의학석사 학위논문

도시지역 노인에서 비타민 D와 염증표지자의 관련성 및 비타민 D와 흡연의 상호작용

The Relationship of Vitamin D and Smoking with Inflammatory Markers in the Urban Elderly

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의학과 예방의학 전공

이 혜 미

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Abstract

The Relationship of Vitamin D and Smoking with Inflammatory Markers in the Urban Elderly

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Objectives

Epidemiological studies have reported that vitamin D deficiency is associated with inflammatory disease. Smoking is a well-known risk factor for inflammation. However, few studies have investigated the interactive effect of vitamin D deficiency and smoking on inflammation. This study aims to investigate the interaction of vitamin D and smoking with inflammatory markers in the urban elderly.

Methods

We used data from the Korean Elderly Environmental Panel Study, which began in August 2008 and ended in August 2010, and included 560 Koreans 60 years and older living in Seoul. Data was collected

via questionnaires that included items about smoking status at the first visit. Vitamin D levels, high-sensitivity C-reactive protein (hs-CRP), and white blood cell (WBC) counts were repeatedly measured up to three times. To explore the association of vitamin D concentrations with inflammatory markers, we used generalized estimating equations.

Results

The association of vitamin D and hs-CRP was significant after adjusting for known confounders (β = -0.080, p = 0.041). After separate analysis by smoking status, the association of vitamin D deficiency and hs-CRP in smokers was stronger than that in nonsmokers (smokers: β = -0.375, p = 0.013, nonsmokers: β = -0.060, p = 0.150). Smoking status was an effect modifier that changed the association between vitamin D deficiency and hs-CRP (interaction estimate: -0.254, p = 0.032). Vitamin D was not significantly associated with WBC count (β = 0.003, p = 0.805).

Conclusions

Vitamin D deficiency was associated with hs-CRP in the urban elderly. Smoking status was an effect modifier of this association. Vitamin D deficiency was not significantly associated with WBC count.

Keywords vitamin D, 25-hydroxyvitamin D2, smoking, C-reactive protein, leukocytes, inflammation

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Introduction

Vitamin D concentration is increased by exposure to sunlight. Urban residents spend most of their time in indoor spaces, resulting in vitamin D deficiency, the prevalence of which is high worldwide. Vitamin D insufficiency (≤20 ng/mL) is 41.6% in U.S. adults, based on data from the 2005–2006 National Health and Nutrition Examination Survey [1].

Researchers have been concerned with health outcomes in relation to vitamin D deficiency. It is well known that vitamin D deficiency is associated with osteoporosis through its effects on parathyroid hormone [2, 3]. Several studies show that vitamin D deficiency is also associated with chronic diseases such as cardiovascular disease [4, 5] and cancer [6, 7]. Other studies have found vitamin D deficiency to be associated with inflammatory disease. In the Iowa Women's Health Study, low vitamin D ingestion was associated with rheumatoid arthritis [8], and vitamin D deficiency has been associated with disease severity in systemic lupus erythematosus patients [9].

The harmful effects of vitamin D deficiency are relevant to all of the people. However, it is more efficient to find the risk groups of vitamin D deficiency and to supply vitamin D to the groups. Elderly people are especially vulnerable to the risks of vitamin D deficiency, because they tend to spend more time indoors, receive less dietary vitamin D, be more obese, and have reduced renal function [10]. Smokers might be vulnerable to the risks of vitamin D deficiency. Smoking is associated with vitamin D levels [11] and is a well-known risk factor for inflammation [12, 13]. However, few studies have quantitatively assessed whether smoking modifies the impact of vitamin D on inflammation.

The aims of our study were to investigate the association of vitamin D and inflammatory markers and to evaluate whether the association changes with smoking status in the urban elderly. If smoking is an effect modifier of the vitamin D-inflammation relationship, vitamin D deficiency of elderly smokers would be more risky than that of elderly non-smokers.

