbar spine	-0.6 ± 1.8	-0.9 ± 1.8	-1.6 ± 2.1	<0.001[a,b,c]
Femur neck	-0.6 ± 1.4	-0.9 ± 1.6	-1.4 ± 1.6	<0.001[a,b,c]
Total hip	-0.0 ± 1.2	-0.4 ± 1.4	-1.00 ± 1.5	<0.001[a,b,c]

Results expressed as mean ± SD

p^a for male to premenopausal female; p^b for male to postmenopausal female; p^c for premenopausal to postmenopausal female

Table 3. Association of annual rate of lumbar spine BMD with biochemical and metabolic parameters after adjusted for age, baseline BMD andbaseline weight.

Variables	Male		Female			
			Premenopausal		Postmenopausal	
	β ± SE	p value	β ± SE	p value	β ± SE	p value
Height	-0.015 ± 0.021	0.494	-0.029 ± 0.014[a]	0.036	-0.025 ± 0.017	0.145
Waist circumference	0.003 ± 0.014	0.811	0.008 ± 0.008	0.303	0.008 ± 0.010	0.462
SBP	0.002 ± 0.007	0.789	-0.005 ± 0.004	0.225	0.001 ± 0.005	0.908
DBP	-0.005 ± 0.009	0.626	-0.003 ± 0.005	0.543	0.003 ± 0.007	0.690
Δ Height/year	-0.121 ± 0.193	0.531	-0.327 ± 0.126 [a]	0.010	0.062 ± 0.164	0.704
Δ Weight/year	-0.044 ± 0.075	0.557	-0.013 ± 0.048	0.792	0.201 ± 0.062 [a]	0.001
Education grade	0.122 ± 0.122	0.316	-0.011 ± 0.088	0.905	0.093 ± 0.087	0.290
Income grade	-0.013 ± 0.046	0.780	0.025 ± 0.028	0.366	-0.041 ± 0.035	0.241
Parturition	-	-	-0.056 ± 0.068	0.412	0.060 ± 0.065	0.357
Laboratory data						
WBC	0.005 ± 0.065	0.934	0.022 ± 0.043	0.617	0.091 ± 0.053	0.085

Hb	0.008 ± 0.100	0.934	0.013 ± 0.048	0.793	0.006 ± 0.083	0.943
Hct	-0.004 ± 0.035	0.899	-0.003 ± 0.019	0.890	-0.010 ± 0.028	0.712
Platelet	-0.001 ± 0.002	0.758	0.000 ± 0.001	0.715	0.002 ± 0.001	0.259
ESR	-0.017 ± 0.013	0.189	-0.019 ± 0.007 [a]	0.006	-0.017 ± 0.007 [a]	0.016
hs CRP	-0.040 ± 0.311	0.898	0.739 ± 0.495	0.136	0.787 ± 0.424	0.064
Calcium	-0.002 ± 0.299	0.995	-0.137 ± 0.169	0.415	-0.014 ± 0.198	0.944
Phosphorus	0.134 ± 0.220	0.543	-0.174 ± 0.143	0.224	-0.201 ± 0.167	0.229
Glucose	0.007 ± 0.006	0.247	0.007 ± 0.005	0.178	0.011 ± 0.005 [a]	0.033
Hb A1c	0.203 ± 0.161	0.209	-0.201 ± 0.168	0.232	0.070 ± 0.152	0.645
Insulin	-0.066 ± 0.034	0.054	-0.036 ± 0.033	0.281	0.050 ± 0.029	0.086
BUN	0.020 ± 0.033	0.552	-0.036 ± 0.020	0.076	-0.009 ± 0.022	0.697
Creatinine	-1.612 ± 0.755 [a]	0.033	-2.455 ± 0.594 [a]	<0.001	-2.609 ± 0.721 [a]	<0.001
Total cholesterol	0.008 ± 0.003 [a]	0.017	0.003 ± 0.002	0.213	0.002 ± 0.002	0.396
Triglyceride	-0.001 ± 0.001	0.584	0.001 ± 0.001	0.681	0.002 ± 0.001	0.269
LDL cholesterol	0.011 ± 0.003 [a]	0.002	0.004 ± 0.002	0.099	0.003 ± 0.002	0.212
HDL cholesterol	-0.006 ± 0.008	0.500	-0.004 ± 0.005	0.425	-0.008 ± 0.006	0.141
Total protein	0.263 ± 0.280	0.349	-0.063 ± 0.165	0.701	0.289 ± 0.187	0.122

