의학석사 학위논문

한국 중년 남성에서 흡연량, 폐 기능 및 골 밀도의 관계 : 2008-2011 년 국민 건강 영양 조사

The relationships between Smoking amount, pulmonary function, and bone mineral density in middle-aged Korean Men: KNHANES 2008-2011

2016 년 02 월

서울대학교 대학원

의학과 중개의학 전공

이 지 현

A thesis of the Master's degree

The relationships between Smoking amount, pulmonary function, and bone mineral density in middle-aged Korean Men: KNHANES 2008-2011

한국 중년 남성에서 흡연량, 폐 기능 및 골 밀도의 관계 : 2008-2011 년 국민 건강 영양 조사

February 2016

The Department of Internal medicine,

Seoul National University

College of Medicine

Ji Hyun Lee

ABSTRACT

The relationships between smoking amount, pulmonary function and bone mineral density in middle-aged Korean Men : KNHANES 2008-2011

Ji Hyun Lee
Department of Medicine
Degree of Master of Science
in Translational medicine
The Graduate School Seoul National University

Introduction: Smoking induces bone loss; however, data on the relationship between smoking amount and bone mineral density (BMD) are lacking. Age and pulmonary function can affect BMD. We investigated the relationships between pack-years (PY) of smoking, pulmonary function, and BMD in middle-aged Korean men (50-64 years).

Methods: This cross-sectional study used data from the Korean National Health and Nutrition Examination Survey, 2008-2011. All subjects underwent BMD measurements using dual energy X-ray absorptiometry and pulmonary function tests using standardized spirometry.

Results: Herein, 388 never-smokers and 1088 ever-smokers were analyzed. PY of smoking negatively correlated with total hip BMD ($r=-0.083$; $p=0.006$) after adjusting for age and body

mass index (BMI). Ever-smokers were classified into 3 groups according to PY of smoking; the highest tertile (n=482) showed a significantly lower total hip bone mass than the lowest tertile (n=214) after adjusting for confounding factors (age, BMI, FEV_1, alcohol consumption, physical activity, and vitamin D) that could affect bone metabolism (<15 PY, 1.137±0.010; 15-30 PY, 1.123±0.007; ≥ 30 PY, 1.104±0.006 g/cm2; p=0.007). Forced expiratory volume in 1 second (FEV_1) and Forced vital capacity (FVC) positively correlated with femur neck BMD (r=0.069, p=0.024; r=0.113, p=0.027, respectively). No significant relationship was observed between FEV_1 and FVC tertiles and BMD at all other sites after adjusting for age and BMI.

Conclusions: Smoking for >30 PY was significantly associated with low hip BMD after adjusting for pulmonary function in middle-aged Korean men. Long-term smoking may be a risk factor for bone loss in middle-aged men, independent of age, BMI, and pulmonary function.

Keywords: Smoking, Bone density, Vital Capacity
Student number: 2014-21167

CONTENTS

Abstract i
Contents iii
List of tables and figures iv

Introduction 1
Materials and Methods 5
Results 9
Discussion 18
References 23
Abstract in Korean 26

LIST OF TABLES AND FIGURES

Table 1 Clinical characteristics of study subjects according to smoking history.....10

Table 2 Partial correlations between pack years of smoking, pulmonary function, and BMD..... 11

Table 3 Clinical Characteristics of ever smokers according to smoking pack years..... 13

Figure 1 Adjusted mean BMD at TH (A), FN (B), and LS (C) of ever smokers according to smoking amount.....14

Table 4 Comparison of age and BMI adjusted pulmonary function and BMD between never smoker and different PY smoking groups.....15

Table 5 BMD according to FVC tertile in ever-smokers.....16

Figure 2 Odds ratios for low bone density according to pack years of smoking.....17

LIST OF ABBREVIATIONS

BMD Bone mineral density, *WHO* World Health Organization,

KNHANES Korea National Health and Nutrition Examination

study, *BMI* Body mass index, *WC* waist circumference

TH total hip, *LS* lumbar spine, FN femur neck,

SBP systolic blood pressure, *DBP* diastolic blood pressure,

FPG fasting plasma glucose, *TC* total cholesterol,

TG total triglyceride, *HDL* high-density lipoprotein cholesterol,

25(OH)D 25-hydroxy vitamin D,

FEV_1 Forced expiratory volume in 1 second,

FVC Forced vital capacity, *BMD* Bone mineral density,

PY Pack-years of smoking,

HDL high-density lipoprotein cholesterol,

NCEP National Cholesterol Education Program,

MetS metabolic syndrome,

ANOVA analysis of variance, ANCOVA analysis of covariance.