Methods

Study population

We used data from the Korean Elderly Environmental Panel Study, which included 560 Koreans aged 60 years or older living in Seongbuk-gu, Seoul, Republic of Korea. The study began in August 2008 and ended in August 2010. Baseline surveys and the first measurement were performed between August 2008 and December 2008. The second measurement was performed between April 2009 and October 2009, and the third between March 2010 and August 2010. We excluded participants with an acute inflammatory condition, levels of high- sensitivity C-reactive protein (hs-CRP) ≥1 mg/dL, or a white blood cell (WBC) count ≥ 10,000/μL [14, 15]. We also excluded participants with missing measures of vitamin D, hs-CRP, and WBC count. A final total of 529 participants were included in our study. Among them, the numbers of participants that visited once, twice, or three times were 213, 204, and 112, respectively. All participants submitted written informed consent. Seoul National University Hospital approved the study protocol (IRB No. H-0804-045-241).

Surveys and laboratory measurements

Skilled interviewers collected information using standard questionnaires. These included questions about age, sex, smoking status (smoked at least 400 cigarettes in life: yes/no) [16], alcohol consumption (alcohol drinking at least once a month in life: yes/no), and physical activity (exercise to the point of sweating in last week: <1–2 days or ≥1–2 days). Height and weight were measured in each series of the study.

Blood samples were taken from overnight–fasting participants at around 10 AM and stored at −70° C in light–proof bottles. Vitamin D levels were measured in blood samples as 25–hydroxyvitamin D (25(OH)D) concentrations; 25(OH)D is a widely used measure that reflects sun exposure and dietary intake [17]. 25(OH)D was measured using LIAISON equipment for chemiluminescent immunoassay (DiaSorin Inc., Stillwater, MN, USA); the limit of detection was 4 ng/mL. Hs–CRP levels were measured using latex agglutination turbidimetry with an automated analyzer (Hitachi 7180, Hitachi High–Technologies, Tokyo, Japan) and reagents (Pure Auto S CRP latex, Daiichi Pure Chemicals, Tokyo, Japan) .

Quality control was performed using an hs-CRP calibrator according to the protocol. WBC counts were measured using a cell counter.

We collected the middle stream of urine in order to measure cotinine levels. Cotinine, the metabolite of nicotine, is a biomarker for smoking status or smoking amount. The samples of urine were stored at -20° C. Urinary cotinine concentrations were measured using urine cotinine test strips (Accutest NicAlert Strip; Jant Pharmaceutical Co., Encino, California, USA). The limit of detection was 1–10,000 μg/L.

Statistical analysis

Continuous variables (vitamin D, hs-CRP, WBC count, body mass index (BMI)) were right-skewed, so they were natural log-transformed before further analysis. We used the χ^2 test and Student's t-test to analyze baseline characteristics and distribution of variables. To explore the association of vitamin D concentration with inflammatory markers, we used generalized estimating

equations (GEE). Model 1 had only one explanatory variable (vitamin D concentration). Model 2 had three adjustment variables (age, sex, visit number) in addition to model 1. Model 3 had five adjustment variables (smoking status, alcohol consumption status, exercise status, BMI, month of visit) in addition to the variables of model 2. We adjusted for the month of the visit in consideration of the seasonal variation of vitamin D and inflammatory markers [18, 19]. Model 3 plus an interaction term (log −transformed vitamin D*smoking) in GEE was used to evaluate the vitamin D−smoking interaction on inflammation. The statistical programs SAS 9.3 (Cary, NC, USA) and R 2.15.2 (The Comprehensive R Archive Network) were used for all analyses.

Results

Table 1 shows the participant characteristics, stratified by smoking status. There were 61 smokers (11.5%) among the participants. 91.8% of smokers and 16.7% of non-smokers were male. Given the sex difference in smoking status, we described participant characteristics separately by sex. Among all participants, smokers had higher vitamin D concentrations than non-smokers, and the difference is statistically significant ($p = 0.001$). However, there is no significant difference after stratification by sex. Smokers had slightly higher hs-CRP concentrations than non-smokers among all participants and among males ($p = 0.085$ in total, $p = 0.040$ in males). Additionally, smokers had higher WBC counts than nonsmokers among all participants and among males ($p < 0.001$ in total, $p < 0.001$ in males). Age was not different between smokers and non-smokers.

