Original Article

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한국인에서 높은 혈청 페리틴 수치와 당뇨와의 상관관계

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Serum Ferritin Levels Are Associated with the Higher Risk of Diabetes Mellitus in Men and Post-menopausal Women, Based on the 2010-2012 KNHANES

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Background: The aim of this study was to investigate the relationship between serum ferritin and diabetes mellitus (DM) in the Korean population.
Methods: This cross-sectional study included 9,576 subjects (4,264 men, 2,394 pre-menopausal women, and 2,918 post-menopausal women) older than 19 years using data from the 2010-2012 Korean National Health and Nutrition Examination Survey. DM was defined as fasting plasma glucose ≥126 mg/dL, glycosylated hemoglobin ≥6.5%, or use of any glucose-lower medication including insulin therapy.
Results: The overall prevalence of DM was 12.0, 3.6, and 17.3% in men, pre-menopausal women, and post-menopausal women, respectively. DM prevalence was greater with ferritin levels from Q1 to Q4: 10.3, 10.2, 12.7, and 14.8% in men; 2.0, 2.8, 2.8, and 6.4% in pre-menopausal women; and 13.9, 14.4, 18.1, and 22.9% in post-menopausal women, respectively. Compared with participants in Q1, the odds ratios (95% confidence intervals) for DM among participants in Q4 were 1.67 (1.20-2.32) in men, 2.06 (0.91-4.66) in pre-menopausal women, and 1.60 (1.09-2.35) in post-menopausal women after adjusting for age and other covariates.
Conclusion: Serum ferritin concentration was positively associated with a higher risk of DM in adult men and post-menopausal women.
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Keywords: Diabetes mellitus, Ferritin, Insulin resistance

INTRODUCTION

In 2014, an estimated 422 million people worldwide were living with diabetes-roughly a four-fold increase over the past 35 years.[1)] About 4.8 million Korean people (13.7%) aged 30 years or older had type 2 diabetes in 2014, based on fasting glucose level, and 25.0% of adults had prediabetes.[2)] Diabetes mellitus (DM) is burdensome to health authorities because it is associated with a higher risk

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of cardiovascular, renal, neurological, metabolic, and other various chronic complications.[3]

Ferritin, a ubiquitous intracellular protein that controls iron homeostasis, is a clinical biomarker for the diagnosis of iron deficiency and systemic inflammation.[4,5] Several researchers have hypothesized that high iron stores cause pancreatic β-cell damage and insulin resistance through oxidative stress.[6,7] Because, in addition to oxidative stress, low-grade chronic inflammation plays an important role in the etiology of DM,[8-10] inflammatory markers such as C-reactive protein (CRP) are considered risk factors for DM. Higher ferritin level may be related to greater inflammation and oxidative stress. We hypothesized that higher serum ferritin level was related to the development of DM through oxidative stress and inflammation. However, there are still conflicting findings between serum ferritin level and the risk of DM in some epidemiological studies.

The aim of this study was to investigate the association between serum ferritin level and the prevalence of DM in the Korean adults based on data from the 2010-2012 Korean National Health and Examination Survey (KNHANES).

METHODS

1. Study population

This was a cross-sectional study based on data obtained from the 2010-2012 KNHANES, which was conducted by the Korean Ministry of Health and Welfare. Sampling units consisted of households that were chosen with a stratified, multistage, probability sampling design based on geographic area, sex distribution, and age group. A sampling weight representative of the probability of being sampled was allocated to each participant, ensuring that the results obtained reflected the overall Korean population. Participants completed four components of a questionnaire including a health interview survey, a health behavior survey, a health examination survey, and a nutrition survey. Health examinations were composed of a medical history, a physical examination, a questionnaire about health-related behaviors, and anthropometric and biochemical measurements. Trained medical staff performed the physical examination using standardized procedures. Participants also completed questions regarding their lifestyle behaviors, including cigarette smoking, alcohol consumption, exercise habits, and dietary habits. Participants voluntarily joined the study with the right to refuse their participation according to the National Health Enhancement Act. All participants provided informed consent and agreed that blood samples could be used for further research. This study was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention.