INTRODUCTION

Osteoporosis is a common and complex disorder characterized by reduced bone mineral density (BMD), deterioration of bone integrity, skeletal fragility, and increased risk of fractures. It may occur owing to peak bone mass that is lower than normal values and bone loss that is greater than normal levels. Osteopenia and osteoporosis are diagnosed based on the BMD criteria of the World Health Organization (WHO) (osteopenia: T−score between −1.0 and −2.5; osteoporosis: T−score below −2.5, at any site from among the lumbar spine, femoral neck, or total hip) [1]. Osteoporosis is a rapidly increased health problem and its incidence increases with age. It affects men as well as women. However, osteoporosis in men remains underdiagnosed and the prevalence is increasing.

According to one study, an estimated 2.0 million adult men in the United States were living with osteoporosis in 2010 [2]. The prevalence of osteoporosis in Korea is 7.3% for men aged 50 years and older, as per the Korea National Health and Nutrition Examination Survey (KNHANES), 2008–2011 [3]. According to a prospective community−based cohort study in Korea that consisted of 1,547 men aged 40−79, the crude prevalence of osteoporosis was

13.1% for men, based on the World Health Organization (WHO) criteria [4].

Several factors are thought to increase the risk of osteoporosis and osteoporotic fracture including aging, hypogonadism and menopause, history of fracture, glucocorticoid therapy, parenteral history of hip fracture, low body weight, rheumatoid arthritis, chronic liver disease, endocrine disorder such as diabetes mellitus, thyrotoxicosis, and primary hyperparathyroidism. Many lifestyle habits have been associated with increased risk of osteoporosis included active or passive smoking, alcohol (3 or more drinks/day), low calcium intake, vitamin D insufficiency, high caffeine intake, inadequate physical activity, immobilization, falls, malabsorption, and medications (anticonvulsants, cancer chemotherapeutic drug, and aromatase inhibitors) [1].

Smoking is well-established risk factor that induces bone loss as a secondary cause of osteoporosis. It reduces the BMD and increases the risk of fractures [5-7]. Moreover, a decline of BMD in smokers is reported to be higher in men than in women. The deleterious effects of smoking were 50-300% higher in men than women and were most pronounced in the older subjects aged over 60 years [6, 8-10]. Elderly men and women who smoke experience considerable

bone loss [11]. Many cohort studies have included older individuals aged 65 years or more. A study of osteoporotic fractures in men recruited from community-dwellings aged 65 years or more [12], Gothenburg I cohorts including men and women aged 70 years or above [13], and women aged 75 years or older were analyzed in the Sheffield cohort study conducted in the United Kingdom [14]. However, there is a lack of data focusing on middle-aged men.

Smoking leads to a decline in pulmonary function [15]. Impairment of lung function has been known to be associated with osteoporosis or fracture. Low BMD is prevalent in patients with chronic obstructive lung diseases with airflow limitations [16-18]. Furthermore, low forced expiratory volume in 1 s (FEV_1) was shown as an independent risk factor for decreased bone mass [18]. However, the relationship between FEV_1 and BMD is not in accordance with several studies [19, 20]. Aging and pulmonary function could be significant confounding factors that affect bone mass and lead to osteoporosis in smokers. Data on the relationship between a specific amount of smoking and significant bone loss are limited.

Therefore, we aimed to study the effect of smoking amount on BMD in middle-aged Korean men considering several confounding

factors such as age and pulmonary function that might affect bone mass.

MATERIALS AND METHODS

1. Study participants and data collection

Our study was a cross-sectional investigation using data from the KNHANES, 2008-2011, conducted by the Korea Centers for Disease Control and Prevention. The KNHANES is a nationwide survey designed to evaluate annually the health and nutritional status of the Korean population since 1998. The study included middle-aged Korean men, 50-64 years; all subjects underwent dual energy X-ray absorptiometry and pulmonary function tests using standardized spirometry.

Subjects with a history of thyroid or liver disease, malignancy, rheumatoid arthritis, and those who were receiving anti-osteoporosis medications affecting bone metabolism were excluded.

The subjects were interviewed to collect data on their sex, age, smoking and alcohol history, physical activity (PA), and medical conditions. Trained staff measured height, weight, waist circumference, and blood pressure using standard protocols. Detailed information for collecting data is available on the KNHANES website [21]. Alcohol consumption was indicated as

"yes" when the subjects had more than 3 units of alcohol per day. The PA level was evaluated using the International Physical Activity Questionnaire (IPAQ) by WHO [22]. The PA of the group was categorized into 3 subgroups: high intensity, moderate intensity, and walking. High-intensity PA was defined as a high intensity exercise, for at least 20 min, more than 3 times a week. Moderate-intensity PA or walking was defined as a moderate intensity exercise or walking, for at least 30 min, more than 5 times a week.

2. BMD and pulmonary function test

BMD was measured at the lumbar spine (LS), L1-4, and the femur using dual-energy X-ray absorptiometry (Hologic Inc., USA). Spirometry (SensorMedics, USA) was performed as per the American Thoracic Society/European Respiratory Society criteria for standardization.

Pulmonary function was assessed on the basis of the FEV_1, Forced vital capacity (FVC), and the percentage predicted values for FEV_1 and FVC. The maximum value of FEV_1 and FVC was obtained from at least three acceptable tests.