Albumin	0.014 ± 0.455	0.975	-0.655 ± 0.279 [a]	0.019	0.028 ± 0.329	0.932
Total bilirubin	0.317 ± 0.260	0.223	-0.246 ± 0.181	0.175	-0.455 ± 0.221 [a]	0.039
ALP	0.000 ± 0.007	0.956	-0.014 ± 0.005 [a]	0.003	0.008 ± 0.004	0.069
AST	0.000 ± 0.010	0.974	-0.008 ± 0.008	0.325	0.001 ± 0.009	0.875
ALT	-0.003 ± 0.006	0.624	-0.003 ± 0.005	0.612	-0.003 ± 0.007	0.699
GGT	0.002 ± 0.002	0.382	-0.004 ± 0.005	0.412	0.000 ± 0.004	0.946
TSH	0.022 ± 0.076	0.767	0.022 ± 0.054	0.690	-0.019 ± 0.025	0.449
Free T4	-0.930 ± 0.518	0.073	-0.196 ± 0.386	0.613	0.286 ± 0.399	0.475
LH	-	-	-0.012 ± 0.032	0.714	0.001 ± 0.015	0.928
FSH	-	-	-0.042 ± 0.024	0.083	0.006 ± 0.006	0.314
Estradiol	-	-	0.001 ± 0.002	0.361	0.001 ± 0.001	0.970
25(OH) viatamin D3	-	-	0.008 ± 0.035	0.832	-0.119 ± 0.046 [a]	0.012
CTX	-	-	-5.505 ± 2.866	0.066	-3.297 ± 1.440 [a]	0.027
Osteocalcin	-	-	0.043 ± 0.055	0.435	0.069 ± 0.047	0.146

The enter method was applied to the model with the annual rate of lumbar spine BMD of male, premenopausal and postmenopausal female. This model was adjusted with age, baseline lumbar spine BMD and weight as confounding independent variables.

[a] $P<0.05$

Table 4.Association of annual rate of femur neck BMD with biochemical and metabolic parametersafter adjusted for age, baseline BMD and baseline weight..

Variables	Male		Female			
			Premenopausal		Postmenopausal	
	β ± SE	p value	β ± SE	p value	β ± SE	p value
Height	-0.023± 0.012	0.063	0.017 ± 0.009	0.064	0.023 ± 0.010 [a]	0.030
Waist circumference	0.025 ± 0.002 [a]	0.002	0.007 ± 0.005	0.186	-0.005 ± 0.006	0.467
SBP	0.008 ± 0.004 [a]	0.044	0.000 ± 0.003	0.863	0.001 ± 0.003	0.705
DBP	0.007 ± 0.005	0.178	-0.001 ± 0.004	0.853	0.001 ± 0.004	0.751
Δ Height/year	0.057 ± 0.110	0.604	-0.054 ± 0.084	0.518	-0.517 ± 0.099 [a]	<0.001
Δ Weight/year	-0.045 ± 0.043	0.292	0.050 ± 0.031	0.110	0.080 ± 0.038 [a]	0.036
Education grade	-0.045 ± 0.072	0.529	0.020 ± 0.057	0.718	0.065 ± 0.053	0.220
Income grade	0.016 ± 0.027	0.568	0.015 ± 0.019	0.425	0.026 ± 0.021	0.221
Parturition	-	-	0.039 ± 0.045	0.390	0.076 ± 0.039	0.055
Laboratory data						
WBC	-0.001 ± 0.037	0.988	0.018 ± 0.029	0.524	-0.016 ± 0.033	0.629