Table 2 shows the participants' vitamin D status. We used average values calculated from repeated measures on the same participants. Only 28.4% of males and 21.0% of females had optimal vitamin D concentrations. About half of the participants were of vitamin D insufficiency status (males: 58.2%, females: 47.1%), and some were

at vitamin D deficient status (males: 13.4%, females: 31.9%). The reference value for vitamin D insufficiency and the reference value for vitamin D deficiency was defined according to Tracher et al [20]

The association of serum vitamin D concentration with inflammatory markers is shown in Table 3. After adjusting for known confounders, the association of vitamin D deficiency and hs-CRP was significant. (β = -0.080, p = 0.041). However, there was no significant association between vitamin D deficiency and WBC count (β = 0.003, p = 0.805).

Effect modification was observed when we analyzed separately according to smoking status (Table 4). In smokers, vitamin D deficiency was significantly associated with hs-CRP after controlling for known confounders (β = -0.375, p = 0.013). In non-smokers, the estimate of association was smaller than in smokers and was not statistically significant (β = -0.060, p= 0.150).

Table 5 shows that the estimate of interaction between vitamin D concentration and smoking status on hs-CRP was significant (β = -0.254, p = 0.032). The estimate of association in smokers is considered to be significantly different from that in non-smokers,

because the p-value of the interaction is significant in multiple linear regression [21]. Fig. 1 shows slopes of vitamin D-hs-CRP association curves differ depending on smoking status. Because most smokers were males, we analyzed separately by sex. In females, there was a stronger interaction effect (β = -1.047, p < 0.001). In males, the interaction effect was not significant (β = -0.255, p = 0.126). However, the interaction estimate in males was not attenuated in comparison with that in total subjects, and its direction did not change, so the non-significant result might simply be due to the weaker statistical power in analyzing males separately (smaller sample size).

The association of vitamin D and inflammatory markers, stratified by sex, is shown in Table 6. The estimate of the association in men was slightly different from that in females, and the interaction effect of vitamin D-sex on hs-CRP was not significant (β = -0.077, p = 0.428).

In a sensitivity analysis, we included participants considered at acute or severe inflammatory status (hs-CRP ≥1 mg/dL, WBC count ≥ 10,000/μL). This analysis included the total 538 participants, 999 measurements. The results of this analysis were presented in Table

7-9. The association of vitamin D and hs-CRP was stronger than that of main results (Table 3), and still significant. The association of vitamin D and WBC count was not significant, that is similar to main results. The associations of vitamin D and hs-CRP were significant in both smokers and non-smokers, after adjusting for known confounders (Table 8). Table 9 shows the interaction effect of vitamin D and smoking status on hs-CRP. In total participants, the value of interaction effect was similar to that of the main analysis, and borderline significant (β = -0.255, p = 0.085). In males and females, the interaction effects were significant, respectively. The interaction effect of vitamin D and smoking status on hs-CRP might remain after including acute or severe inflammatory status.

Previous studies suggested other factors associated with levels of hs-CRP. Hs-CRP could be associated with blood glucose concentrations, systolic blood pressure, or pulse pressure [22-24]. After we analyzed the data adjusting for blood glucose concentrations and systolic blood pressure in addition to model 3, the results were not largely different compared to main results (the interaction effect in total: β = -0.254, p = 0.035). After analyzed adjusting for glucose concentrations and pulse pressure in addition to model 3, we

found similar results compared to main results (the interaction effect in total: $\beta = -0.253$, $p = 0.036$).

Table 10 shows the association of vitamin D and hs-CRP, stratified by urinary cotinine level. Urinary cotinine levels were creatinine-corrected, divided into quartiles. The highest quartile (Q4) had stronger estimates than the lowest quartile (Q1). The association of vitamin D and hs-CRP was significant in the highest quartile (Q4).

After we divided smoking status into 3 groups (current smoker, ex-smoker, non-smoker), we analyzed the data. The results were presented in Table 11. After adjusting for known confounders, the estimate of vitamin D-hs-CRP association was highest in current smokers, and lowest in non-smokers.

Discussion

The main findings of this study are that there is a significant association of vitamin D deficiency and hs-CRP, and that smoking status is an effect modifier of this association. We found that smokers have a stronger association of vitamin D deficiency and hs-CRP than non-smokers.

Previous studies have reported the association of vitamin D deficiency and hs-CRP. Mellenthin et al. reported that 25(OH)D concentrations were inversely associated with hs-CRP in the general adult population [18]. Patel et al. showed that concentrations of 25(OH)D and 1,25-dihydroxyvitamin D (1,25(OH)2D), a bioactive form of vitamin D, were inversely associated with CRP in patients with early inflammatory polyarthritis [25]. A meta-analysis investigated the association of dietary supplemental vitamin D with hs-CRP and reported a pooled effect of -1.08 mg/L (95%CI, -2.13 to -0.03, $p < 0.01$) [26]. Our results are in line with these studies.