3. Smoking history

Subjects, based on their smoking history, were categorized into never- or ever-smokers. Ever-smokers were defined as those who smoked more than 100 cigarettes in their lifetime. The smoking amount was divided by the pack-years (PY) smoked. PY of smoking were calculated by multiplying the number of cigarettes smoked per day with the years of smoking, divided by 20. Ever-smokers were categorized into three groups: light (<15 PY), moderate (15-30 PY), or heavy (≥30 PY) based on their smoking amount.

4. Biochemical parameters

Blood samples were collected and directly transported to the Central Testing Institute in Seoul, Korea. Serum 25-(OH)D levels were measured by the radioimmunoassay kit (DiaSorin Inc).

5. Statistical analysis

In order to analyze baseline characteristics according to smoking history and amount, data were expressed as means and standard deviations for continuous variables after one-way analysis of variance (ANOVA) and as percentage for categorical variables after chi-square test. Pearson correlation coefficients were calculated in

order to assess the correlations among age, body mass index (BMI), the pulmonary function tests, and BMD at all the skeletal sites. Comparisons of the BMD between the PY of smoking subgroups were identified by analysis of covariance (ANCOVA) after adjusting for confounders including age, BMI, FEV_1, 25(OH)D levels, moderate PA, alcohol consumption. Bonferroni correction was performed for multiple comparisons. Multiple binary logistic regression analysis was used to predict the variables independently associated with BMD loss. All statistical analyses were performed using SPSS version 20 (IBM SPSS Statistics; IBM Corp). Statistical significance was reached if the p value was less than 0.05.

RESULTS

Clinical characteristics according to smoking history

The clinical characteristics for 1476 men, aged 50–64 years, according to their smoking status are shown in Table 1. A total of 388 never-smokers (26.3%) and 1088 (73.7%) ever-smokers were included in the study. The mean smoking exposure of ever-smokers was 30 PY. The FEV1 value of ever-smokers was lower than that of the never smokers (3.09±0.53 vs.3.19±0.53, p=0.002), and the BMI was also lower in ever-smokers (p=0.008). Clinical parameters including age, serum 25(OH)D levels, PA, alcohol consumption, and BMD at all the sites did not differ according to the smoking status.

Table 1 Clinical characteristics of study subjects according to smoking history

	Never smokers	Ever smokers	*p*
Number	388	1088	
Age (years)	56.3±4.3	56.6±4.4	0.401
BMI (kg/ m^2)	24.7±2.7	24.2±2.7	0.008
WC (cm)	86.3±7.2	86.2±7.7	0.962
BMD (g/cm^2)			
Total hip	1.128±0.142	1.117±0.152	0.249
Femur neck	0.790±0.109	0.780±0.111	0.123
Lumbar spine	0.964±0.140	0.952±0.143	0.140
FEV_1 (L)	3.19±0.53	3.09±0.53	0.002
FVC (L)	4.09±0.64	4.14±0.63	0.177
25(OH)D (ng/dL)	21.3±6.9	21.3±7.3	0.622
Physical activity, n (%)			
High intensity	87 (22.4)	216 (19.9)	0.305
Moderate intensity	46 (11.9)	147 (13.5)	0.431
Walking	174 (44.8)	468 (43.0)	0.551
Alcohol ≥3U/d, n (%)	279 (71.9%)	763 (70.1%)	0.517

Data are presented as mean±SD or n (%)

Correlations between pack-years of smoking, pulmonary function, and BMD

The PY of smoking negatively correlated with total hip (TH) BMD (r=−0.083; p=0.006) after adjusting for age and BMI, whereas the lumbar spine (LS) BMD did not correlate in ever-smokers (Table 2). The FEV_1 was associated with BMD at FN in ever-smokers after adjusting for age and BMI (r=0.069; p=0.024, Table 2). The FVC positively correlated with the FN-BMD after adjusting for age and BMI (r=0.113; p=0.027 in never-smokers; r =0.075; p=0.013 in ever-smokers, Table 2).

Table 2 Partial correlations between pack years of smoking, pulmonary function, and BMD

	Never smoker			Ever smoker		
	Correlation coefficient (r) with BMD					
	TH	FN	LS	TH	FN	LS
Pack years				−0.083**	−0.024	−0.040
FEV_1 (L)	0.036	0.074	−0.027	0.049	0.069*	−0.019
FVC (L)	0.089	0.113*	0.036	0.051	0.075*	0.0002

** p<0.01, * p<0.05 after adjusting for age and BMI

Comparison of characteristics including pulmonary function and BMD according to smoking pack-years

To further investigate the relationships between smoking PY, BMD, and pulmonary function, the ever-smokers were divided into 3 subgroups as light, moderate, and heavy smokers according to the PY of smoking history of <15, 15-30, and ≥30 PY, respectively (Table 3). The heavy smokers showed a significantly lower TH-BMD compared to light smokers after adjusting for factors such as age, BMI, FEV1, 25(OH)D levels, PA, and alcohol consumption that could have affected bone metabolism (Figure 1A). Mean LS- and FN-BMD generally showed a downward trend with increasing PY, but it was not statistically significant (Figure 1B, 1C). Furthermore, heavy smokers had significantly lower TH-BMD than never-smokers after adjusting for age and BMI (Table 4). Current smokers were more prevalent in heavy smokers (69.4%). The FEV1 value of heavy smokers was lower than those of moderate and light smokers after adjusting for age and BMI (3.04±0.02 vs. 3.12±0.03, 3.16±0.03, respectively, p=0.013, Table 3).