Hb	0.036 ± 0.057	0.526	-0.003 ± 0.032	0.916	0.031 ± 0.051	0.540
Hct	0.016 ± 0.020	0.414	0.004 ± 0.012	0.763	0.017 ± 0.017	0.333
Platelet	-0.001 ± 0.001	0.517	0.005 ± 0.001	0.966	-0.001 ± 0.001	0.441
ESR	0.005 ± 0.007	0.522	0.002 ± 0.005	0.736	-0.004 ± 0.004	0.310
hs CRP	0.115 ± 0.165	0.347	0.095 ± 0.308	0.759	0.013 ± 0.255	0.960
Calcium	0.045 ± 0.174	0.798	-0.083 ± 0.112	0.458	-0.009 ± 0.122	0.940
Phosphorus	-0.053 ± 0.128	0.676	0.100 ± 0.095	0.293	-0.169 ± 0.103	0.100
Glucose	0.004 ± 0.004	0.233	0.005 ± 0.004	0.185	0.001 ± 0.003	0.806
Hb A1c	-0.033 ± 0.092	0.717	-0.155 ± 0.112	0.164	-0.215 ± 0.093 [a]	0.021
Insulin	-0.006 ± 0.019	0.762	0.016 ± 0.021	0.440	0.009 ± 0.019	0.627
BUN	-0.008 ± 0.019	0.673	-0.027 ± 0.013 [a]	0.045	-0.022 ± 0.014	0.102
Creatinine	0.169 ± 0.441	0.703	0.632 ± 0.396	0.111	0.079 ± 0.446	0.859
Total cholesterol	0.003 ± 0.002	0.182	0.001 ± 0.001	0.659	-0.001 ± 0.001	0.391
Triglyceride	0.000 ± 0.001	0.583	-0.001 ± 0.001	0.168	0.000 ± 0.001	0.690
LDL cholesterol	0.002 ± 0.002	0.368	0.002 ± 0.001	0.273	-0.002 ± 0.001	0.266
HDL cholesterol	0.009 ± 0.005	0.076	-0.002 ± 0.003	0.579	0.003 ± 0.003	0.460
Total protein	0.165 ± 0.163	0.312	-0.055 ± 0.109	0.615	0.049 ± 0.115	0.672

Albumin	0.099 ± 0.265	0.710	-0.246 ± 0.185	0.186	0.184 ± 0.203	0.364
Total bilirubin	0.143 ± 0.152	0.345	-0.015 ± 0.120	0.902	-0.095 ± 0.136	0.484
ALP	-0.001 ± 0.004	0.836	-0.001 ± 0.003	0.788	0.004 ± 0.003	0.096
AST	0.004 ± 0.006	0.500	-0.001 ± 0.005	0.848	-0.003 ± 0.006	0.618
ALT	0.003 ± 0.003	0.307	0.000 ± 0.004	0.966	-0.004 ± 0.004	0.304
GGT	0.002 ± 0.001	0.097	-0.001 ± 0.003	0.651	0.000 ± 0.002	0.854
TSH	0.059 ± 0.044	0.184	-0.027 ± 0.037	0.470	0.029 ± 0.016	0.068
Free T4	0.025 ± 0.305	0.934	-0.384 ± 0.264	0.146	0.192 ± 0.251	0.446
LH	-	-	-0.010 ± 0.024	0.684	-0.003 ± 0.009	0.772
FSH	-	-	0.002 ± 0.018	0.905	-0.002 ± 0.004	0.637
Estradiol	-	-	-0.001 ± 0.001	0.444	-0.001 ± 0.003	0.626
25(OH) viatamin D3	-	-	0.011 ± 0.031	0.715	0.034 ± 0.029	0.249
CTX	-	-	-2.803 ± 2.940	0.350	-1.286 ± 1.016	0.212
Osteocalcin	-	-	-0.009 ± 0.049	0.848	-0.021 ± 0.029	0.465

The enter method was applied to the model with the annual rate of femur neck BMD of male, premenopausal and postmenopausal female. This model was adjusted with age, baseline femur neck BMD and weight as confounding independent variables.

[a]$P<0.05$

Table 5.Association of annual rate of total hip BMD with biochemical and metabolic parametersafter adjusted for age, baseline BMD and baseline weight.

Variables	Male		Female			
			Premenopausal		Postmenopausal	
	β ± SE	p value	β ± SE	p value	β ± SE	p value
Height	-0.031 ± 0.010[a]	0.002	-0.012 ± 0.009	0.176	0.000 ± 0.010	0.966
Waist circumference	0.008 ± 0.007	0.226	0.009 ± 0.005	0.072	0.004 ± 0.006	0.481
SBP	0.002 ± 0.003	0.614	0.001 ± 0.002	0.566	0.001 ± 0.003	0.631
DBP	0.002 ± 0.004	0.646	0.003 ± 0.003	0.341	0.003 ± 0.004	0.470
Δ Height/year	0.076 ± 0.092	0.412	0.248 ± 0.078 [a]	0.002	-0.096 ± 0.092	0.294
Δ Weight/year	-0.071 ± 0.036	0.074	0.017 ± 0.030	0.558	0.178 ± 0.034 [a]	<0.001
Education grade	0.024 ± 0.059	0.683	0.033 ± 0.054	0.548	0.043 ± 0.046	0.350
Income grade	0.015 ± 0.023	0.510	0.026 ± 0.017	0.132	0.012 ± 0.019	0.531
Parturition	-	-	-0.060 ± 0.042	0.157	0.049 ± 0.036	0.175
Laboratory data						
WBC	0.007 ± 0.031	0.828	0.009 ± 0.027	0.737	-0.020 ± 0.030	0.494

