Master of Science in Clinical medical sciences

Association between serum ferritin levels and significant coronary artery stenosis in asymptomatic Korean adults

무증상 한국 성인에서 혈중 ferritin 농도와 관상동맥 협착 간의 연관성

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Association between serum ferritin levels and significant coronary artery stenosis in asymptomatic Korean adults

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Abstract

Objective: Iron hypothesis was first proposed in 1981 suggesting that body iron stores were positively related to coronary heart disease. However there have been conflicting results regarding association between serum ferritin and cardiovascular disease. Therefore, we aimed to evaluate association between ferritin and significant coronary artery stenosis (CAS) in asymptomatic Korean adults.

Methods: Our population is composed of 1,511 (710 male and 801 female) subjects over 40 aged who took routine health check-ups including coronary computed tomography angiography(CTA) at Seoul National University Hospital Health Promotion Center. Significant CAS was defined as any more than a 50% diameter stenosis. In multivariate logistic analysis, we assessed association between serum ferritin levels and significant CAS adjusting for age, sex, body mass index, smoking status, hypertension, diabetes, hypercholesterolemia and chronic kidney disease. Additionally, we assessed interaction between ferritin and cardiovascular risk factors.

Results: The prevalence of significant CAS was 5.4%. In univariate logistic regression analysis, the odds ratio (OR) for subjects with serum ferritin ≥ 300 ng/mL was 2.92 (95% confidence interval [CI] 1.38 - 6.18; p value = 0.005) compared with subjects with serum ferritin < 100 ng/mL. However, After adjusting for demographic, clinical, life style variables or C-reactive protein, ORs for subjects with serum ferritin ≥ 300 ng/mL was 2.31 (95% CI 1.02 - 5.23; p value = 0.045) in model 1, 2.11 (95% CI 0.92 - 4.84; p value = 0.096) in model 2 and 1.87 (0.80 - 4.35; p value = 0.147) in model 3 compared with subjects with serum ferritin < 100 ng/mL, respectively. In a subgroup analysis for interaction between ferritin and diabetes, smoking status, hypertension or hypercholesterolemia, there was a significant interaction only in smoking status.

Conclusion: We conclude that association between elevated serum

ferritin levels (≥ 300 ng/mL) and significant CAS is not significant in asymptomatic Korean. . However, significant association between ferritin levels more than 300 ng/mL and significant CAS compared with ferritin < 100 ng/mL was observed in non-diabetic subjects and current smoker. Further replicative studies are needed to elucidate this important association for specific population.

Keyword: ferritin, coronary artery stenosis, interaction, diabetes, current smoker
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I. Introduction

There are conflicting results regarding association between serum ferritin and cardiovascular disease. In 1981, Sullivan et al. first proposed the 'iron hypothesis', suggesting that body iron stores were positively related to coronary heart disease risk.[1] Since then, a number of studies have also noted association between body iron stores and metabolic syndrome[2, 3], especially insulin resistance.[4, 5] Some epidemiologic studies have reported ferritin can play a role as potential predictor for coronary artery disease.[6, 7]

Serum ferritin is regarded as the most sensitive and feasible biomedical measure of body iron stores.[8] Elevated serum ferritin concentrate on may reflect systemic inflammation as well as elevated iron stores.[9] Although the mechanisms of iron on the risk of cardiovascular disease are unclear, it has been hypothesized that elevated iron stores may interfere with hepatic insulin extraction leading to peripheral hyperinsulinemia.[10] Others have suggested that iron helps to catalyze the oxidation reactions that produce free radicals.[11] Free radicals cause lipid peroxidation, leading to modification at low-density lipoprotein (LDL) molecular level, facilitating its deposition and leading to the formation of atherosclerotic plaque.[12] In addition, it has been demonstrated that

free radicals directly act on the endothelial cell membrane, determining alterations in its defense mechanisms, probably facilitating leukocyte migration in to the arterial wall. The linked iron induced inflammation may contribute to increase risk of atherosclerosis.[4]

Meanwhile, many previous studies have not demonstrated the direct association between the body iron state and cardiovascular disease.[13, 14] In case-control study, adjustment for the traditional risk factors made this association non-significant. They concluded that there was no positive association between ferritin and coronary heart disease (CHD).[13] Moreover, a 17-years follow up prospective study has reported that there was little evidence on ferritin as a risk factor for cardiovascular disease.[14]

Given this conflicting association, we aimed to evaluate the association between serum ferritin levels and asymptomatic coronary artery stenosis as defined by coronary computed tomography angiography (CTA) in Korean population. Additionally, we assessed interaction between ferritin and well-known cardiovascular risk factors.

II. Methods

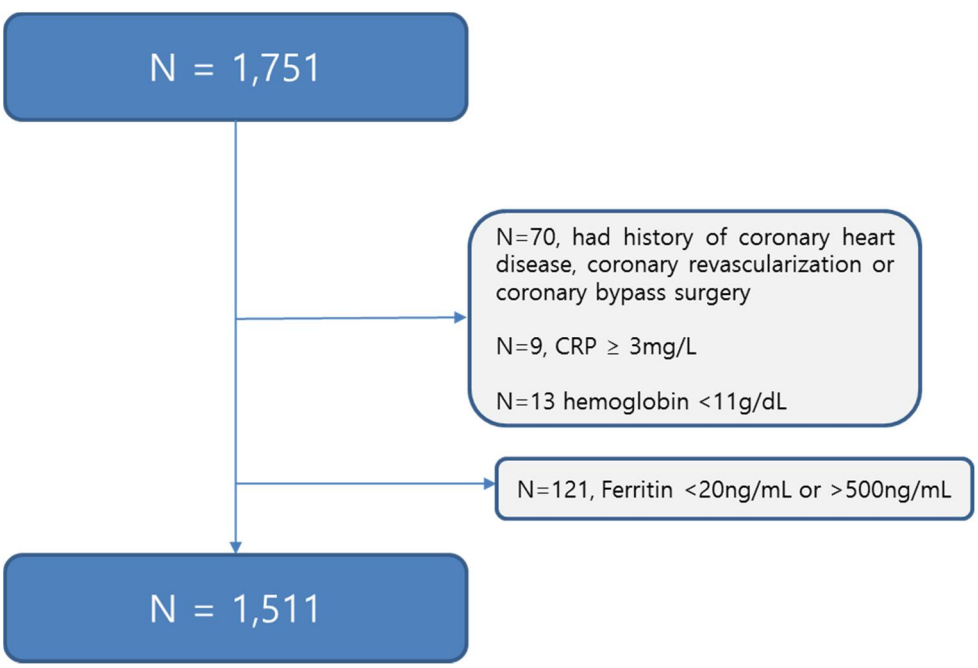
1. Study population.