Some studies report conflicting results, however Shea et al. reported that vitamin D levels were inconsistently associated with inflammatory markers. They did not find an association of 25(OH)D

levels and hs-CRP levels; however, their study had some different factors (age of participants, exclusion criteria, analysis method) from those in our study [17]. Eren et al. showed that vitamin D levels are not associated with inflammatory markers in patients with acute coronary syndrome; however, their participants did not represent the general population [27].

Few studies have investigated the interaction between smoking and vitamin D on inflammation. Merlino et al. previously suggested such an interaction in a cohort study in older females. Compared to nonsmokers with low vitamin D intake, smokers with higher vitamin D intake had a trend of lower risk of rheumatoid arthritis, while smokers with lower vitamin D intake were at increased risk of the disease. However, the estimate of interaction was not significant [8].

Some studies explained the mechanism that vitamin D3 treatment modulated oxidative stress by reducing lipid peroxidation and superoxide dismutase activity [28-30]. Oxidative stress can lead to inflammation by activation of transcription factors related inflammatory system such as nuclear factor kappa-light-chain-enhancer of activated B cells, activator protein-1, and nicotinamide adenine dinucleotide phosphate-oxidase [31]. In cigarettes, there

are a lot of oxidants that induce lipid peroxidation such as production of F_2-isoprostanes [32, 33]. This mechanism may explain that smoking is an effect modifier of vitamin D deficiency-inflammation association.

Some studies showed that females are more sensitive to smoking effects than males in chronic diseases such as lung cancer or cardiovascular disease [34, 35]. Our results are similar to those studies in that females had stronger relations of vitamin D with inflammation than males.

We found that smoking status (smoker or non-smoker) would change the association of vitamin D and hs-CRP. Furthermore, our results show that an increase of smoking level would strengthen the association of vitamin D and hs-CRP in a certain degree.

There are few epidemiological studies showing the association of vitamin D and WBC count. Mellenthin et al. investigated the association of vitamin D deficiency and WBC count in the general adult population and found that vitamin D deficiency was associated with WBC count in smokers (n = 718) but not in non-smokers (n = 2005) [18]. Yildirim et al. reported no significant difference in WBC count between vitamin D deficient patients and control groups [36].

We did not find a significant association between vitamin D deficiency and WBC count. After analyzing separately by smoking status, we did not find significant associations in either smokers or non-smokers (data not shown). Moreover, we did not find any vitamin D-smoking interaction effect on WBC count (β = -0.040, p = 0.680). However, some studies have investigated the associations of vitamin D and specific types of WBC. Some studies have found that 1,25(OH)D prevented differentiation and maturation of dendritic cells [37, 38], while Groot et al. showed that vitamin D treatment lowered the eosinophil count in non-atopic asthma patients who had a high baseline eosinophil count [39]. We suggest that evaluation of different forms of inflammatory cells, not just the total WBC count, may be a useful method to identify the association of vitamin D and inflammation.

We found that more than 70% of older adults in our study were vitamin D insufficient. The arithmetic mean level of vitamin D concentration was 16.73 (SD: 6.91) in males and 14.57 (SD: 7.32) in females. According to the 2010-2011 Korean National Health and Nutrition Examination Survey(KNHANES), the mean vitamin D concentrations were 20.13- 20.51 ng/mL in males ≥60 years and

18.20−18.92 ng/mL in females ≥ 60 years [40]. Vitamin D concentrations in our study participants may be slightly lower than the national level. There might be several reasons. First, all of our participants are in an urban area (Seoul); some studies have reported differences in vitamin D levels between urban and rural areas [40, 41]. Second, our measurement method was different from that of KNHANES. We measured vitamin D using chemiluminescent immunoassay, but KNHANES measured using radioimmunoassay (equipment; 1470 WIZARD gamma−Counter, PerkinElmer, Finland, reagent; 25−Hydroxyvitamin D 125I RIA Kit, DiaSorin, USA).