Hb	0.078 ± 0.048	0.103	-0.042 ± 0.030	0.157	-0.018 ± 0.046	0.704
Hct	0.027 ± 0.017	0.101	-0.015 ± 0.012	0.197	-0.003 ± 0.016	0.874
Platelet	0.001 ± 0.001	0.790	0.001 ± 0.001	0.289	0.001 ± 0.001	0.405
ESR	-0.002 ± 0.006	0.702	0.001 ± 0.004	0.895	0.003 ± 0.004	0.511
hs CRP	0.062 ± 0.148	0.676	-0.152 ± 0.286	0.597	0.193 ± 0.235	0.410
Calcium	-0.255 ± 0.146	0.081	-0.259 ± 0.105 [a]	0.014	-0.050 ± 0.111	0.651
Phosphorus	-0.253 ± 0.107 [a]	0.018	-0.061 ± 0.089	0.493	-0.164 ± 0.094	0.081
Glucose	0.004 ± 0.003	0.141	-0.001 ± 0.003	0.872	0.000 ± 0.003	0.892
Hb A1c	0.017 ± 0.077	0.826	-0.062 ± 0.105	0.553	-0.039 ± 0.085	0.651
Insulin	-0.017 ± 0.017	0.329	0.000 ± 0.020	0.993	-0.012 ±0.017	0.488
BUN	0.019 ± 0.016	0.246	-0.032 ± 0.012 [a]	0.011	-0.010 ± 0.012	0.418
Creatinine	-1.245 ± 0.367 [a]	0.001	0.015 ± 0.373	0.967	-0.545 ± 0.406	0.180
Total cholesterol	0.002 ± 0.002	0.133	-0.001 ± 0.001	0.250	0.001 ± 0.001	0.473
Triglyceride	-0.001 ± 0.001	0.139	0.001 ± 0.001	0.945	-0.002 ± 0.001	0.046
LDL cholesterol	0.003 ± 0.002	0.138	-0.001 ± 0.001	0.469	0.001 ± 0.001	0.559
HDL cholesterol	0.007 ± 0.004	0.089	-0.003 ± 0.003	0.265	0.005 ± 0.003	0.105
Total protein	0.219 ± 0.137	0.111	0.013 ± 0.103	0.899	0.140 ± 0.105	0.182

Albumin	0.157 ± 0.223	0.480	-0.249 ± 0.174	0.154	0.188 ± 0.185	0.308
Total bilirubin	0.040 ± 0.127	0.756	-0.152 ± 0.113	0.177	-0.081 ± 0.124	0.516
ALP	-0.002 ± 0.003	0.631	-0.003 ± 0.003	0.351	0.003 ± 0.002	0.192
AST	0.001 ± 0.005	0.898	-0.004 ± 0.005	0.362	-0.002 ± 0.005	0.647
ALT	0.002 ± 0.003	0.383	-0.003 ± 0.003	0.326	-0.008 ± 0.004	0.063
GGT	0.001 ± 0.001	0.185	-0.001 ± 0.003	0.800	-0.003 ± 0.002	0.231
TSH	0.012 ± 0.038	0.746	-0.011 ± 0.035	0.754	0.017 ± 0.014	0.238
Free T4	-0.218 ± 0.258	0.400	-0.002 ± 0.249	0.995	0.154 ± 0.230	0.504
LH	-	-	0.002 ± 0.019	0.918	0.003 ± 0.008	0.673
FSH	-	-	0.007 ± 0.014	0.613	0.000 ± 0.003	0.977
Estradiol	-	-	0.000 ± 0.001	0.669	0.001 ± 0.002	0.658
25(OH) viatamin D3	-	-	0.024 ± 0.026	0.362	0.031 ± 0.025	0.230
CTX	-	-	-0.820 ± 1.628	0.619	-0.465 ± 0.823	0.575
Osteocalcin	-	-	-0.007 ± 0.042	0.864	0.020 ± 0.027	0.456

The enter method was applied to the model with the annual rate of total hip BMD of male, premenopausal and postmenopausal female. This model was adjusted with age, baseline total hip BMD and weight as confounding independent variables.