The study population consisted of 1,511 individuals aged more than 40 years who underwent coronary CTA for health screening in Seoul National University Hospital from January 2010 to December 2015. We excluded individuals with symptoms related to angina such as chest pain after reviewing medical record retrospectively. We also excluded those with previous history of coronary heart disease, coronary revascularization, or coronary bypass surgery (n = 70), those with insufficient medical records (n = 27). C-reactive protein (CRP) is a representative acute phase reactant and CRP level greater than 3 mg/L which is related to quite an elevated cardiovascular risk. [15] Therefore, we excluded those with CRP greater than 3mg/L (n = 9). World Health Organization (WHO) anemia criteria defines mild anemia (hemoglobin 11 - 12.9 (men), 11.9 (women) g/dL), moderate anemia (8 - 10.9 g/dL) and severe (less than 8 g/dL).[16] According to WHO criteria, we excluded moderate to severe anemia which hemoglobin is less than 11 g/dL (n = 13). Additionally, we excluded serum ferritin levels less than

20 ng/mL (n = 85) and more than 500 ng/mL (n = 36). Although there has not been established ferritin normal range, previous studies defined hyperferritinemia as more than 500 ng/mL.[17] Finally, total 1,511 asymptomatic Korean adults were enrolled (Figure 1). All subjects were asked to fill out questionnaire that detailed medical history, regular medication and personal life style habits.

This study was approved by the Seoul National University Hospital institutional review board (IRB number: 1610-033-797) and the requirement for informed consent was waived.

Figure 1. Flow diagram of inclusion or exclusion of study population



2. Coronary artery stenosis

CT scans were performed with 64-slice MDCT (multidetector computed tomography) scanner. CAS was evaluated and described as the percentage of lumen diameter reduction. Each segment was described as significant (≥ 50% lumen diameter reduction) or non-significant (< 50% lumen diameter reduction). Previous radiologic study recommended coronary artery stenosis grading mild (25 - 49%), moderate (50 - 69%) and severe (70 - 90%).[18] Also many previous studies have demonstrated that significant coronary artery stenosis was related to prognosis of cardiovascular mortality. All coronary artery segments with a diameter > 1mm were included for analysis. Finally, we defined significant CAS as over half of lumen diameter reduction at least one coronary artery segment with more than 1mm diameter.

3. Biochemical measurements

Overnight fasting blood samples were taken in the morning for ferritin, fasting glucose, hemoglobin A1c, lipid, creatinine and c-reactive protein on the same day of the study. Concentration of ferritin was estimated by chemiluminescent microparticle

immunoassay (6C11 ARCHITECT, Abbott Park, IL, USA). The estimating glomerular filtration rate (eGFR, ml/min/1.73m2) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (GFR = 175 × serum creatinine − 1.154 × age − 0.203 × 0.742 [if, females]).

4. Clinical variables

Height and weight were used for calculation of body mass index [BMI=weight (kg)/height^2 (m^2)]. Smoking status were assessed as never, ever or current smoker. Hypertension was defined as a self−reported history of hypertension or use of antihypertensive medication or resting systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes was defined as a self−reported history of diabetes or use of oral hypoglycemic medication or subcutaneous insulin injection or a fasting plasma glucose ≥ 126 mg/dL or hemoglobin A1c ≥ 6.5%. Hyperlipidemia was defined as a self−reported history of hyperlipidemia or used of lipid lowering agents or total cholesterol ≥ 240 mg/dL. Chronic kidney disease was and defined as eGFR less than 60 mL/min/1.73 m^2

5. Statistical analysis

All statistical analyses were performed with STATA version 14.1 (Stata Corporation, College Station, Texas, USA). Data were expressed as percentages with number for categorical variables and mean ± standard deviation (SD) for continuous variables. χ^2-test was performed to compare the categorical variables and t-test was used to test the difference of continuous variables between subjects with non-significant CAS and with significant CAS. The variables related to significant CAS at a p value of less than 0.10 were included for further evaluation. We used multivariate logistic analysis to investigate the association between ferritin and presence of significant CAS through three model. Model 1 was adjusted for demographic information (age and sex); model 2 was adjusted for the same variables as model 1 plus clinical factors (hypertension, diabetes, hypercholesterolemia and chronic kidney disease); and model 3 was adjusted for the same variables as model 2 plus life style factors (BMI and smoking) and CRP.

A trend test for a linear trend was used to assess p for trend across three ferritin levels categories. To investigate whether the associations differed by well-known cardiovascular risk factors such as diabetes, hypertension and hypercholesterolemia, we

analyzed univariate and multivariates logistic regression adding multiplicative interaction terms (ferritin × variables).

III. Results

1. Baseline characteristics

The baseline characteristics of total subjects in this study are presented in table 1. Among 1,511 subjects, 81 (5.4%) had significant CAS, which is composed of male (n = 53) and female (n = 29). The mean age was 57.5 ± 8.4 years, 53.0% were female in total subjects. The average serum concentration of ferritin was significantly higher in subjects with significant CAS (152.2 ± 108.4 ng/mL) than non-significant CAS (127.1 ± 87.9 ng/mL) (Table 1). The proportion of those with ferritin levels more than 300 ng/mL were much higher in subjects with significant CAS (12.3%) than without significant CAS (5.2%). The subjects with significant CAS were likely to be older, smoker and have higher BMI compared with non-significant CAS. Hypertension, diabetes, hypercholesterolemia and chronic kidney disease were reported more frequently in subjects with significant CAS. Baseline hemoglobin showed significant difference (p value = 0.043) between two groups but the gap of average hemoglobin levels (14.4

± 1.4 g/dL and 14.7 ± 1.5 g/dL) was not significant clinically. CRP showed no significant differences between two groups (p value = 0.167).

Table 1. Baseline characteristics of study population.