Previous studies have shown that smokers have lower vitamin D concentrations than non−smokers [11, 42]. In our study, smokers had higher vitamin D concentrations. This may result from sex differences in vitamin D concentrations; females tend to have lower vitamin D concentrations [40, 41]. In our study, most smokers were males. We calculated the estimate of interaction between vitamin D and sex, but no effect modification was observed. Therefore, the effect modification between vitamin D and smoking on hs−CRP were resulted from a true effect of smoking and not from an effect of sex.

Our study has several limitations. First, we investigated participants living in one region. Because of regional differences influencing vitamin D level and smoking status, investigation of representatively selected regions could increase the validity of the study. Second, we could not completely exclude the presence of inflammatory diseases. We collected diagnoses of the diseases through questionnaires completed by participants. However, we further excluded participants with high levels of inflammatory markers suggestive of acute inflammatory status. Third, the measurable inflammatory markers in our study were limited. We used only two markers, hs-CRP and WBC count. CRP is a well-known non-specific inflammatory marker. The high-sensitivity CRP method can detect very low levels of CRP (lower detection limits of 0.02 mg/dL) [43]. Hs-CRP concentrations increase slightly with low-level inflammation (coronary artery disease, mild chronic infection, and tissue damage, etc.), and are markedly increased with high-level inflammation (bacterial or fungal infection) [44]. The total WBC count is also a well-known non-specific inflammatory marker. The WBC count increased with low-level inflammation (chronic inflammation, smoking, stress, etc.) and markedly increased with

high-level inflammation (bacterial infection, bone marrow disease, etc.). Given the potential for high-level inflammation to distort the association of vitamin D and inflammatory markers, we excluded participants considered to be in an acute or severe inflammatory state from our analysis. These two non-specific inflammatory markers may not be enough, however, to represent chronic low-level inflammation. Therefore, further studies are needed to investigate the association of vitamin D level and other inflammatory markers such as cytokines or specific WBC types. To our knowledge, this is the first study reporting that smoking status is a significant effect modifier of the vitamin D deficiency-hs-CRP association.

Conclusion

We have found that significant association of vitamin D deficiency and hs-CRP in the urban elderly. Smoking status is an effect modifier of this association. In urban elderly smokers, vitamin D deficiency appears to be more risky for increasing hs-CRP. However, we could not find a significant association of vitamin D and WBC count. Larger longitudinal studies are needed to investigate associations of vitamin D and other inflammatory markers and any causal relationships.

Table 1. Participant Characteristics

	Total (n = 529)			Male (n = 134)			Female (n = 395)		
	n (%)								p^3
Smoking status									
Smoker[1]	61 (100.0)			56 (91.8)			5 (8.2)		0.001
Non-smoker	468 (100.0)			78 (16.7)			390 (83.3)		
	Smoker	Non-smoker	p^3	Smoker	Non-smoker	p^3	Smoker	Non-smoker	p^3
Alcohol consumption									
Non-drinking	19 (31.7)	389 (83.5)	<.001	15 (25.0)	42 (9.0)	0.002	4 (6.7)	347 (74.5)	0.441
Drinking	41 (68.3)	77 (16.5)		40 (66.7)	35 (7.5)		1 (1.6)	42 (9.0)	
Exercise									
<1-2 times/week	23 (37.7)	169 (36.2)	0.817	23 (37.7)	26 (5.6)	0.359	0 (0.0)	143 (30.6)	0.164
≥1-2 times/week	38 (62.3)	298 (63.8)		33 (54.1)	52 (11.1)		5 (8.2)	246 (52.7)	
Month of visit[2]									
March-October	69 (62.7)	581 (68.6)	0.215	63 (57.3)	108 (12.8)	0.003	6 (5.4)	473 (55.8)	0.275

