Original Article

Effect of Secondhand Smoking, Determined by Urinary Cotinine Level on Bone Health

Abstract

Background: We evaluated the relationship between secondhand smoke (SHS) inhalation, as verified by urinary cotinine levels, and bone health. **Methods:** We analyzed the nationwide, population-based, cross-sectional health survey. We included 1936 men aged 50 years or older who checked bone mineral density (BMD) from the Korean National Health and Nutrition Examination Survey (2008–2010). Current smokers assessed by urinary cotinine levels higher than 500 ng/mL were excluded ($n = 616$). Exposure to SHS was determined using a 50 ng/mL urinary cotinine threshold. **Results:** The estimated prevalence of SHS exposure in our cohort was 13.9%. After adjusting for age and body mass index (BMI), T-scores at total femur ($P < 0.001$), femoral neck ($P < 0.001$), and lumbar spine ($P = 0.004$) were lower in SHS exposure versus nonexposure groups. Impaired bone health (osteopenia or osteoporosis) at femoral neck or lumbar spine was evident in 61.7% and 48.6% of SHS exposure and nonexposure cases, respectively ($P = 0.004$). Moreover, after adjusting for age, BMI, and health habits, the odds ratio for impaired bone health in the SHS exposure group was 1.89 (95% confidence interval: 1.31–2.74). **Conclusions:** Our findings suggest that SHS exposure, determined by urinary cotinine levels, is negatively associated with BMD and is a leading cause of impaired bone health in Korean men.

Keywords: *Biomarker, bone density, cotinine, tobacco smoke pollution*

**Ji Hyun Moon[1,2],
Mi Hee Kong[1,3],
Hyeon Ju Kim[1,3]**

[1]Department of Family Medicine, Jeju National University Hospital, Jeju Self-governing Province, Republic of Korea, [2]Department of Medicine, Graduate School of Jeju National University, Jeju Self-governing Province, Republic of Korea, [3]Department of Family Medicine, School of Medicine, Jeju National University, Jeju Self-governing Province, Republic of Korea

Introduction

The incidence of osteopenia and osteoporosis in men has increased. According to a recent report, the prevalence of osteopenia is 46.5% and that of osteoporosis is 7.3% in Korean men aged 50 years and older.[1] The lifetime fracture risk associated with osteoporosis in men of this age group is 13%–30%.[2] Furthermore, once a hip fracture has occurred, men have a 2–3 times higher mortality rate than women.[3] Thus, osteoporosis in men is not as well-known as it is in women; nevertheless, it is a major public health concern.[4]

Inhalation of secondhand smoke (SHS) consists of 15% mainstream smoke and 85% sidestream smoke. Sidestream smoke that originates from the ends of burning cigarettes is considered more toxic than mainstream (inhaled) smoke.[5] SHS exposure is known to be associated with several health problems, including asthma,[6] diabetes,[7] cardiovascular disease,[8] and reduces the quality of life.[9] Firsthand tobacco smoke is an important risk factor for impaired bone health (osteopenia and osteoporosis).[10,11] However, the effect of SHS exposure on bone mineral density (BMD) is not well understood, especially in Asian men.

The status of tobacco smoke exposure can be estimated by determining concentrations of urinary cotinine, a major metabolite of nicotine. Cotinine has a relatively long half-life (16–20 h) and is present in higher concentrations in body fluids than other biological markers of tobacco.[12] Furthermore, urinary cotinine is easy to collect. The aim of this study was to evaluate the significance of SHS exposure, as verified by urinary cotinine levels, on bone health in Korean men, aged 50 years and older.

Methods

Study design and participants

We analyzed the nationwide, population-based, cross-sectional health survey. The participants were 1320 male participants of the Korean National Health and Nutrition Examination

Address for correspondence:
*Prof. Hyeon Ju Kim,
Department of Family Medicine, Jeju National University Hospital, Jeju-si, Jeju Self-governing Province, 63241, Republic of Korea.
E-mail: fmhjukim@hanmail.net*

www.SID.ir

Survey (2008–2010), conducted since 1998, by the Korea Centers for Disease Control and Prevention. It is a nationwide survey representing the health status of the entire Korean population. In our study, we selected men aged 50 years and older who had undergone dual-energy X-ray absorptiometry (DXA) and measurements of urinary cotinine concentration. We excluded individuals with chronic liver or kidney disease, thyroid disease, rheumatic arthritis, asthma, osteoporosis, or any form of malignancy. Obvious current smokers (urinary cotinine levels higher than 500 ng/mL) were also excluded.