Table 3 Clinical Characteristics of ever smokers according to pack years of smoking

	< 15PY	15−30PY	≥ 30PY	*p*
Number	214	392	482	
Age (years)	56.8±4.5	55.7±4.4	57.2±4.2	<0.001 [a,b]
BMI (kg/ m^2)	24.4±2.6	24.2±2.7	24.2±2.9	0.648
Pack years	11.2±3.0	23.4±4.7	44.6±15.4	N/A
Current smoker, n (%)	75 (23.0)	180 (45.9%)	333 (69.4%)	<0.001
BMD (g/cm^2)				
Total hip	1.139±0.155	1.124±0.160	1.102±0.143	0.007 [c]
Femur neck	0.792±0.106	0.780±0.108	0.775±0.114	0.178
Lumbar spine	0.965±0.147	0.952±0.141	0.946±0.144	0.289
FEV_1 (L)	3.14±0.53	3.15±0.49	3.02±0.56	<0.001 [b,c]
FVC (L)	4.15±0.66	4.18±0.57	4.11±0.66	0.173
25(OH)D (ng/dL)	20.9±7.6	21.0±7.1	21.7±7.4	0.272
Physical activity, n (%)				
High intensity	46 (21.5)	80 (20.4)	90 (18.7)	0.650
Moderate intensity	26 (12.1)	54 (13.8)	67 (13.9)	0.808
Walking	90 (42.1)	171 (43.6)	207 (42.9)	0.932
Alcohol ≥3U/d, n (%)	156 (72.9)	272 (69.4)	335 (69.5)	0.614

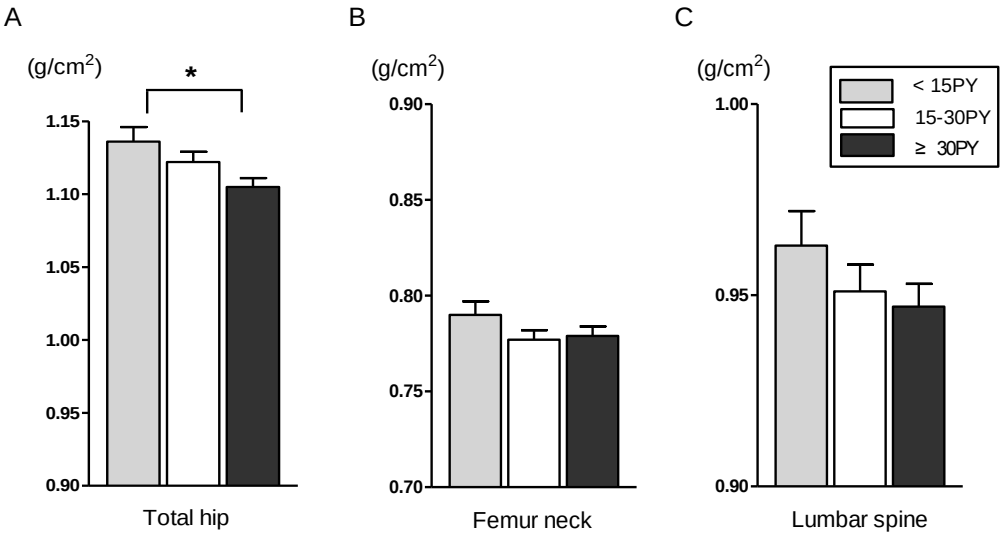
N/A, not applicable

Data are presented as mean ± SD or n (%)

p<0.05 following Bonferroni correction

[a,] 15PY vs. 15−30PY, [b] 15−30PY vs. >30PY, [c] <15PY vs. >30PY

Figure 1 Adjusted mean BMD at TH (A), FN (B), and LS (C) of ever smokers according to smoking amount



* $p < 0.05$, compared to <15PY vs. ≥ 30PY by ANCOVA after adjusting for age, BMI, FEV_1, serum 25(OH)D levels, moderate physical activity, and alcohol consumption

Table 4 Comparison of age and BMI adjusted pulmonary function and BMD between never smoker and different PY smoking groups