November–April	41 (37.3)	266 (31.4)		38 (34.5)	27 (3.2)		3 (2.8)	239 (28.2)	
	Mean (Standard deviation)[4]								
Age[2]	70.96 (4.20)	70.69 (5.35)	0.540	71.24 (4.03)	71.51 (4.58)	0.634	67.89 (5.01)	70.54 (5.48)	0.149
Vitamin D[2] (ng/mL)	15.43 (1.76)	12.53 (1.89)	0.001	15.64 (1.78)	14.57 (1.62)	0.303	13.29 (1.48)	12.18 (1.94)	0.693
hs–CRP[2] (mg/dL)	0.12 (1.95)	0.10 (2.05)	0.085	0.11 (1.94)	0.09 (1.97)	0.040	0.16 (2.06)	0.10 (2.07)	0.091
WBC count[2] (thousand/μL)	6.10 (1.27)	5.46 (1.27)	<.001	6.17 (1.27)	5.52 (1.26)	<.001	5.37 (1.24)	5.45 (1.27)	0.854
BMI[2] (kg/m^2)	24.01 (1.14)	24.67 (1.12)	0.040	23.90 (1.44)	24.13 (1.12)	0.549	25.31 (1.05)	24.77 (1.12)	0.240

hs–CRP, high–sensitivity C–reactive protein; WBC, white blood cell; BMI, body mass index

[1]Smokers are participants who have smoked at least 400 cigarettes in life.

[2]The total number of repeated measures was 957 (smokers: 110, non–smokers: 847).

[3]p–value for categorical variables(sex, alcohol consumption status, exercise status, month of visit); we used χ^2 test. . If expected values were < 5, we described the Fisher exact p–value.

p–value for continuous variables(age, vitamin D, hs–CRP, WBC count, BMI); we used Student t–test. All variables except age were log–transformed.

[4]Age: arithmetic mean, SD of the mean; Vitamin D, hs–CRP, WBC, BMI: geometric mean, SD of the geometric mean.

Table 2. Vitamin D status

Vitamin D status	Men (n = 134)	Women (n =395)
	n (%)	
Vitamin D deficiency (<10 ng/mL)	18 (13.4)	126 (31.9)
Vitamin D insufficiency (10–<20 ng/mL)	78 (58.2)	186 (47.1)
Vitamin D optimal (≥20 ng/mL)	38 (28.4)	83 (21.0)
	Mean[1] SD	
Vitamin D concentration	16.730 (6.908)	14.573 (7.324)

[1]Mean: Arithmetic mean for comparison to previous studies; SD, standard deviation

Table 3. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) count.

	hs-CRP		WBC	
	β (SE)	p-value	β (SE)	p-value
Model 1[1]	-0.082 (0.039)	0.036	-0.005 (0.011)	0.666
Model 2[2]	-0.070 (0.040)	0.079	0.007 (0.012)	0.584
Model 3[3]	-0.080 (0.039)	0.041	0.003 (0.012)	0.805

SE, standard error

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, smoking status, alcohol consumption status, exercise status, body mass index, month of visit

Table 4. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP): stratification by smoking status

	hs-CRP			
	Smoker		Non-smoker	
	β (SE)	p-value	β (SE)	p-value
Model 1[1]	−0.320 (0.102)	0.002	−0.061 (0.042)	0.152
Model 2[2]	−0.315 (0.110)	0.004	−0.049 (0.042)	0.249
Model 3[3]	−0.375 (0.150)	0.013	−0.060 (0.042)	0.150

SE, standard error

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, alcohol consumption status, exercise status, body mass index, month of visit

Table 5. Interaction effect of serum vitamin D concentration and smoking status on serum high-sensitivity C-reactive protein (hs-CRP)

	hs-CRP					
	Total		Male		Female	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Vitamin D *smoking[1]	−0.254 (0.118)	0.032	−0.255 (0.167)	0.126	−1.047 (0.093)	<0.001

SE, standard error

[1]Adjusted for age, sex, visit number, alcohol consumption status, exercise status body mass index, month of visit. In males and females, adjusted for the same variables except sex.