Measurements

Spot urine samples collected for the measurement of urinary cotinine levels were assayed by gas chromatography and mass spectrometry, using a PerkinElmer Clarus 600T Mass Spectrometer (PerkinElmer Inc., Turku, Finland). All data were reviewed internally by our quality control center. Cutoff values for distinguishing SHS exposure from nonexposure and current smokers from SHS exposure are varied. No validated cutoff values for urinary cotinine levels have been published in the Korean population. According to previous studies, urinary cotinine levels below 50 ng/mL have defined nonexposure to tobacco smoke,[13] whereas a cutoff threshold of above 500 ng/mL is most commonly set for classifying an obvious current smoker.[14] In our study, individuals with urinary cotinine levels above the 500 ng/mL threshold were classified as current smokers and removed from further analyses. Individuals with urinary cotinine levels >50 ng/mL but ≤500 ng/mL were defined as having been exposed to SHS.

BMD at total femur, femoral neck, and lumbar spine (L1–L4) were measured using the DXA scanner (Hologic Inc., Bedford, MA, USA). T-scores were calculated by the Asian equation: (BMD minus reference BMD) divided by (reference standard deviation). Owing to the lack of Korean diagnostic criteria, maximum BMD values for Japanese patients were substituted as reference measurements instead. In our study, osteopenia and osteoporosis were defined as impaired bone health. In our study, impaired bone health (osteopenia and osteoporosis) was defined by T-scores of <−1.

Statistical analyses

All quantitative variables have been reported as mean ± standard error (SE), and qualitative variables as estimated proportion (SE). To reflect the sampling method and to represent the health status of the entire Korean population, we used a weighted population sample in our study. A Complex Samples General Linear Model was used to estimate means and SEs for BMD, and T-scores at total femur, femoral neck, and lumbar spine. A Complex Samples Logistic Regression Analysis was applied to estimate proportions and SEs for impaired bone health (osteopenia and osteoporosis). Multivariable

logistic regression analyses were also carried out to assess the relationship between urinary cotinine levels and impaired bone health. All analyses were performed using Statistical Package of the Social Sciences for Windows version 20.0 (IBM, New York, NY, USA). $P < 0.05$ were considered statistically significant.

Results

General characteristics of the study participants are summarized in Table 1. Among the total number of study participants, 13.9% were classified as having been exposed to SHS. The average level of urine cotinine in the nonexposed group was 7.89 ng/mL, in comparison to 260.08 ng/mL in the exposed group ($P < 0.001$). Differences in mean age and body mass index (BMI) between the two groups were not statistically significant ($P = 0.656$ and $P = 0.433$, respectively). The frequency of alcohol consumption and exercise did not differ meaningfully between the two groups.

Table 2 presents the relationship between urinary cotinine levels and bone health. The SHS-exposed group

Table 1: General characteristics of the study participants according to secondhand smoke exposure

	Not-exposed (*n*=1137)	Exposed (*n*=183)	*P**
Age (years)	60.60±0.30	60.98±0.81	0.656
Height (cm)	166.99±0.20	166.79±0.48	0.691
Weight (kg)	67.54±0.36	67.97±0.83	0.635
BMI (kg/m²)	24.19±0.11	24.39±0.23	0.433
Urine cotinine level (ng/mL)	7.89±0.39	260.08±14.14	<0.001
Alkaline phosphatase (IU)	227.85±2.32	244.91±7.00	0.020
25-hydroxy vitamin D3 (ng/mL)	21.86±0.33	22.22±0.84	0.654
Parathyroid hormone (pg/dL)	63.83±1.02	64.99±2.23	0.640
Hypertension	35.9 (1.8)	31.0 (3.9)	0.266
Diabetes	12.3 (1.1)	15.6 (3.2)	0.425
Alcohol			
None	24.1 (1.4)	15.0 (3.0)	0.058
Once a week or less frequent	37.9 (1.8)	44.8 (4.7)	
More than twice a week	38.1 (1.8)	40.2 (4.5)	
Exercise			
None	57.8 (1.8)	57.8 (4.3)	0.531
Less than two times a week	18.7 (1.4)	15.3 (3.4)	
Three times a week or more	23.5 (1.5)	26.9 (3.9)	