	Never smoker	<30PY	≥30PY	*p*	*p*, adjusted for age, BMI
Number	388	606	482		
Age (years)	56.3±4.3	56.1±4.4	57.1±4.2	<0.001[b,c]	
BMI (kg/ m^2)	24.7±2.7	24.3±2.6	24.2±2.9	0.029[c]	
Pack years		19.0±7.1	44.6±15.4	<0.001	
Current smoker, n (%)		240 (39.6)	333 (69.1)	<0.001	
FEV_1 (L)	3.19±0.53	3.15±0.50	3.02±0.56	<0.001[b,c]	<0.001
FVC (L)	4.09±0.64	4.17±0.60	4.11±0.66	0.080	0.285
BMD (g/cm^2)					
Total hip	1.128±0.142	1.129±0.158	1.102±0.143	0.007[b,c]	0.020
Femur neck	0.790±0.109	0.784±0.108	0.775±0.114	0.123	0.637
Lumbar spine	0.964±0.140	0.957±0.143	0.946±0.144	0.169	0.484

Data are presented as mean±SD or n (%)

p<0.05 following Bonferroni correction, [a] non-smoker vs. <30PY, [b] <30PY vs. ≥ 30PY, [c] non-smoker vs. > 30PY

The relationship between pulmonary function and BMD in ever smokers

To investigate the relationship between pulmonary function and BMD, the ever-smokers were stratified according to FEV_1 and FVC tertile. However, BMD at all the sites did not differ according to FEV_1 tertile (Table 5). No significant relationship was observed between FVC tertile and BMD at all the sites after adjusting for age and BMI (data not shown)

Table 5 BMD according to FEV_1 tertile in ever-smokers

	1st tertile	2nd tertile	3rd tertile	*p*	*p*, adjusted for age, BMI
Number	361	364	363		
Age (years)	58.4±4.2	56.3±4.4	54.9±3.9	<0.001 [a,b,c]	
BMI (kg/ m^2)	24.4±3.0	24.4±2.7	23.9±2.4	0.022 [b,c]	
FEV_1 (L)	2.51±0.34	3.11±0.12	3.65±0.26	N/A	
BMD ($g/cm^{2)}$					
Total hip	1.107±0.147	1.125±0.164	1.121±0.145	0.699	0.309
Femur neck	0.769±0.109	0.781±0.112	0.791±0.110	0.027 [c]	0.181
Lumbar spine	0.953±0.150	0.956±0.144	0.947±0.135	0.261	0.871

Data are presented as mean±SD

N/A, not applicable

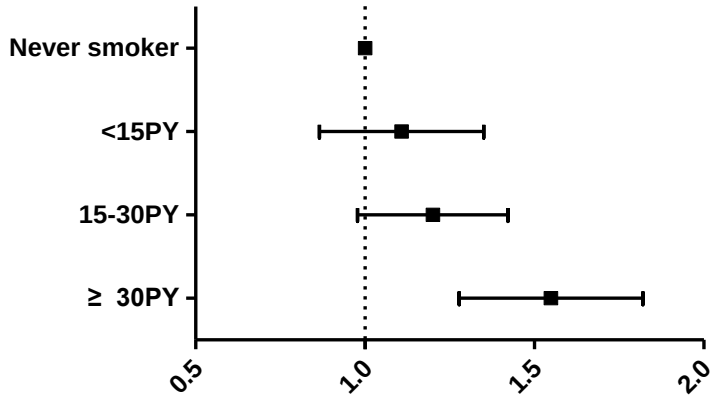
[a] $p<0.05$, compared to <1st vs. 2nd tertile , [b] $p<0.05$, compared to 2nd vs. 3rd tertile,

[c] $p<0.05$, compared to 1st vs. 3rd tertile by Bonferroni correction

Multivariate analysis of factors associated with TH-BMD in ever smokers

To assess independent determinants of low BMD defined as the lowest tertile of TH-BMD, logistic regression analysis was performed. Smoking history of more than 30 PY was associated with low bone density [OR=1.501 (95% CI: 1.105-2.041)] after adjusting for age, BMI, FEV1, serum 25(OH)D levels, moderate PA, and alcohol consumption (Figure 2).

Figure 2 Odds ratios for low bone density according to pack years of smoking



Low bone density : Lowest tertile of TH-BMD distribution

Odds ratio and 95% CI after adjusting for age, BMI, FEV_1, serum 25(OH)D levels, moderate physical activity, alcohol consumption

DISCUSSION

Our findings suggest a need for osteoporosis and fracture prevention to be focused on middle-aged men with a smoking history, even younger than 65 years. In this cross-sectional study using data from the KNHANES, 2008-2011, we showed the negative correlation between smoking amount and BMD at TH. Furthermore, subjects with >30 PY had significantly lower TH-BMD compared to those with <15 PY after adjusting for confounding variables. Moreover, heavy smokers with >30 PY had a 1.5-fold increased risk of low BMD than never-smokers.

This study has important strengths. We evaluated the association between quantity of smoking and lower BMD in the hip in a dose-dependent manner using population-based data. The total hip includes a much larger region of bone than FN, enhancing measurement precision [23]. When there was a discrepancy between T-scores of the TH, FN, and LS, the TH was more-closely related to predicting osteoporotic fracture risk [23].