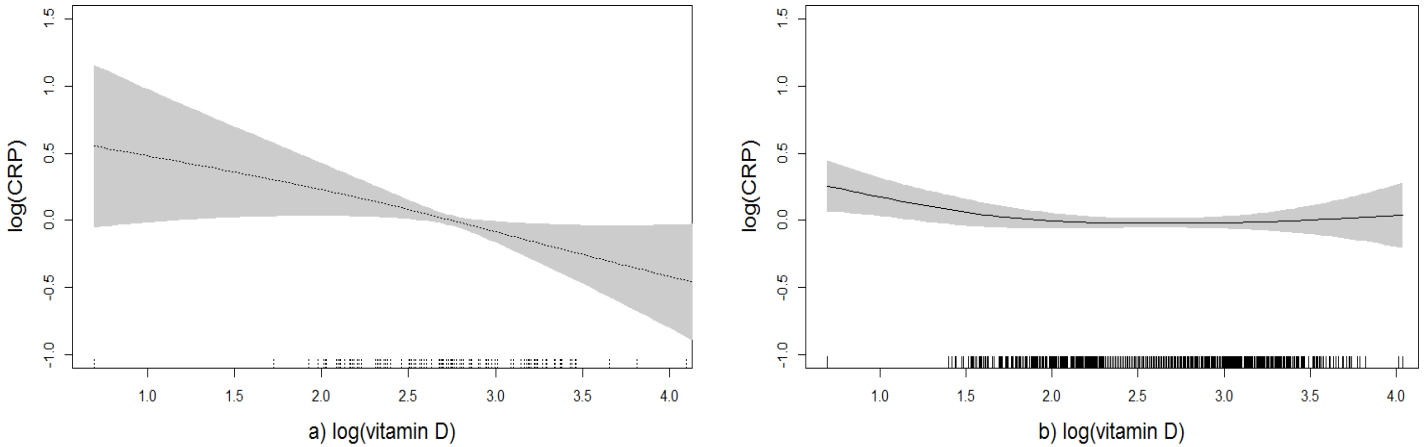

Figure 1. Association of serum vitamin D and serum high-sensitivity C-reactive protein (hs-CRP): using generalized additive model plots, in a) smokers and b) non-smokers. Adjusted for age, sex, visit number, alcohol consumption status, exercise status, body mass index, month of visit.

Table 6. Associations of serum vitamin D concentration or serum high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) count: stratification by sex

	hs-CRP				WBC			
	Male		Female		Male		Female	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Model 1[1]	−0.134 (0.086)	0.118	−0.067 (0.044)	0.134	−0.045 (0.023)	0.535	−0.006 (0.013)	0.629
Model 2[2]	−0.145 (0.091)	0.110	−0.054 (0.044)	0.223	−0.009 (0.024)	0.713	0.008 (0.013)	0.545
Model 3[3]	−0.146 (0.093)	0.118	−0.062 (0.043)	0.156	0.019 (0.024)	0.430	0.003 (0.013)	0.827

SE, standard error; p, p-value

[1]Not adjusted
[2]Adjusted for age, visit number
[3]Adjusted for age, visit number, smoking status, alcohol consumption status, exercise status, body mass index, month of visit

Table 7. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) count (Including participants considered at acute or severe inflammatory status)

	hs-CRP		WBC	
	β (SE)	p-value	β (SE)	p-value
Model 1[1]	−0.174 (0.047)	<0.001	−0.019 (0.013)	0.131
Model 2[2]	−0.147 (0.047)	0.002	−0.010 (0.013)	0.439
Model 3[3]	−0.159 (0.049)	0.001	−0.014 (0.013)	0.290

SE, standard error

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, smoking status, alcohol consumption status, exercise status, body mass index, month of visit

Table 8. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP): stratification by smoking status (Including participants considered at acute or severe inflammatory status).

	hs-CRP			
	Smoker		Non-smoker	
	β (SE)	p-value	β (SE)	p-value
Model 1[1]	−0.364 (0.122)	0.003	−0.151 (0.051)	0.003
Model 2[2]	−0.439 (0.145)	0.003	−0.115 (0.050)	0.021
Model 3[3]	−0.502 (0.173)	0.004	−0.131(0.050)	0.009

SE, standard error

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, alcohol consumption status, exercise status, body mass index, month of visit

Table 9. Interaction effect of serum vitamin D concentration and smoking status on serum high-sensitivity C-reactive protein (hs-CRP) (Including participants considered at acute or severe inflammatory status).

	hs-CRP					
	Total		Male		Female	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Vitamin D *smoking[1]	-0.255 (0.148)	0.085	-0.363 (0.180)	0.044	-0.810 (0.176)	<0.001

SE, standard error

[1]Adjusted for age, sex, visit number, alcohol consumption status, exercise status body mass index, month of visit. In males and females, adjusted for the same variables except sex.