*Complex sample general linear model (mean±SE) for qualitative data and complex sample logistic regression analysis (estimated proportion [SE]) for quantitative data. BMI=Body mass index, SE=Standard error, SHS=Secondhand smoke

demonstrated lower BMD at total femur and femoral neck compared to the nonexposed group, which was statistically significant (P = 0.004 and P = 0.003, respectively). At lumbar spine, however, although the SHS-exposed group demonstrated lower BMD than the nonexposed group, the result was not statistically significant (P = 0.486). After adjustments were made for age and BMI, T-scores at total femur and femoral neck were significantly lower in the SHS-exposed group compared to the nonexposed group (all P < 0.001). Furthermore, the average T-score at lumbar spine of the non-exposed group was −0.57 ± 0.04 compared to −0.68 ± 0.10 in the SHS-exposed group (P = 0.004) [Figure 1].

To reveal the independent relationship between SHS exposure, as verified by urinary cotinine levels, and impaired bone health, we conducted multivariate logistic regression. The prevalence of impaired bone health was higher in the SHS-exposed group than the nonexposed group, regardless of the location measured. The prevalence of impaired bone health at femoral neck or lumbar spine,

for example, was 48.6% and 61.7% in the nonexposed and SHS-exposed groups, respectively (P = 0.004). After adjusting for age, BMI, and health habits, participants identified in the SHS-exposed group, as verified by urinary cotinine levels, were found to be associated with an increased risk of impaired bone health at femoral neck or lumbar spine with an odds ratio of 1.89 (95% confidence interval: 1.31–2.74) [Table 3].

Discussion

The results of our study indicate that exposure to SHS, as verified by urinary cotinine levels, is negatively associated with bone health in Korean men. Only a few studies have investigated the relationship between urinary cotinine levels and impaired bone health in Asian men. In a Korean study of adults, aged 30 years or older, participants with urinary cotinine levels above 10 mcg/mL were associated with lower femoral neck T-scores than participants with urinary cotinine levels of 10 mcg/mL or less.[15] Moreover, urinary cotinine levels and T-scores at femoral neck and lumbar spine exhibited a negative association that was

Table 2: Association between secondhand smoke exposure and bone health parameters

	Not-exposed (n=1137)	Exposed (n=183)	$P*$
BMD (g/cm^2)			
Total femur	0.95±0.00	0.92±0.01	0.004
Femoral neck	0.77±0.00	0.74±0.01	0.003
Lumbar spine	0.96±0.01	0.94±0.01	0.486
T-score			
Total femur	−0.06±0.03	−0.16±0.07	0.004
Femoral neck	−0.62±0.03	−0.86±0.07	0.003
Lumbar spine	−0.58±0.04	−0.65±0.10	0.486

*Calculated using a complex sample general linear model (mean±SE). Adjusted for age and BMI. BMI=Body mass index, BMD=Bone mineral density, SE=Standard error, SHS=Secondhand smoke
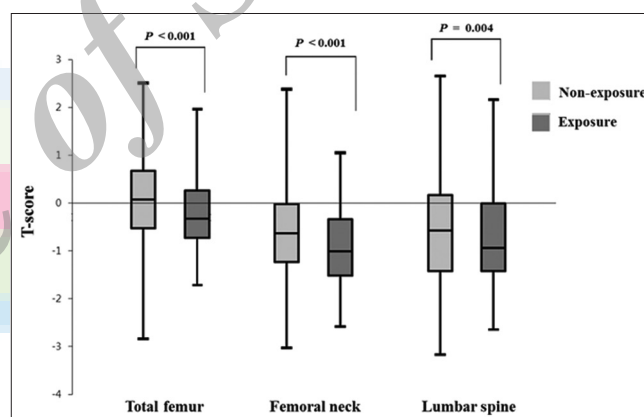
Figure 1: Comparison of SHS exposure age, BMI-adjusted T-scores at total femur, femoral neck, and lumbar spine, calculated using a complex sample general linear model. SHS=Secondhand smoke, BMI=Body mass index

Table 3: Multivariate logistics regression analysis of association between secondhand smoke exposure and the risk of osteopenia or osteoporosis at total femur, femoral neck, and lumbar spine