Both current smoking and ever smoking are negatively associated with BMD [7, 24, 25]. In several epidemiologic studies, smoking was

suggested as an independent risk factor for hip fractures [26-28]. However, previous studies have mainly investigated older populations and less so middle-aged men. There are very few studies on the relationship between smoking amount and BMD. The present study is in close agreement with previous studies that reported that smokers, whose mean duration of smoking was 38.4 years, had significantly lower FN-BMD compared to ex-smokers or never-smokers [29]. A female twins study also suggested that a subtle decrease in the FN-BMD is found in pairs who were discordant by 20 or more PY but not by 10 PY of smoking [30]. In this study, the mechanism by which long-term smoking of >30 PY decreases bone mass is not clear. Previous reports suggested that the LS- and trochanter-BMD and the cortical thickness of the radius bone are lesser in young male smokers compared to nonsmokers [7]. Moreover, a 5-year longitudinal study showed that smoking impairs bone growth in young adult men [31]. These results support that smoking in early adulthood could result in a failure to achieve peak bone mass. In this study, we presumed that the middle-aged men with >30 PY had started smoking in early adulthood. However, we cannot exclude the fact that smoking had aggravated the decrease in bone mass among these subjects.

The pathophysiologic mechanisms of underlying bone loss in smoking have not been clarified. The deleterious effect of urinary cotinine in a dose-dependent manner on BMD at all sites was observed in 2,086 postmenopausal women in the KNHANES IV [32]. The nicotine in cigarettes regulates the number of osteoblasts [33, 34]. Walker's et al. showed that nicotine at high levels (>1 mmol/L) had anti-proliferative effects on human primary osteoblasts, controlling the upregulation of c-fos and osteopontin expression [35]. Nicotine suppressed the expression of various cytokines related to angiogenesis and osteoblast differentiation in New Zealand white rabbits after spine fusion with bone graft [36].

In this study, pulmonary function, including FEV_1 and FVC positively correlated with BMD at FN in ever smokers aged 50-64 years after adjusting for age and BMI. The correlation between pulmonary function and BMD has been inconsistent in previous studies. Lekamwasam et al. showed a positive correlation between the FEV_1 and hip BMD in men aged 65-76 years and women aged 45-76 years independent of smoking habits [37, 38]. Denise et al. also found significant correlations between the T-scores of FN and LS and pulmonary function in men and women [39]. However, BMD did not correlate with the FEV_1 and FVC in postmenopausal women without

smoking history in KHANES, 2010 [40]. There was no association between pulmonary function and BMD in 496 men aged 60–72 years in the Hertfordshire cohort study [41]. The association between the FEV_1 and BMD at TH and FN was significant only in premenopausal women aged 40–56 years and not in men aged 40–91 years or in postmenopausal women aged 40–86 years after adjustment for age, BMI, and smoking status in KNHANES, 2010–2011 [42]. However, we observed a positive correlation between FEV_1, FVC and BMD at FN after adjusting for age and BMI focused on the ever smokers aged 50–64 years in KNHANES 2008–2011. No association was found between FEV1 and BMD at all sites in never smokers. The mechanism of this discordant association between FEV_1 and BMD according to smoking history was not clear, however, it might be influenced by oxidative stress and inflammation related to smoking [43].

There were some limitations to our study. We showed a negative trend between smoking amount and BMD at FN and LS, while only significant association was shown at the hip. A larger population might be needed to verify the association between smoking amount and BMD at other sites among the smoking subgroups. Information on the duration of quitting smoking and history of endocrine disease

that might affect BMD were not available. This cross-sectional design might not reflect the life-long effect of cigarette smoking and pulmonary function on BMD. Moreover, we evaluated the relationships between smoking, pulmonary function, and BMD with a focus on middle-aged men; therefore, our data might not be applicable to the general population.

In conclusion, a smoking amount of >30 PY may be an independent risk factor associated with bone loss in middle-aged Korean men after adjusting for confounders including age and pulmonary function. The prevalence of smoking remains high in many countries. We suggest that the smoking amount as well as pulmonary function should be considered as important factors that influence bone health.