[a]*P*<0.05

Table 6. Clinical characteristics according to themetabolic syndrome status at baseline

Variables	Metabolic syndrome(+)	Metabolic syndrome(-)	*p*
Male	n=111	n=436	
Baseline BMD (g/cm^2)			
Lumbar spine	1.203 ± 0.171	1.149 ± 0.186	0.005
Femur neck	0.957 ± 0.124	0.919 ± 0.127	0.004
Total hip	1.026 ± 0.129	0.986 ± 0.135	0.004
Age (years)	58.8 ± 9.7	57.9 ± 9.8	0.422
Height (cm)	168.3 ± 5.9	169.1 ± 5.7	0.197
Weight (kg)	72.3 ± 9.5	68.9 ± 7.8	< 0.001
BMI (kg/m^2)	24.2 ± 3.0	22.7 ± 2.7	< 0.001
Waist circumference (cm)	87.3 ± 8.6	82.5 ± 7.4	< 0.001
SBP (mmHg)	121.2 ± 16.1	113.6 ± 15.3	< 0.001
DBP (mmHg)	78.5 ± 12.8	72.6 ± 11.3	< 0.001
Abdominal obesity (n, %)	48 (43.2)	46 (10.6)	< 0.001
Hypertension (n, %)	87 (78.4)	136 (31.2)	< 0.001
Hyperglycemia (n,%)	95 (85.6)	167 (38.3)	< 0.001
Hypertriglyceridemia (n, %)	78 (70.3)	93 (21.3)	< 0.001
Low HDL cholesterol (n, %)	52 (46.8)	37 (8.5)	< 0.001
Premenopausal	n=134	n=1091	
Baseline BMD (g/cm^2)			
Lumbar spine	1.193 ± 0.148	1.179 ± 0.150	0.304
Femur neck	0.943 ± 0.107	0.923 ± 0.109	0.044
Total hip	0.997 ± 0.116	0.968 ± 0.114	0.005
Age (years)	46.9 ± 3.5	45.9 ± 3.2	0.001

Height (cm)	158.7 ± 5.4	158.8 ± 4.7	0.812
Weight (kg)	58.9 ± 7.9	54.6 ± 6.7	< 0.001
BMI (kg/m^2)	24.3 ± 3.1	22.5 ± 3.0	< 0.001
Waist circumference (cm)	87.0 ± 6.9	81.6 ± 8.1	< 0.001
SBP (mmHg)	124.3 ± 17.8	113.3 ± 15.4	< 0.001
DBP (mmHg)	79.0 ± 12.7	71.9 ± 11.4	< 0.001
Abdominal obesity (n, %)	120 (89.6)	564 (51.7)	<0.001
Hypertension (n, %)	98 (73.1)	204 (18.7)	< 0.001
Hyperglycemia (n,%)	68 (50.7)	103 (9.4)	< 0.001
Hypertriglyceridemia (n, %)	58 (43.3)	45 (4.1)	< 0.001
Low HDL cholesterol (n, %)	94 (70.1)	172 (15.8)	< 0.001
Postmenopausal	n=263	n=883	
Baseline BMD (g/cm^2)			
Lumbar spine	1.051 ± 0.171	1.071 ± 0.152	0.072
Femur neck	0.852 ± 0.108	0.868 ± 0.110	0.039
Total hip	0.916 ± 0.113	0.918 ± 0.116	0.821
Age (years)	58.6 ± 6.4	55.7 ± 5.7	< 0.001
Height (cm)	156.4 ± 5.1	157.0 ± 4.9	0.087
Weight (kg)	58.7 ± 7.0	55.6 ± 6.5	< 0.001
BMI (kg/m^2)	23.8 ± 2.5	22.4 ± 2.8	< 0.001
Waist circumference (cm)	85.7 ± 6.6	81.6 ± 7.9	< 0.001
SBP (mmHg)	122.0 ± 17.2	113.0 ± 15.2	< 0.001
DBP (mmHg)	77.8 ± 11.8	71.5 ± 11.4	< 0.001
Abdominal obesity (n, %)	216 (82.1)	433 (49.0)	<0.001
Hypertension (n, %)	187 (71.1)	215 (24.3)	< 0.001
Hyperglycemia (n,%)	172 (65.4)	127 (14.4)	< 0.001

Hypertriglyceridemia (n, %)	145 (55.1)	85 (9.6)	< 0.001
Low HDL cholesterol (n, %)	159 (60.5)	140 (15.9)	< 0.001

Results were presented as the mean ± SD or as numbers and percentages. Chi-square tests for categorical data, and Student's t tests for continuous variables.