Table 10. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP): stratification by urinary cotinine level

	hs-CRP							
	Cotinine Q1		Cotinine Q2		Cotinine Q3		Cotinine Q4	
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p
Model 1[1]	−0.141 (0.068)	0.038	0.090 (0.064)	0.163	−0.093 (0.080)	0.247	−0.260 (0.100)	0.008
Model 2[2]	−0.126 (0.070)	0.071	0.119 (0.065)	0.067	−0.100 (0.081)	0.216	−0.238 (0.100)	0.017
Model 3[3]	−0.120 (0.079)	0.129	0.049 (0.063)	0.439	−0.091 (0.075)	0.226	−0.268 (0.111)	0.016

SE, standard error; p, p-value; Q, quartile
Q1; creatinine-corrected urinary cotinine < 0.882 μg/g, Q2; 0.882- 2.210 μg/g, Q3; 2.211- 4.885 μg/g, Q4; ≥ 4.886 μg/g

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, alcohol consumption status, exercise status, body mass index, month of visit

Table 11. Associations of serum vitamin D concentration with serum high-sensitivity C-reactive protein (hs-CRP): stratification by detailed smoking status

	hs-CRP					
	Current smoker		Ex-smoker		Non-smoker	
	β (SE)	*p*-value	β (SE)	*p*-value	β (SE)	*p*-value
Model 1[1]	−0.325 (0.118)	0.006	−0.381 (0.184)	0.038	−0.061 (0.042)	0.152
Model 2[2]	−0.312 (0.118)	0.008	−0.569 (0.221)	0.010	−0.049 (0.042)	0.249
Model 3[3]	−0.543 (0.240)	0.024	−0.374 (0.296)	0.206	−0.060 (0.042)	0.150

SE, standard error
Ex-smoker; 33 participants, 54 measurements

[1]Not adjusted
[2]Adjusted for age, sex, visit number
[3]Adjusted for age, sex, visit number, alcohol consumption status, exercise status, body mass index, month of visit

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국문초록

도시지역 노인에서 비타민 D 와 염증표지자의 관련성 및 비타민 D 와 흡연의 상호작용

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목적: 많은 역학 연구들은 비타민 D 결핍과 염증성 질환과 관계가 있다고 보고하고 있다. 흡연은 염증의 위험인자로 잘 알려져 있다. 하지만, 비타민 D 결핍과 흡연의 상호작용이 염증에 미치는 영향에 대한 연구는 거의 없다. 본 연구는 비타민 D 와 염증표지자의 관련성 및 비타민 D 와 흡연의 상호작용과 염증표지자의 관련성을 도시지역 거주 노인 대상으로 연구하고자 하였다.

방법: 한국노령인구패널(Korean Elderly Environmental Panel, KEEP)자료를 이용하였으며, 이 조사는 2008 년 8 월부터 2010 년 8 월까지 수행되었으며, 서울에 거주하는 60 세 이상 노인을 대상으로 하였다. 첫 방문 시에 흡연에 대한 항목을 포함한 설문조사가 이루어졌고, 비타민 D, 고감도 C-반응단백 (high-sensitivity C-reactive protein, hs-CRP), 백혈구 수치는 최대 3 회까지 반복측정

되었다. 비타민 D 와 염증표지자의 관련성 분석에는 일반화추정방정식(generalized estimating equations)을 이용하였다.

결과: 알려진 혼란변수들을 보정한 후 비타민 D 와 hs-CRP 와의 관련성은 통계적으로 유의하였다 (β = -0.080, p = 0.041). 흡연 상태에 따라 구분하여 분석한 결과, 흡연자에게서 비타민 D 결핍과 hs-CRP 의 관련성의 정도가 비흡연자보다 강하였다. (흡연자: β = -0.375, p = 0.013, 비흡연자: β = -0.060, p = 0.150). 흡연은 비타민 D 결핍과 hs-CRP 와의 관련성을 변화시키는 효과변경인자(effect modifier)이었다. (상호작용의 추정치: -0.254, p = 0.032). 비타민 D 와 백혈구 수치는 유의한 관련성을 나타내지 않았다. (β = 0.003, p = 0.805).

결론: 도시지역 거주 노인에게서 비타민 D 결핍은 hs-CRP 와 유의한 관련성이 있었다. 흡연은 이 관련성의 효과변경인자이었다. 비타민 D 결핍은 백혈구 수치와는 유의한 관련성이 나타나지 않았다.

키워드: 비타민 D, 흡연, C-반응단백, 백혈구, 염증

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