	Total (N = 1,511)	Significant CAS		*p* value
		without Significant CAS (N = 1,430)	With Significant CAS (N = 81)	
Age – year ± SD	57.5 ± 8.4	57.3 ± 8.3	62.2 ± 9.0	<0.001
Sex – N (%)				0.001
Male	710 (47.0)	657 (45.9)	53 (65.4)	
Female	801 (53.0)	773 (54.1)	29 (34.6)	
BMI – kg/m^2 ± SD	24.0 ± 3.1	24.0 ± 3.1	25.1 ± 2.5	<0.001
Smoking – N (%)				<0.001
Non-smoker	900 (59.6)	870 (60.8)	30 (37.0)	
Ex-smoker	360 (23.8)	332 (23.2)	28 (34.6)	
Current Smoker	251 (16.6)	228 (15.9)	23 (28.4)	
Ferritin – ng/mL ± SD	128.4 ± 89.2	127.1 ± 87.9	152.2 ± 108.4	0.014
< 100	724 (47.9)	692 (28.4)	32 (39.5)	0.015
100-300	703 (46.5)	664 (46.4)	39 (48.2)	
300 ≤	84 (5.6)	74 (5.2)	10 (12.3)	
Hypertension [a] – N (%)				<0.001
No	928 (61.4)	896 (62.7)	32 (39.5)	
Yes	583 (38.6)	534 (37.3)	49 (61.5)	
Diabetes [b] – N (%)				<0.001
No	1,273 (84.3)	1,223 (85.5)	50 (61.7)	
Yes	238 (15.7)	207 (14.5)	31 (38.3)	
Hypercholesterolemia [c] – N (%)				0.023
No	1,131 (74.8)	1,079 (75.5)	52 (64.2)	
Yes	380 (25.2)	351 (24.5)	29 (35.8)	
CKD [d] – N (%)				0.058
No	1,431 (94.7)	1,358 (95.0)	73 (90.1)	
Yes	80 (5.3)	72 (5.0)	8 (9.9)	

SBP – mmHg ± SD	125.7 ± 16.2	125.5 ± 16.2	130.2 ± 15.5	0.011
DBP – mmHg ± SD	75.8 ± 10.7	75.8 ± 10.8	76.3 ± 10.2	0.666
FBG – mg/dL± SD	96.4 ± 21.8	95.7 ± 20.8	109.9 ± 32.9	<0.001
TC – mg/dL± SD	203.6 ± 36.9	203.5 ± 37.0	206.7 ± 36.7	0.448
TG – mg/dL± SD	112.8 ± 67.8	111.2 ± 66.4	140.8 ± 84.9	<0.001
LDL – mg/dL± SD	130.4 ± 35.5	130.0 ± 35.4	135.6 ± 36.5	0.169
HDL – mg/dL± SD	55.4 ± 14.7	55.8 ± 14.7	48.2 ± 12.7	<0.001
Hemoglobin – g/dL± SD	14.4 ± 1.4	14.4 ± 1.4	14.7 ± 1.5	0.043
CRP – mg/L ± SD	0.13 ± 0.25	0.13 ± 0.24	0.17 ± 0.32	0.167

Abbreviation: CAS = coronary artery stenosis. BMI = body mass index. CKD = chronic kidney disease. SBP = systolic blood pressure. FBG = fasting blood glucose. TC = total cholesterol. TG = triglycerides. LDL = low density lipoprotein. HDL = high density lipoprotein. CRP = C-reactive protein.

Data represented as mean ± standard deviation (SD) or number (%)

[a] Hypertension was defined as those who were taking antihypertensive drugs or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg.

[b] Diabetes was defined as those who were taking oral hypoglycemic agents or insulin or hemoglobin A1c ≥ 6.5%, or fasting glucose ≥ 126 mg/dL.

[c] Hypercholesterolemia was defined as those who were taking lipid lowering drugs or total cholesterol ≥ 240 mg/dL.

[d] Chronic kidney disease was defined as eGFR less than 60 mL/min/1.73 m^2

2. Association between ferritin and significant CAS

In univariate logistic analysis, the odds ratio (OR) for subjects with serum ferritin ≥ 300 ng/mL was 2.92 (95% confidence interval [CI] 1.38 – 6.18; p value = 0.005) compared with subjects with serum ferritin < 100 ng/mL (Table 2). After adjusting for demographic, clinical, life style variables and CRP, ORs for subjects with serum ferritin ≥ 300 ng/mL was 2.31 (95% CI 1.02 – 5.23; p value = 0.045) in model 1, 2.11 (95% CI 0.92 – 4.84; p value = 0.078) in model 2 and 1.87 (0.80 – 4.35; p value = 0.147) in model 3 compared with subjects with serum ferritin < 100 ng/mL, respectively.

Table 2. Association of ferritin levels with significant CAS

	Univariable Analysis		Model 1		Model 2		Model 3	
All (N = 1,511)	OR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
Age (1-year difference)	1.07 (1.04 – 1.09)	< 0.001	1.08 (1.05 – 1.10)	<0.001	1.06 (1.03 – 1.09)	< 0.001	1.07 (1.04 – 1.11)	< 0.001
Sex (Female)	0.45 (0.28 – 0.72)	0.001	0.45 (0.27 – 0.75)	0.002	0.42(0.25 – 0.70)	0.001	0.80 (0.38 – 1.70)	0.563
Ferritin (ng/mL)								
< 100	1.00		1.00		1.00		1.00	
100-300	1.27 (0.79 – 2.05)	0.328	1.08 (0.65 – 1.81)	0.755	1.05 (0.63 – 1.77)	0.843	0.93 (0.55 – 1.59)	0.803
300 ≤	2.92 (1.38 – 6.18)	0.005	2.31 (1.02 – 5.23)	0.045	2.11 (0.92 – 4.84)	0.078	1.87 (0.80 – 4.35)	0.147
p for trend	0.019		0.138		0.201		0.390	
Hypertension [a]	2.57 (1.62 – 4.06)	< 0.001			1.87 (1.15 – 3.04)	0.011	1.60 (0.97 – 2.64)	0.067
Diabetes [b]	3.66 (2.28 – 5.87)	< 0.001			2.52 (1.54 – 4.11)	< 0.001	2.30 (1.40 – 3.79)	0.001
Hypercholesterolemia [c]	1.71 (1.07 – 2.74)	0.025			1.66 (1.01 – 2.72)	0.044	1.62 (0.98 – 2.67)	0.058
Chronic kidney disease [d]	2.07 (0.96 – 4.45)	0.064			1.11 (0.49 – 2.51)	0.796	1.08 (0.47 – 2.47)	0.848
BMI ($1kg/m^2$ difference)	1.12 (1.05 – 1.20)	0.001					1.09 (1.01 – 1.18)	0.029
Smoking								
Non-smoker	1.00						1.00	

Ex-smoker	2.44 (1.44 – 4.15)	0.001	2.25 (1.04 – 4.87)	0.039
Current Smoker	2.92 (1.66 – 5.13)	< 0.001	3.51 (1.60 – 7.72)	0.002
CRP	1.61 (0.81 – 3.21)	0.173	1.11 (0.49 – 2.52)	0.800

Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval; BMI = body mass index; CRP = C−reactive protein.