Table 7.Comparison of rates of annual change at the lumbar spine, femoral neck, and total hip between subjects with and without metabolic syndrome.

Annual rates of BMD	Metabolic syndrome(+)	Metabolic syndrome(-)	*p* value
Male	n=111	n=436	
Lumbar spine	0.7 ± 0.2	1.1 ± 0.1	0.089
Femur neck	-0.5 ± 0.1	-0.6 ± 0.1	0.704
Total hip	-0.2 ± 0.1	0.0 ± 0.1	0.041
Premenopausal female	n=134	n=1091	
Lumbar spine	-0.4 ± 0.2	-0.0 ± 0.1	0.079
Femur neck	-1.0 ± 0.1	-0.9 ± 0.0	0.834
Total hip	-0.5 ± 0.1	-0.4 ± 0.0	0.793
Postmenopausal female	n=263	n=883	
Lumbar spine	-0.6 ± 0.2	-0.8 ± 0.1	0.157
Femur neck	-1.4 ± 0.1	-1.4 ± 0.1	0.516
Total hip	-1.0 ± 0.1	-0.9 ± 0.1	0.390

Resultspresentedmeans (± standard error). Multivariate-adjusted least-square mean annual BMD changes of subjects with and without metabolic syndrome were compared by ANCOVA adjusted by age, baseline BMD, and weight.