REFERENCES

1. Cosman, F., et al., *Clinician's guide to prevention and treatment of osteoporosis.* Osteoporosis international, 2014. **25**(10): p. 2359-2381.
2. Wright, N.C., et al., *The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine.* Journal of Bone and Mineral Research, 2014. **29**(11): p. 2520-2526.
3. Park, E.J., et al., *Prevalence of osteoporosis in the Korean population based on Korea National Health and Nutrition Examination Survey (KNHANES), 2008-2011.* Yonsei medical journal, 2014. **55**(4): p. 1049-1057.
4. Shin, C.S., et al., *Prevalence and risk factors of osteoporosis in Korea: a community-based cohort study with lumbar spine and hip bone mineral density.* Bone, 2010. **47**(2): p. 378-387.
5. Roy, D., et al., *Determinants of incident vertebral fracture in men and women: results from the European Prospective Osteoporosis Study (EPOS).* Osteoporosis International, 2003. **14**(1): p. 19-26.
6. Ward, K.D. and R.C. Klesges, *A meta-analysis of the effects of cigarette smoking on bone mineral density.* Calcified tissue international, 2001. **68**(5): p. 259-270.
7. Lorentzon, M., et al., *Smoking is associated with lower bone mineral density and reduced cortical thickness in young men.* The Journal of clinical endocrinology & metabolism, 2007. **92**(2): p. 497-503.
8. Kiel, D., et al., *The effect of smoking at different life stages on bone mineral density in elderly men and women.* Osteoporosis International, 1996. **6**(3): p. 240-248.
9. Egger, P., et al., *Cigarette smoking and bone mineral density in the elderly.* Journal of epidemiology and community health, 1996. **50**(1): p. 47-50.
10. Jaramillo, J.D., et al., *Reduced Bone Density and Vertebral Fractures in Smokers. Men and COPD Patients at Increased Risk.* Annals of the American Thoracic Society, 2015. **12**(5): p. 648-656.
11. Jones, G., et al., *Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study.* Bmj, 1994. **309**(6956): p. 691-695.
12. Cawthon, P.M., et al., *Loss of hip BMD in older men: the osteoporotic fractures in men (MrOS) study.* Journal of Bone and Mineral Research, 2009. **24**(10): p. 1728-1735.
13. Johansson, C., et al., *Bone mineral density is a predictor of survival.* Calcified tissue international, 1998. **63**(3): p. 190-196.
14. Johansson, H., et al., *Optimization of BMD measurements to identify high risk groups for treatment—a test analysis.* Journal of bone and mineral research, 2004. **19**(6): p. 906-913.
15. Burchfiel, C.M., et al., *Effects of smoking and smoking cessation on*

longitudinal decline in pulmonary function. American journal of respiratory and critical care medicine, 1995. **151**(6): p. 1778-1785.
16. Elkin, S., et al., *Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study.* Osteoporosis International, 2001. **12**(5): p. 366-372.
17. Vrieze, A., et al., *Low bone mineral density in COPD patients related to worse lung function, low weight and decreased fat-free mass.* Osteoporosis International, 2007. **18**(9): p. 1197-1202.
18. Watanabe, R., et al., *Osteoporosis is highly prevalent in Japanese males with chronic obstructive pulmonary disease and is associated with deteriorated pulmonary function.* Journal of bone and mineral metabolism, 2014: p. 1-9.
19. Incalzi, R.A., et al., *Correlates of osteoporosis in chronic obstructive pulmonary disease.* Respiratory medicine, 2000. **94**(11): p. 1079-1084.
20. Moayyeri, A., et al., *Respiratory function as a marker of bone health and fracture risk in an older population.* Journal of Bone and Mineral Research, 2009. **24**(5): p. 956-963.
21. Korea Centers for Disease Control and Prevention. Ministry of Health and Welfare, South Korea. Korea National Health and Nutrition Examination Survey (KNHANES). 2011., https://knhanes.cdc.go.kr/knhanes/index.do. Accessed 18 November 2015.
22. Jöström, M., et al., *Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ)–Short and Long Forms. IPAQ core group 2005*.
23. Leslie, W.D., et al., *Single-site vs multisite bone density measurement for fracture prediction.* Archives of internal medicine, 2007. **167**(15): p. 1641-1647.
24. Jutberger, H., et al., *Smoking predicts incident fractures in elderly men: Mr OS Sweden.* Journal of bone and mineral research, 2010. **25**(5): p. 1010-1016.
25. Tamaki, J., et al., *Smoking among premenopausal women is associated with increased risk of low bone status: the JPOS Study.* Journal of bone and mineral metabolism, 2010. **28**(3): p. 320-327.
26. Grisso, J.A., et al., *Risk factors for hip fracture in men.* American Journal of Epidemiology, 1997. **145**(9): p. 786-793.
27. Kato, I., et al., *Diet, smoking and anthropometric indices and postmenopausal bone fractures: a prospective study.* International journal of epidemiology, 2000. **29**(1): p. 85-92.
28. Meyer, H.E., A. Tverdal, and J.A. Falch, *Risk factors for hip fracture in middle-aged Norwegian women and men.* American Journal of Epidemiology, 1993. **137**(11): p. 1203-1211.
29. Nguyen, T., et al., *Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention.* Journal of Bone and Mineral Research, 1994. **9**(9): p. 1339-1346.