Model 1−3 are multivariable analysis models adjusted for each following variables including ferritin Model 1: age and sex; Model 2: model 1 + hypertension, diabetes, hypercholesterolemia and chronic kidney disease; Model 3: model 2 + BMI, smoking status and CRP.

[a] Hypertension was defined as those who were taking antihypertensive drugs or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg.

[b] Diabetes was defined as those who were taking oral hypoglycemic agents or insulin or hemoglobin A1c ≥ 6.5%, or fasting glucose ≥ 126 mg/dL.

[c] Hypercholesterolemia was defined as those who were taking lipid lowering drugs or total cholesterol ≥ 240 mg/dL.

[d] Chronic kidney disease was defined as eGFR less than 60 mL/min/1.73 m^2

3. Association between ferritin and significant CAS by presence of diabetes

Considering the strong association between diabetes and significant CAS (OR = 3.85; p value <0.001) in univariate analysis and importance of diabetes that is regarded as CHD risk equivalent, we performed subgroup analysis dividing into those with diabetes and those without diabetes. Baseline characteristics according to presence of diabetes were presented in table 3. The subjects with diabetes did not show different prevalence of significant CAS across ferritin categories (p value = 0.917). Meanwhile, the subjects without diabetes showed significant different distribution for significant CAS across ferritin categories (p value = 0.006). There was not a significant interaction between ferritin as a continuous variable and diabetes (p for interaction= 0.054 in univariate analysis) in table 4. In non-diabetic group, aORs in subjects with serum ferritin ≥ 300 ng/mL were attenuated to 3.39 (95% CI 1.25 - 9.16; p value = 0.016) in model 1, 3.53 (95% 1.29 - 9.68; p value = 0.014) in model 2 and 3.16 (1.14 - 8.73; p value = 0.027) in model 3 compared with subjects with serum ferritin < 100 ng/mL, respectively. However, the subjects with diabetes did not have significant association. Figure 2 shows the different association of

ferritin with significant CAS according to existence of diabetes.

Furthermore, it is possible that diabetes may act as a mediator between ferritin and significant CAS considering that significance was disappeared after adjusting diabetes in model 2. *P* values related to significant CAS in subjects with serum ferritin ≥ 300 ng/mL were 0.033 and 0.078 before and after adding diabetes variable in model 2. In a meta-analysis study also suggested that elevated ferritin levels is risk factor for type 2 diabetes.[19] Other studies has been proposed that high oxidative stress led by ferritin contributes to decrease pancreatic beta cells function, decreased insulin secretion, insulin resistance and subsequently the development of type 2 diabetes.[20]

Table 3. Baseline characteristics of study population according to presence of diabetes

	Presence of diabetes [a]					
	without diabetes [a] (N = 1,273)			with diabetes [a] (N = 238)		
	without significant CAS (N = 1,223)	with significant CAS (N = 50)	*p* value	without significant CAS (N = 207)	with significant CAS (N = 31)	*p* value
Age ± SD	56.7 ± 8.2	61.7 ± 9.1	< 0.001	60.6 ± 8.2	63.1 ± 8.9	0.119
Sex - N (%)			0.015			0.130
Male	545 (44.6)	31 (62.0)		112 (54.1)	22 (71.0)	
Female	678 (55.4)	19 (38.0)		95 (45.9)	9 (29.0)	
BMI - kg/m^2 ± SD	23.8 ± 3.0	24.9 ± 2.3	0.013	24.7 ± 3.2	25.5 ± 2.7	0.215
Smoking - N (%)			0.037			0.005
Non-smoker	758 (62.0)	22 (44.0)		112 (54.1)	8 (25.8)	
Ex-smoker	274 (22.4)	17 (34.0)		58 (28.0)	11 (35.5)	
Current Smoker	191 (15.6)	11 (22.0)		37 (17.9)	12 (38.7)	
Ferritin - ng/mL ± SD	124.0 ± 84.9	160.3 ± 111.3	0.003	145.7 ± 101.9	139.1 ± 104.0	0.738
< 100	1,027 (84.0)	20 (40.0)	0.006	88 (42.5)	12 (38.7)	0.917
100-300	142 (11.6)	23 (46.0)		99 (47.8)	16 (51.6)	
300 ≤	54 (4.4)	7 (14.0)		20 (9.7)	3 (9.7)	
Hypertension [b] - N (%)			0.006			0.050
No	797 (65.2)	23 (46.0)		99 (47.8)	9 (29.0)	
Yes	426 (34.8)	27 (54.0)		108 (52.2)	22 (71.0)	
Hypercholesterolemia [c] - N (%)			0.002			0.495
No	938 (76.7)	29 (58.0)		141 (68.1)	23 (74.2)	
Yes	285 (23.3)	21 (42.0)		66 (31.8)	8 (25.8)	
CKD [d] - N (%)			0.066			0.857
No	1,169 (95.6)	45 (90.0)		189 (91.3)	28 (90.3)	
Yes	54 (4.4)	5 (10.0)		18 (8.7)	3 (9.7)	

Abbreviation: CAS = coronary artery stenosis. BMI = body mass index. CKD = chronic kidney disease.

Data represented as mean ± standard deviation (SD) or number (%)

[a] Diabetes was defined as those who were taking oral hypoglycemic agents or insulin or hemoglobin A1c ≥ 6.5%, or fasting glucose ≥ 126 mg/dL.

[b] Hypertension was defined as those who were taking antihypertensive drugs or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg.

[c] Hypercholesterolemia was defined as those who were taking lipid lowering drugs or total cholesterol ≥ 240 mg/dL.