BMD bone mineral density

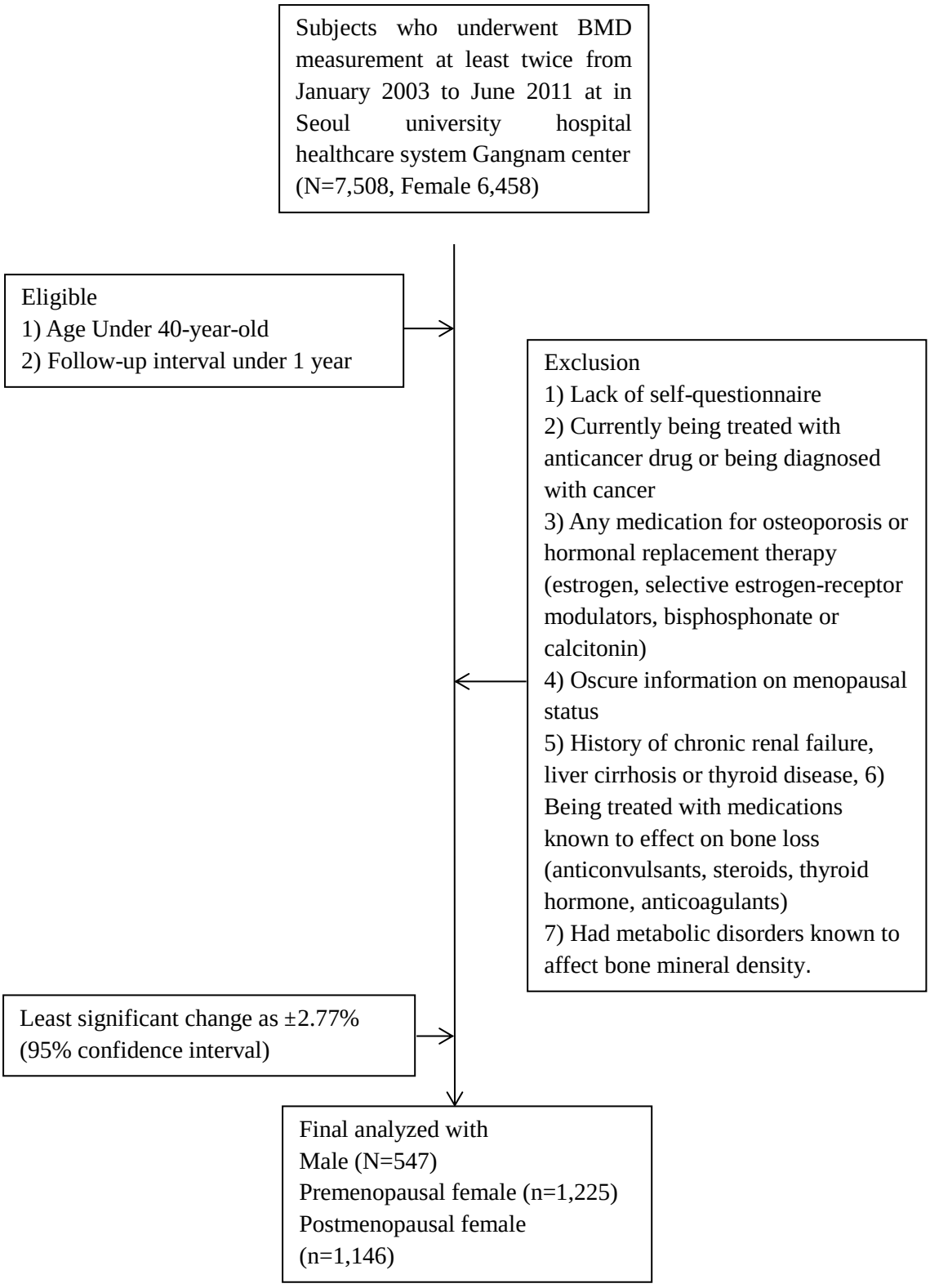
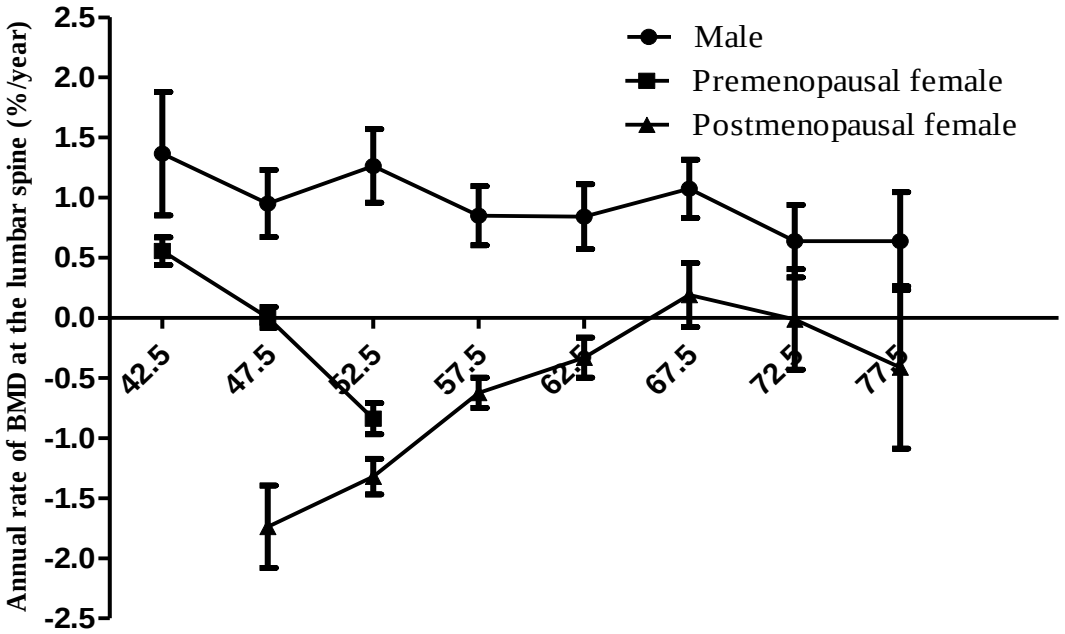
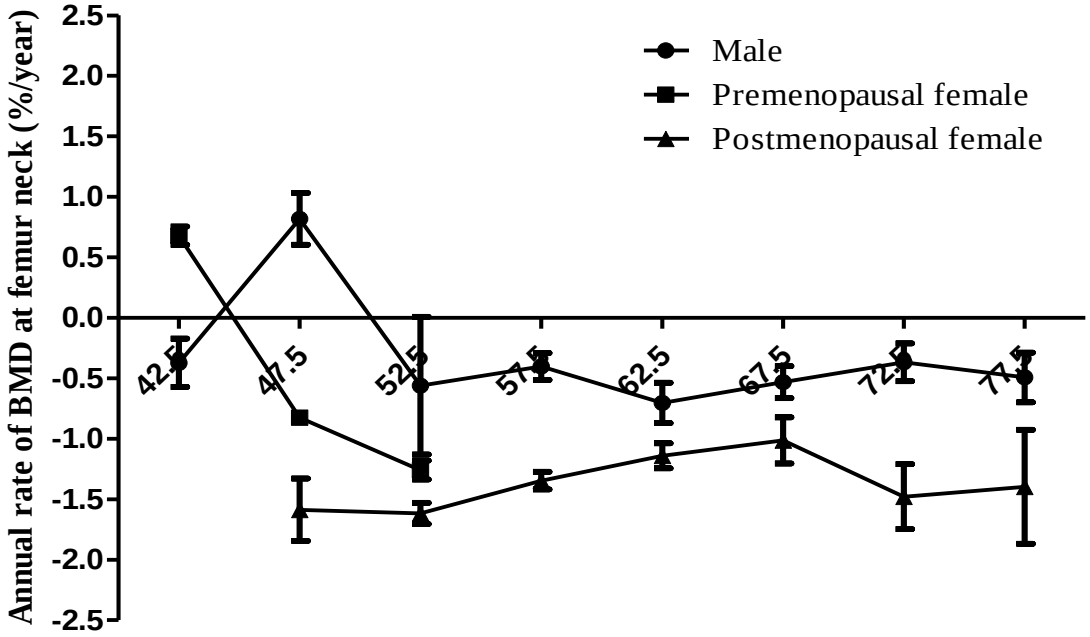