Initially, a total of 19,599 adults (age more than 19 years) were identified. Participants were excluded for the following reasons: missing laboratory data (n=7,630), incomplete questionnaires on medical history and health-related behaviors (n=524), participants who had not fasted overnight before providing blood samples (n=256), pregnant (n=28), history of chronic inflammatory or infectious disease (n=177), neoplastic disease (n=342), anemia (n=524) as defined as hemoglobin (Hb) concentration <13.0 g/dL in men and 12.0 g/dL in women, leukocytosis (white blood cell [WBC] count ≥10,000 cells/mL, n=396), and/or increased serum creatinine (>1.4 mg/dL; n=125). Individuals with exceptionally high serum ferritin level (>800 ng/mL; n=21) were excluded to rule out those who could potentially have hemochromatosis. After these exclusions, 9,576 participants (4,264 men and 5,312 women including 2,394 pre-menopausal women and 2,918 post-menopausal women) were included in our final analysis.

2. Measurement of anthropometric and laboratory data

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, while participants were wearing light indoor clothing without shoes. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m^2). Blood pressure was measured on three occasions using a standard mercury sphygmomanometer (Baumanometer; Baum, Copiague, NY, USA) on the right arm and averaged for a final blood pressure reading. Blood samples were obtained from the antecubital vein after an overnight fast. Fasting plasma glucose, total cholesterol, creatinine, iron, and total iron binding capacity were measured using a Hitachi Automatic Analyzer 7600 (Hitachi Co, Tokyo, Japan). Glycosylated hemoglobin (HbA1c) was measured using a HLC-723G7 (Tosoh, Tokyo, Japan), WBC count and Hb were determined using n XE-2100D

(Sysmex, Kobe, Japan), and ferritin was quantified using a 1470 WIZARD gamma-Counter (PerkinElmer, Kurku, Finland).

3. Definitions of diabetes mellitus, menopause, and life-style factors

We defined DM as follows: receiving treatment with a hypoglycemic medication (insulin or oral hypoglycemic agents) as determined from self-report questionnaires, fasting plasma glucose level ≥126 mg/dL, or HbA1c ≥6.5%.

The menopausal state was described as self-reported amenorrhea caused by natural or artificial menopause (e.g., induced by oophorectomy). Because mean ferritin level was significantly different according to sex and menopausal status, it was necessary to examine this association after stratification according to sex and menopausal status. Regular alcohol drinkers were defined as participants who drink alcohol more than twice a week. Smoking status was divided into current smokers and others (former and non-smokers). Regular exercise was defined as exercise including walking for more than 30 minutes per day more than 4 days per week. High educational status was defined as graduation from college or more.

4. Statistical analysis

Sampling weights were used to account for the complex sampling method, thereby maintaining the degree of representation of the entire Korean population and avoiding biased estimates. All analyses were performed separately after stratifying to men, pre-menopausal women, and post-menopausal women.

Ferritin levels were categorized into four quartile groups for men, pre-menopausal women, and post-menopausal women—Q1: ≤68.3 ng/mL, Q2: 68.4-104.6 ng/mL, Q3: 104.7-158.5 ng/mL, and Q4 >158.5 ng/mL in men; Q1: ≤ 14.3 ng/mL, Q2: 14.4-27.3 ng/mL, Q3: 27.4-44.4 ng/mL, and Q4: >44.4 ng/mL in pre-menopausal women; and Q1: ≤36.5 ng/mL, Q2: 36.6-57.7 ng/mL, Q3: 57.8-87.3 ng/mL, and Q4: >87.3 ng/mL in post-menopausal women. In order to analyze the differences among the quartile groups of serum ferritin concentrations, general linear models for continuous variables and Chi-square tests for categorical variables were used. All data are presented as mean (or percentage)±standard error.

Logistic regression analyses were conducted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for DM prevalence according to ferritin quartile after adjusting for confounding variables that might confound the relationship between serum ferritin and incident diabetes, which include: age, BMI, systolic blood pressure, total cholesterol, WBC count, alcohol intake, smoking status, physical activity, and education level.

All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Statistical significance was determined at a *P*-value <0.05.