30. Hopper, J.L. and E. Seeman, *The bone density of female twins discordant for tobacco use.* New England Journal of Medicine, 1994. **330**(6): p. 387-392.
31. Rudäng, R., et al., *Smoking is associated with impaired bone mass development in young adult men: A 5-year longitudinal study.* Journal of bone and mineral research, 2012. **27**(10): p. 2189-2197.
32. Myong, J.-P., et al., *Dose-related effect of urinary cotinine levels on bone mineral density among Korean females.* Osteoporosis International, 2013. **24**(4): p. 1339-1346.
33. Rothem, D.E., et al., *Nicotine modulates bone metabolism-associated gene expression in osteoblast cells.* Journal of bone and mineral metabolism, 2009. **27**(5): p. 555-561.
34. Rothem, D.E., et al., *Nicotinic modulation of gene expression in osteoblast cells, MG-63.* Bone, 2011. **48**(4): p. 903-909.
35. Walker, L., et al., *Nicotinic regulation of c-fos and osteopontin expression in human-derived osteoblast-like cells and human trabecular bone organ culture.* Bone, 2001. **28**(6): p. 603-608.
36. Theiss, S.M., et al., *The effect of nicotine on gene expression during spine fusion.* Spine, 2000. **25**(20): p. 2588-2594.
37. Lekamwasam, S., D. Trivedi, and K.T. Khaw, *An association between respiratory function and bone mineral density in women from the general community: a cross sectional study.* Osteoporosis International, 2002. **13**(9): p. 710-715.
38. Lekamwasam, S., D. Trivedi, and K.T. Khaw, *An association between respiratory function and hip bone mineral density in older men: a cross-sectional study.* Osteoporosis international, 2005. **16**(2): p. 204-207.
39. Silva, D.R., et al., *Osteoporosis prevalence and associated factors in patients with COPD: a cross-sectional study.* Respiratory care, 2011. **56**(7): p. 961-968.
40. Jeon, Y.K., et al., *The relationship between pulmonary function and bone mineral density in healthy nonsmoking women: the Korean National Health and Nutrition Examination Survey (KNHANES) 2010.* Osteoporosis International, 2014. **25**(5): p. 1571-1576.
41. Dennison, E., et al., *Is lung function associated with bone mineral density? Results from the Hertfordshire Cohort Study.* Archives of osteoporosis, 2013. **8**(1-2): p. 1-6.
42. Lee, K., *Is FEV1 an indicator of low bone mineral density in adults? The Fifth Korea National Health and Nutrition Examination Survey.* Journal of bone and mineral metabolism, 2015. **33**(3): p. 335-341.
43. Van der Vaart, H., et al., *Acute effects of cigarette smoke on inflammation and oxidative stress: a review.* Thorax, 2004. **59**(8): p. 713-721.

국문 초록

서론: 흡연은 잘 알려져 있는 골 소실의 위험인자이다. 그러나, 골 소실에 미치는 장기간의 흡연량에 대해서는 잘 알려져 있지 않다. 또한, 폐 기능과 골 밀도 간 연관성에 대해 인구 집단을 대상으로 한 연구 간 결과가 일관되지 않았다. 이에 저자들은 한국 중년 남성에서 흡연량과 폐 기능, 골 밀도의 관계에 대해 연구 하였다.

방법: 50-64 세의 남성을 대상으로 2008-2011 년 국민건강영양조사 자료를 통해 단면적 연구를 시행 하였다. 모든 대상자는 이중에너지 X-선 흡수 계측법을 통하여 골 밀도를 측정하였고, 표준화된 폐활량 측정법을 통하여 폐 기능 검사를 시행 하였다.

결과: 총 388 명의 비흡연자와 1088 명의 흡연자를 분석 하였다. 흡연력은 나이와 체질량지수를 보정 후 대퇴골 전체 골 밀도와 유의하게 음의 상관 관계를 보였다 (r=-0.083; p=0.006). 흡연자는 흡연력에 따라 15 갑년 미만 (214 명), 15-30 (392 명) , 30 갑년 이상 (482 명)으로 분류하였다. 흡연 유 경험자에서 1 초간 노력성 호기량과 노력성 호기량은 나이, 체질량지수를 보정 후 대퇴골 경부 골 밀도와 양의 상관 관계를 보였다. 평균 대퇴골 전체 골 밀도는 30 갑년 이상 흡연력이 있는 대상자 군

에서 다른 두 군보다 교란 변수인 나이, 체질량지수, 1 초간 노력성 호기량, 알코올 섭취력, 신체활동량, 비타민 D 혈중 농도를 보정한 후에 유의하게 낮았다 (<15 PY, 1.137±0.010; 15-30 PY, 1.123±0.007; ≥ 30 PY, 1.104±0.006 g/cm2; p=0.007).

결론: 한국 중년 남성에서 30 갑년 이상의 흡연력은 폐 기능을 포함한 교란 변수를 보정한 후에도 낮은 대퇴골 전체 골 밀도와 유의한 관련성이 있다. 흡연은 한국 중년 남성에서의 골 소실과 관련되어 나이, 체질량 지수, 폐 기능과 독립적인 위험 인자이다.

주요어 : 흡연, 골 밀도, 노력성호기량, 노력성폐활량

학 번 : 2014-21167