[d] Chronic kidney disease was defined as eGFR less than 60 mL/min/1.73 m^2

Table 4. Association of ferritin levels with significant CAS stratified by presence of diabetes

	Significant CAS	Univariate analysis		Model 1		Model 2		Model 3	
Ferritin (ng/mL)	N (%)	OR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
without diabetes [a] (N = 1,273)									
< 100	20 (3.2)	1.00		1.00		1.00		1.00	
100-300	23 (3.9)	1.23 (0.67 – 2.26)	0.507	1.12 (0.59 – 2.13)	0.728	1.12 (0.59 – 2.15)	0.726	1.05 (0.54 –2.02)	0.891
300 ≤	7 (11.5)	3.91 (1.58 – 9.67)	0.003	3.39 (1.25 – 9.16)	0.016	3.53 (1.29 – 9.68)	0.014	3.16 (1.14 – 8.73)	0.027
p for trend		0.026		0.084		0.078		0.131	
with diabetes [a] (N = 238)									
< 100	12 (12.0)	1.00		1.00		1.00		1.00	
100-300	16 (13.9)	1.18 (0.53 – 2.64)	0.678	0.87 (0.36 – 2.11)	0.765	0.76 (0.30 – 1.94)	0.571	0.51 (0.18 – 1.41)	0.193
300 ≤	3 (13.0)	1.10 (0.28 – 4.26)	0.890	0.81 (0.19 – 3.47)	0.776	0.85 (0.19 – 3.73)	0.831	0.60 (0.12 – 3.03)	0.538
p for trend		0.758		0.733		0.685		0.315	
p for interaction [b]		0.054		0.095		0.116		0.114	

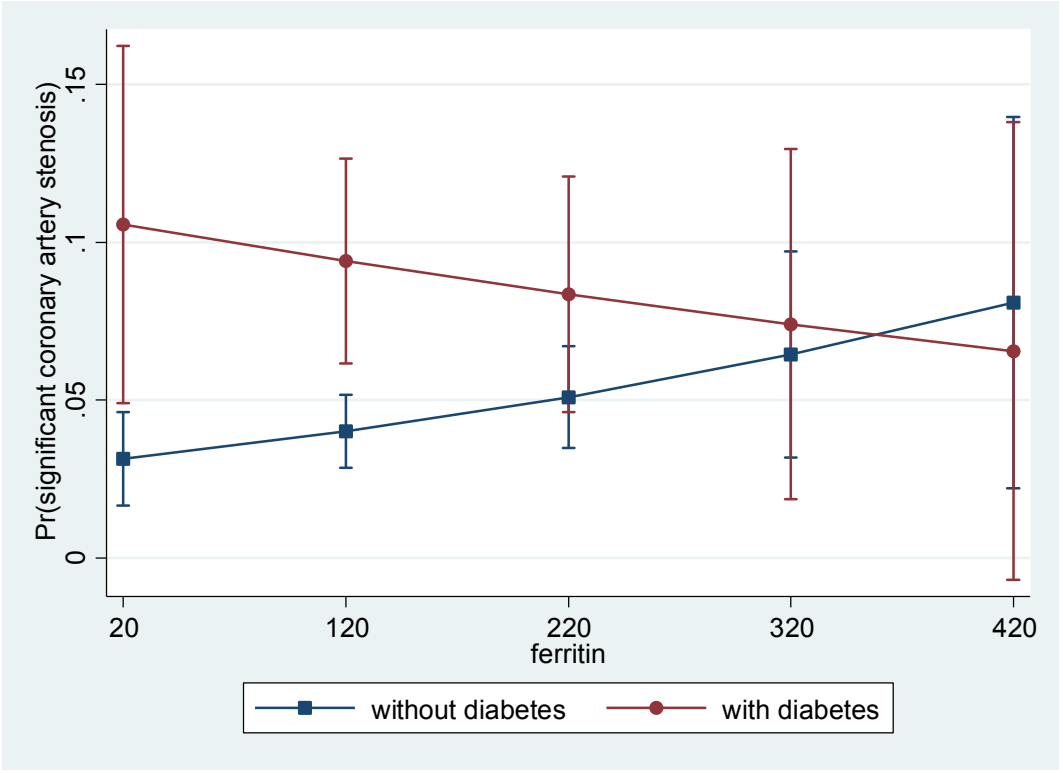
Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

Model 1−3 are multivariable analysis models adjusted for each following variables including ferritin Model 1: age and sex; Model 2: model 1 + hypertension, hypercholesterolemia and chronic kidney disease; Model 3: model 2 + BMI, smoking status and C−reactive protein.

[a] Diabetes was defined as those who were taking oral hypoglycemic agents or insulin or hemoglobin A1c ≥ 6.5%, or fasting glucose ≥ 126 mg/dL.

[b] *p* value for interaction between ferritin and diabetes was calculated by adding multiplicative term (ferritin x diabetes).

Figure 2. Association between ferritin and significant CAS by presence of diabetes



CAS indicates coronary artery stenosis; and Pr, predicted probabilities. Probability of CAS prevalence with 95% confidence interval associated with serum ferritin levels in non-diabetes(square) and diabetes(circle) subjects illustrated using margins plot adjusted for age, sex, hypertension, hypercholesterolemia, chronic kidney disease, body mass index, smoking status and C-reactive protein

4. Association between ferritin and significant CAS by smoking status

Besides diabetes, association between smoking state and significant CAS was significant after adjusting demographic variables, other cardiovascular risk factors, BMI and CRP. Ex-smoker (aOR = 2.25; *p* value = 0.039) and current smoker (aOR = 3.51; *p* value = 0.002) had higher possibility to have significant CAS compared with non-smoker in model 3 (Table 2). Therefore, we performed additional subgroup analysis stratified by smoking status. There was a significant interaction between ferritin as a continuous variable and smoking status (*p* for interaction= 0.013 in model 3) in table 5. Despite small number of current smoker (n = 251), aORs (7.81; 95% CI 1.21 – 50.52; *p* value = 0.026) in subjects with serum ferritin ≥ 300 ng/mL were significant compared to subjects with serum ferritin < 100 ng/mL in model 3, respectively. *P* for trend (*p* value = 0.026) was also significant in model 3. However, non-smoker or ex-smoker did not have significant association. Figure 3 shows that current smoker has significantly different association between ferritin and significant CAS compared with non-smoker or ex-smoker. Odds ratios in current smoker with ferritin ≥ 300 ng/mL were significantly higher than reference group (aOR 5.16; 95% CI

1.66–16.02) in table 6. Further evaluation considering that smoking quantity is needed to elucidate the association between ferritin and significant CAS in current smoker.