Figure1.Study population

A


Annual rate of BMD at the lumbar spine (%/year)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
42.5
47.5
52.5
57.5
62.5
67.5
72.5
77.5
Male
Premenopausal female
Postmenopausal female

B.


Annual rate of BMD at femur neck (%/year)
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
47.5
52.5
62.5
67.5
Male
Premenopausal female
Postmenopausal female

C

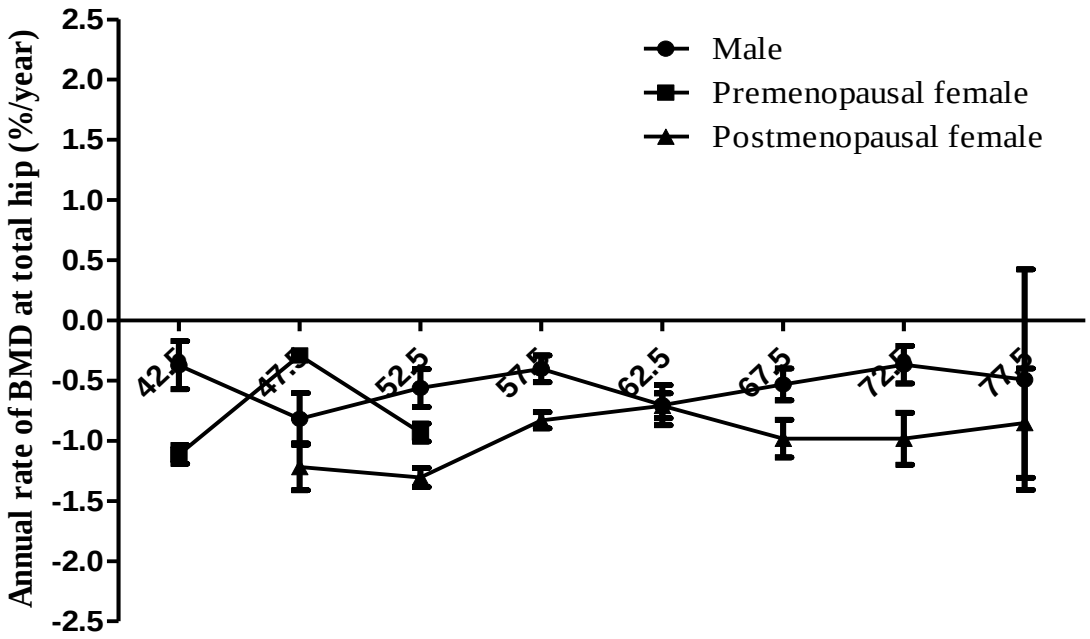


Figure 2. Annual rate of BMD change for each age group of male, premenopausal, and postmenopausal female at the multiple skeletal sites.

A. Lumbar spine, B. Femur neck, C.Total hip