	Estimated proportion percentage (SE)	Unadjusted OR (95% CI)	Multivariate OR (95% CI)
Total femur			
Nonexposure	11.1 (1.1)	1	1
Exposure	12.7 (3.0)	1.17 (0.66-2.05)	1.34 (0.72-2.50)
Femoral neck			
Nonexposure	33.6 (1.6)	1	1
Exposure	47.0 (4.6)	1.75 (1.20-2.56)	2.03 (1.35-3.05)
Lumbar spine			
Nonexposure	38.0 (1.8)	1	1
Exposure	45.4 (4.3)	1.35 (0.95-1.93)	1.47 (1.00-2.16)
Lumbar spine/femoral neck			
Nonexposure	48.6 (1.8)	1	1
Exposure	61.7 (4.3)	1.71 (1.18-2.46)	1.89 (1.31-2.74)

Multivariate adjusted ORs calculated for age, BMI, alcohol consumption, and frequency of exercise. BMI=Body mass index, CI=Confidence interval, OR=Odds ratio, SE=Standard error, SHS=Secondhand smoke

www.SID.ir

3

statistically significant. However, the group with urinary cotinine levels above 10 mcg/mL contained active smokers and nonsmokers with exposure to SHS. Because the previous study did not distinguish between the group with SHS exposure and the group of current smokers, the effects of SHS exposure on bone health could not be evaluated.

The mechanisms of SHS exposure on impaired bone health are not fully understood. In general, smokers tend to have lower body fat percentage and BMI than nonsmokers.[16] Furthermore, tobacco smoke may lead to increased bone turnover[17] and a decrease in calcium absorption.[18] In one animal study, smoked-exposed rats had fewer bone marrow cells and black carbon dust-like substance in a region found in their bones.[19] In an *in vitro* study, nicotine acted to increase osteoclastogenesis while inhibiting osteoblastogenesis; however, the effects of low-dose nicotine administration on bone health are still not fully understood.[20] Furthermore, in epidemiologic studies with or without a history of tobacco exposure, the levels of 25-hydroxy vitamin D3, parathyroid hormone, and alkaline phosphatase were found to be comparable.[21]

Our study has a number of strengths. Assessment of smoking status (i.e., active smoker, passive smoker, or nonsmoker) by means of a self-reported questionnaire can have important biases that may result in the prevalence of smoking and SHS exposure to be underreported.[22] Estimating exposure to tobacco smoke by measuring urinary cotinine levels can more accurately determine a participant's smoking status than by assessment through self-reported questionnaires. Previously, some studies in women have reported exposure to SHS and osteoporosis to exhibit a positive association, with a dose-response relationship between BMD and urinary cotinine levels.[23,24] However, little information is available regarding exposure to SHS, as verified by urinary cotinine levels, and bone health in men. We classified nonsmoking men as having exposure or nonexposure to SHS, based on urinary cotinine levels, which has not been investigated in previous studies. We also used national data that were representative of the general Korean population of men, aged 50 years and older.

Despite these strengths, however, the current study does have several limitations. First, this was a cross-sectional study, which meant we were unable to establish a causal relationship between SHS exposure and bone health. Second, we used urinary cotinine cutoff points of 50 ng/mL and 500 ng/mL, respectively, to distinguish between nonexposure/exposure to SHS and active smokers. However, urinary cotinine cutoff points have not previously been established for distinguishing passive smokers from active smokers, and in particular, there has been no published guide for the Korean population. Third, through measurements of urinary cotinine levels, we could only estimate the previous 2–3 days of exposure and were not

able to assess the full extent of SHS exposure or the age at which SHS exposure began. Finally, not only smoking habits but also the status of calcium intake can play an important role in the development of osteoporosis. Unfortunately, however, we were unable to evaluate nutrition as part of this study. Additional studies are required, therefore, to assess longitudinal duration of exposure and dietary intake for evaluating the cause-effect relationship between SHS exposure and impaired bone health.

Conclusions

This study suggests that SHS exposure, determined by urinary cotinine levels, is negatively associated with BMD and is a major risk factor for impaired bone health in Korean men.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

References

1. Park EJ, Joo IW, Jang MJ, Kim YT, Oh K, Oh HJ. Prevalence of osteoporosis in the Korean population based on Korea National Health and Nutrition Examination Survey (KNHANES), 2008-2011. Yonsei Med J 2014;55:1049-57.

2. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301:513-21.

3. Holt G, Smith R, Duncan K, Hutchison JD, Gregori A. Gender differences in epidemiology and outcome after hip fracture: Evidence from the Scottish Hip Fracture Audit. J Bone Joint Surg Br 2008;90:480-3.

4. Shetty S, Kapoor N, Naik D, Asha HS, Prabu S, Thomas N, *et al.* Osteoporosis in healthy South Indian males and the influence of life style factors and Vitamin D status on bone mineral density. J Osteoporos 2014;2014:723238.

5. Schick S, Glantz S. Philip Morris toxicological experiments with fresh sidestream smoke: More toxic than mainstream smoke. Tob Control 2005;14:396-404.

6. Comhair SA, Gaston BM, Ricci KS, Hammel J, Dweik RA, Teague WG, *et al.* Detrimental effects of environmental tobacco smoke in relation to asthma severity. PLoS One 2011;6:e18574.

7. Wang Y, Ji J, Liu YJ, Deng X, He QQ. Passive smoking and risk of type 2 diabetes: A meta-analysis of prospective cohort studies. PLoS One 2013;8:e69915.

8. Glantz SA, Parmley WW. Passive smoking and heart disease. Epidemiology, physiology, and biochemistry. Circulation 1991;83:1-12.

9. Kim YW, Lee CH, Park YS, Kim YI, Ahn CM, Kim JO, *et al.* Effect of exposure to second-hand smoke on the quality of life: A nationwide population-based study from South Korea. PLoS One 2015;10:e0138731.

10. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, *et al*. Smoking and fracture risk: A meta-analysis. Osteoporos Int 2005;16:155-62.

11. Law MR, Hackshaw AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: Recognition of a major effect. BMJ 1997;315:841-6.

12. Wong SL, Shields M, Leatherdale S, Malaison E, Hammond D. Assessment of validity of self-reported smoking status. Health Rep 2012;23:47-53.

13. Zielinska-Danch W, Wardas W, Sobczak A, Szoltysek-Boldys I. Estimation of urinary cotinine cut-off points distinguishing non-smokers, passive and active smokers. Biomarkers 2007;12:484-96.

14. Apseloff G, Ashton HM, Friedman H, Gerber N. The importance of measuring cotinine levels to identify smokers in clinical trials. Clin Pharmacol Ther 1994;56:460-2.

15. Lee S, Yoon DH, Kim KN, Shin DA, Ha Y. Association between urine cotinine levels and bone mineral density in lumbar spine and femoral neck among adult males. Spine (Phila Pa 1976) 2014;39:311-7.

16. Khosla T, Lowe CR. Obesity and smoking habits. Br Med J 1971;4:10-3.

17. Ramp WK, Lenz LG, Galvin RJ. Nicotine inhibits collagen synthesis and alkaline phosphatase activity, but stimulates DNA synthesis in osteoblast-like cells. Proc Soc Exp Biol Med 1991;197:36-43.

18. Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorption. J Bone Miner Res 1999;14:215-20.

19. Ajiro Y, Tokuhashi Y, Matsuzaki H, Nakajima S, Ogawa T. Impact of passive smoking on the bones of rats. Orthopedics 2010;33:90-5.

20. Hapidin H, Othman F, Soelaiman IN, Shuid AN, Luke DA, Mohamed N. Negative effects of nicotine on bone-resorbing cytokines and bone histomorphometric parameters in male rats. J Bone Miner Metab 2007;25:93-8.

21. Brot C, Jorgensen NR, Sorensen OH. The influence of smoking on Vitamin D status and calcium metabolism. Eur J Clin Nutr 1999;53:920-6.

22. Wilcox RG, Hughes J, Roland J. Verification of smoking history in patients after infarction using urinary nicotine and cotinine measurements. Br Med J 1979;2:1026-8.

23. Kim KH, Lee CM, Park SM, Cho B, Chang Y, Park SG, *et al*. Secondhand smoke exposure and osteoporosis in never-smoking postmenopausal women: The Fourth Korea National Health and Nutrition Examination Survey. Osteoporos Int 2013;24:523-32.

24. Myong JP, Kim HR, Choi SE, Koo JW. Dose-related effect of urinary cotinine levels on bone mineral density among Korean females. Osteoporos Int 2013;24:1339-46.