Table 5. Association of ferritin levels with significant CAS stratified by smoking status

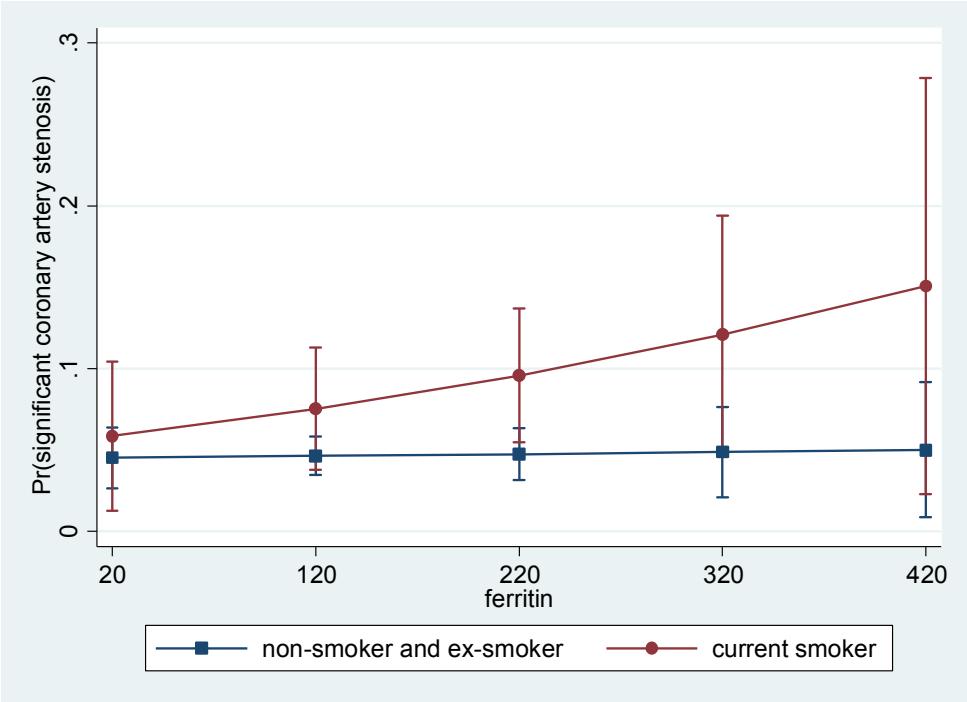
Ferritin (ng/mL)	Significant CAS N (%)	Univariate analysis OR (95% CI)	*p* value	Model 1 aOR (95% CI)	*p* value	Model 2 aOR (95% CI)	*p* value	Model 3 aOR (95% CI)	*p* value
Non-smoker or Ex-smoker (N = 1,260)									
< 100	30 (4.6)	1.00		1.00		1.00		1.00	
100-300	23 (4.2)	0.92 (0.52 – 1.60)	0.762	0.80 (0.44 – 1.44)	0.465	0.80 (0.44 – 1.44)	0.457	0.75 (0.41 – 1.36)	0.339
300 ≤	5 (8.6)	1.97 (0.73 – 5.28)	0.179	1.49 (0.51 – 4.31)	0.466	1.42 (0.48 – 4.15)	0.522	1.27 (0.43 – 3.76)	0.670
p for trend		0.561		0.981		0.942		0.748	
Current smoker (N = 251)									
< 100	2 (2.9)	1.00		1.00		1.00		1.00	
100-300	16 (10.2)	3.74 (0.84 – 16.76)	0.084	3.48 (0.74 – 16.28)	0.114	3.32 (0.68 – 16.16)	0.137	3.22 (0.65 – 15.90)	0.150
300 ≤	5 (19.2)	7.86 (1.42 – 43.52)	0.018	8.87 (1.48 – 53.16)	0.017	8.20 (1.27 – 52.78)	0.027	7.81 (1.21 – 50.52)	0.031
p for trend		0.012		0.012		0.022		0.026	
p for interaction [b]		0.022		0.002		0.011		0.013	

Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

Model 1–3 are multivariable analysis models adjusted for each following variables including ferritin Model 1: age and sex; Model 2: model 1 + hypertension, diabetes, hypercholesterolemia and chronic kidney disease; Model 3: model 2 + body mass index and C–reactive protein.

[a] *p* value for interaction between ferritin and smoking status was calculated by adding multiplicative term (ferritin x smoking status).

Figure 3. Association between ferritin and significant CAS bys moking status



CAS indicates coronary artery stenosis; and Pr, predicted probabilities. Probability of CAS prevalence with 95% confidence interval associated with serum ferritin levels in non-smoker or ex-smoker(square) and current smoker(circle) subjects illustrated using margins plot adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, chronic kidney disease, body mass index and C-reactive protein

Table 6. Odds ratios for significant CAS according to serum ferritin levels and smoking status

Ferritin (ng/mL)	Smoking status	Significant CAS	Univariate analysis		Model 1		Model 2		Model 3	
		N (%)	OR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
< 300	Non-smoker or Ex-smoker	53 (4.4)	1.00		1.00		1.00		1.00	
	Current smoker	18 (8.0)	1.89 (1.08 – 3.28)	0.025	2.15 (1.16 – 3.99)	0.016	1.91 (1.01 –3.59)	0.046	1.86 (0.98 – 3.51)	0.057
300 ≤	Non-smoker or Ex-smoker	5 (8.6)	2.04 (0.79 – 5.33)	0.143	1.70 (0.62– 4.67)	0.302	1.53 (0.59– 4.50)	0.342	1.46 (0.52– 4.05)	0.470
	Current smoker	5 (19.2)	5.16 (0.79–14.22)	0.002	6.69 (2.24 –19.97)	0.001	5.47 (1.76–16.99)	0.003	5.16 (1.66–16.02)	0.005

Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

Model 1−3 are multivariable analysis models adjusted for each following variables Model 1: age and sex; Model 2: model 1 + hypertension, diabetes, hypercholesterolemia and chronic kidney disease; Model 3: model 2 + body mass index and C−reactive protein.

5. Association between ferritin and significant CAS by presence of hypertension

Hypertension showed marginally significant association with significant CAS in model 3 (aOR = 1.62; p value = 0.067). We evaluated association between ferritin and significant CAS stratified by existence of hypertension (Table 7). They did not show a significant interaction between ferritin as a continuous variable and hypertension (p for interaction= 0.683 in univariate analysis) in table 7. In both those with hypertension and without hypertension, ferritin ≥ 300 ng/mL did not have significant association compared with subjects with serum ferritin < 100 ng/mL.

Table 7. Association of ferritin levels with significant CAS stratified by presence of hypertension

Ferritin (ng/mL)	Significant CAS N (%)	Univariate analysis OR (95% CI)	*p* value	Model 1 aOR (95% CI)	*p* value	Model 2 aOR (95% CI)	*p* value	Model 3 aOR (95% CI)	*p* value
without hypertension [a] (N = 928)									
< 100	14 (3.1)	1.00		1.00		1.00		1.00	
100-300	12 (2.8)	0.91 (0.41 – 1.99)	0.811	0.66 (0.28 – 1.51)	0.321	0.66 (0.28 – 1.51)	0.325	0.58 (0.25 – 1.37)	0.216
300 ≤	6 (11.3)	3.98 (1.46 – 10.86)	0.007	2.18 (0.72 – 6.63)	0.168	1.94 (0.63 – 5.98)	0.247	1.66 (0.52 – 5.24)	0.390
p for trend		0.088		0.539		0.638		0.858	
with hypertension [a] (N = 583)									
< 100	18 (6.6)	1.00		1.00		1.00		1.00	
100-300	27(9.7)	1.52 (0.81 – 2.82)	0.188	1.52 (0.78 – 2.95)	0.216	1.44 (0.73 – 2.85)	0.297	1.27 (0.63 – 2.56)	0.510
300 ≤	4 (12.9)	2.10 (0.66 – 6.65)	0.208	2.49 (0.72 – 8.59)	0.150	2.17 (0.61 – 7.69)	0.231	1.79 (0.49 – 6.55)	0.376
p for trend		0.111		0.107		0.177		0.353	
p for interaction [b]		0.683		0.801		0.636		0.780	

Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

Model 1–3 are multivariable analysis models adjusted for each following variables including ferritin Model 1: age and sex; Model 2: model 1 + diabetes, hypercholesterolemia and chronic kidney disease; Model 3: model 2 + body mass index, smoking status and C–reactive protein.

[a] Hypertension was defined as those who were taking antihypertensive drugs or SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg

[b] *p* value for interaction between ferritin and hypertension was calculated by adding multiplicative term (ferritin x hypertension).

6. Association between ferritin and significant CAS by presence of hypercholesterolemia

Hypercholesterolemia is well-known risk factors for coronary artery atherosclerosis. We performed subgroup analysis dividing subjects by existence of hypercholesterolemia. Interaction between ferritin and hypercholesterolemia was not significant (p for interaction= 0.079 in univariate analysis) in table 8. In those without hypercholesterolemia, aOR (2.96; 95% CI 1.10 – 7.90; p value = 0.031) for ferritin ≥ 300 ng/mL were significant compared to serum ferritin < 100 ng/mL in model 2.

Table 8. Association of ferritin levels with significant CAS stratified by presence of hypercholesterolemia

Ferritin (ng/mL)	Significant CAS	Univariate analysis		Model 1		Model 2		Model 3	
	N (%)	OR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
without hypercholesterolemia [a] (N = 1,131)									
< 100	17 (3.1)	1.00		1.00		1.00		1.00	
100-300	27 (5.1)	1.65 (0.89 – 3.06)	0.114	1.31 (0.68 – 2.54)	0.421	1.12 (0.56 – 2.21)	0.749	0.96 (0.48 – 1.93)	0.915
300 ≤	8 (12.9)	4.55 (1.87 – 11.03)	0.001	3.27 (1.25 – 8.57)	0.016	2.96 (1.10 – 7.90)	0.031	2.50 (0.90 – 6.96)	0.901
p for trend		0.002		0.040		0.093		0.224	
With hypercholesterolemia [a] (N = 380)									
< 100	15 (8.1)	1.00		1.00		1.00		1.00	
100-300	12 (6.9)	0.84 (0.38 – 1.86)	0.675	0.80 (0.34 – 1.83)	0.593	0.81 (0.35 – 1.88)	0.625	0.76 (0.32 – 1.80)	0.528
300 ≤	2 (9.1)	1.13 (0.24 – 5.32)	0.874	0.97 (0.18 – 5.13)	0.972	0.97 (0.18 – 5.22)	0.972	0.75 (0.13 – 4.15)	0.742
p for trend		0.857		0.717		0.739		0.554	

p for interaction [b]	0.079	0.093	0.133	0.133

Abbreviation: CAS = coronary artery stenosis; OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval.

Model 1–3 are multivariable analysis models adjusted for each following variables including ferritin Model 1: age and sex; Model 2: model 1 + diabetes, hypertension and chronic kidney disease; Model 3: model 2 + body mass index, smoking status and C-reactive protein.

[a] Hypercholesterolemia was defined as those who were taking lipid lowering drugs or total cholesterol ≥ 240 mg/dL

[b] *p* value for interaction between ferritin and hypercholesterolemia was calculated by adding multiplicative term (ferritin x hypercholesterolemia).

IV. Discussion

The aim of this study was to evaluate the association between serum ferritin levels and significant CAS in asymptomatic subjects. Our findings confirm that elevated serum ferritin level (≥ 300 ng/mL) is associated with higher prevalence of significant CAS compared with serum ferritin < 100 ng/mL. Especially, this association is more prominent in non-diabetic subjects and current smoker with significant, which means that elevated ferritin level has different association with significant CAS.

These findings are supported by many previous studies that have reported association between ferritin and coronary artery disease. In the large cohort study of Finnish men by Salonen et al, the excess risk of acute myocardial infarction at serum ferritin levels more than 200 mg/mL was 2.2-fold higher.[21] However, they included participants with ferritin level more than >2000 mg/mL, even though extremely elevated ferritin over 1000 mg/mL is possible to be associated with significant disorders.[22] Zhou et al. conducted a case-control study using percutaneous coronary angiography in Chinese population including a meta-analysis.[23] This study has reported that a positive relationship between serum

ferritin and risk of coronary artery disease and multivariate random-effect meta-analysis assumed linear association. However, application of meta-analysis of small case-control studies without individual data may not be appropriate to examine association. In study for 76 hemodialysis patients over 3 years follow up, elevated serum ferritin level was an independent risk factor for CAS.[24] Considering that hemodialysis patients usually receive intravenous iron for managing anemia, mean ferritin level was 644.5 ± 325.8 ng/mL. OR for patients with serum ferritin ≥ 600 ng/mL was 6.93 (95% 2.41 - 19.94; p value = 0.001). However, this result cannot be generalized, because of limited small study population who receive hemodialysis. A large cross-sectional study in Korea has demonstrated an independent association between ferritin concentrations and coronary artery calcium scoring as a marker of subclinical atherosclerosis, but they included only male samples and used quartile approach for the statistical analysis.[25]

On the other hand, other studies have indicated that serum ferritin is not a significant predictor of cardiovascular. In a cohort study of Australia, elevated serum ferritin levels did not have significant association with CHD or stroke both before and after adjustment for age and other cardiovascular risk factors.[14] They emphasized the necessity to investigate interaction between ferritin and other risk

factors. Other study revealed that there was possibility to have U-shaped association in women, even though there were no statistically significant associations between serum ferritin levels and the risk of CVD or IHD.[26] However, they defined diabetes and hypertension based on only patients' self-reported doctor diagnoses which seems to be inaccurate.

Our study analyzed association between normal ferritin ranges less than < 500 ng/mL and significant CAS assessed by coronary CTA. Furthermore, we evaluated interaction between coronary artery disease related risk factors such as diabetes, smoking status, hypertension and hypercholesterolemia and ferritin. We also performed stratified subgroup analysis. Since ferritin is regarded as an inflammatory marker, we proved that there was no significant difference in CRP levels before analyzing associations between ferritin and significant CAS.

Our study had several limitations. First, this study is cross-sectional design so we cannot clarify causality between ferritin and significant CAS. Second, we were not able to consider iron supplement that can affect to serum ferritin level. Third, we were not available to perform sex-dependent differences in this association because of small sample size. Previous studies suggested that serum ferritin level of female was lower than that of

male,[4, 14] and showed discrepant association between ferritin and cardiovascular disease according to sex.[27] In addition, our study is limited to one ethnic group.

We conclude that elevated serum ferritin level (≥ 300 ng/mL) is not associated with existence of significant CAS in asymptomatic Korean. However, there was a significant interaction between ferritin and smoking status. In current smoker, association between ferritin levels and significant CAS was more pronounced. Also, current smoker with serum ferritin levels ≥ 300 ng/mL was strongly associated with significant CAS. Even though *p* for interaction was not significant between ferritin and diabetes, non-diabetic subjects showed more pronounced association than diabetic subjects.

Further replicative studies are needed to elucidate this important association and interaction for specific population.

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초 록

서론: 철 가설 (iron hypothesis)은 1981년 폐경 전 여성이 폐경 후 여성 및 남성과 비교하여 관상동맥 질환 발생률이 더 적다는 점에서 처음 제안된 개념으로 그 원인이 저장 철의 차이에 기인한다는 가설이다. 지금까지의 연구결과는 혈중 ferritin 농도와 심혈관계 질환의 연관성에 대해서 상반된 결과를 보고하였다. 본 연구는 무증상 한국성인에서 혈중 ferritin 농도와 유의미한 정도의 관상동맥 협착 간의 연관성을 알아보고자 수행되었다.

방법: 대상인구는 서울대학교병원 건강검진 센터에서 심장혈관 전산화 단층 촬영 (CT) 검사를 시행한 40세 이상 성인을 대상으로 하였다. 심혈관 질환 병력, 중등도 이상의 빈혈 (hemoglobin 11g/dL 미만)이 있거나 C-반응 단백 3mg/dL 이상, ferritin 수치가 20ng/mL 미만 혹은 500ng/mL 초과인 경우를 제외하여 1,511명을 최종분석 대상자로 하였다. 유의미한 관상동맥 협착은 50%이상 지름이 감소하였을 경우로 정의하였다. 다변량 로지스틱 회귀분석을 통해 혈중 ferritin 농도에 따른 유의미한 관상동맥 협착의 연관성을 확인하였다. 또한 ferritin과 당뇨, 흡연력, 고혈압, 고콜레스테롤혈증과 같은 심혈관계 위험인자와의 상호작용을 추가로 분석하였다.

결과: 전체 대상자에서 유의미한 관상동맥 협착의 유병률은 5.4% 이었으며 단변량 분석에서 유의미한 관상동맥 협착이 있는 대상군 (52.2 ± 108.4 ng/mL)의 평균 ferritin 농도가 없는 대상군에 비해 (127.1 ± 87.9 ng/mL) 유의하게 더 높았다 (p value = 0.014). 단변량 로지스틱 회귀분석 결과 혈중 ferritin 농도가 100 ng/mL 미만인 군과 비교하여 300ng/mL 이상의 ferritin 농도의 대상군은 교차비가 2.92로 (95% confidence interval [CI] 1.38 – 6.18; p value = 0.005) 유의하게 더 높았다. 하지만 나이, 성별, 과거병력, 생활습관 관련 변수들과 C-반응 단백 변수를 보정한 후에는 유의한 연관성을 보이지 않았다 (보정 교차비 1.87; p value = 0.147). Ferritin과 심혈관계 위험 인자들 사이의 상호작용을 분석한 결과 흡연 상태에 대해서만 유의한 상호작용을 보였다. 층화분석 결과 당뇨병이 없는 대상군과 현재 흡연자에서는 혈중 ferritin 농도가 100 ng/mL 미만인 군과 비교하여 300ng/mL 이상의 ferritin 농도의 대상군은 유의미한

관상동맥 협착과 유의한 상관관계를 보였다.
결론: 무증상 40세 이상의 한국성인에서 혈중 ferritin 농도는 유의미한 관상동맥 협착과 독립적인 관련성을 보이지 않았으나 당뇨병이 없는 대상군과 현재 흡연자에서는 300 ng/mL 이상의 ferritin 농도에서 유의미한 관상동맥 협착과 유의한 연관성을 보였다. 향후 본 연구의 결과에 대해 추가적인 근거제시를 위해 ferritin과 여러 심혈관계 위험인자에 대한 연관성 및 위험성에 대해서 규명하는 연구가 필요하다.

Keyword: ferritin, 관상동맥 협착, 상호작용, 당뇨병, 흡연자
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