RESULTS

The participant characteristics by sex and menopausal status are presented in Table 1. The mean ages for men, pre-menopausal women, and post-menopausal women were 43.7, 35.4, and 60.0 years, respectively. The mean level of serum ferritin was 128.1 ng/mL in men, 34.9 ng/mL in

Table 1. Participant characteristics by sex and menopausal status

	Men	Women	
		Pre-menopausal	Post-menopausal
Unweighted N	4,264	2,394	2,918
Age, y	43.7±0.3	35.4±0.2	60.0±0.3
BMI, kg/m²	24.2±0.1	22.6±0.1	24.4±0.1
SBP, mmHg	119.9±0.3	108.4±0.3	124.4±0.5
DBP, mmHg	79.1±0.2	72.2±0.3	76.0±0.3
FPG, mg/dL	99.9±0.5	91.8±0.5	101.5±0.6
HbA1c, %	5.85±0.02	5.5±0.02	6.0±0.02
Hemoglobin, g/dL	15.5±0.02	13.3±0.02	13.4±0.02
Ferritin, ng/mL	128.1±1.9	34.9±0.8	68.6±1.2
Iron, μg/dL	134.1±1.0	110.9±1.2	105.2±0.7
TIBC, μg/dL	310.6±0.9	324.5±1.1	314.9±1.0
Cholesterol, mg/dL	188.5±0.8	180.9±0.8	202.5±0.8
Triglyceride, mg/dL	154.1±2.3	98.3±2.9	136.9±2.0
HDL-C, mg/dL	46.7±0.2	54.0±0.3	49.9±0.3
Creatinine, mg/dL	0.97±0.00	0.71±0.00	0.73±0.00
WBC, $\times 10^9$/L	6.3±0.03	5.7±0.04	5.7±0.04
Regular drinker, %	38.9±0.9	13.1±0.8	6.1±0.6
Current smoker, %	44.4±1.0	8.6±0.8	4.9±0.5
Regular exerciser, %	41.2±1.0	37.3±1.2	32.7±1.1
Higher education, %	36.8±1.1	42.6±1.3	10.5±0.9
DM, %	12.0±0.7	3.6±0.4	17.3±1.0

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TIBC, total iron binding capacity; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cells; DM, diabetes mellitus.
Values are presented as mean±standard error.

Table 2. Participant characteristics according to ferritin quartiles

Men	Q1	Q2	Q3	Q4	*P*	*P* for trend
Ferritin levels	≤68.4	68.4-104.6	104.7-158.5	>158.5		
Age, y	45.1±0.6	42.6±0.5	43.2±0.6	44.0±0. 6	0.008	0.290
BMI, kg/m²	23.6±0.1	24.0±0.1	24.3±0.1	25.0±0.2	<0.001	<0.001
SBP, mmHg	119.6±0.5	118.9±0.6	119.5±0.6	121.6±0.5	<0.001	0.05
DBP, mmHg	77.9±0.5	78.2±0.4	79.1±0.4	81.3±0.4	<0.001	<0.001
FPG, mg/dL	96.6±0.8	98.0±0.8	100.1±1.0	104.9±1.1	<0.001	<0.001
HbA1c, %	5.7±0.03	5.7±0.03	5.7±0.04	5.8±0.04	0.001	0.012
Hb, g/dL	15.2±0.1	15.5±0.04	15.5±0.04	15.7±0.04	<0.001	<0.001
Ferritin, ng/mL	45.2±0. 7	86.6±0.4	129.2±0.6	252.9±4.2	<0.001	<0.001
Iron, μg/dL	127.6±2.2	133.6±1.9	135.8±1.9	139.4±2.0	0.001	<0.001
TIBC, μg/dL	323.4±1.6	307.9±1.4	305.6±0.3	306.0±1.5	<0.001	<0.001
Cholesterol, mg/dL	182.9±1.3	186.1±1.3	191.1±1.4	193.8±1.3	<0.001	<0.001
Creatinine, mg/dL	0.96±0.00	0.97±0.01	0.97±0.00	0.96±0.00	0.069	0.765
WBC, $\times 10^9$/L	6.1±0.1	6.3±0.1	6.3±0.05	6.4±0.05	0.003	<0.001
Regular drinker, %	27.2±1.7	37.0±1.9	39.7±1.8	51.6±2.0	<0.001	<0.001
Current smoker, %	39.0±2.0	44.4±2.0	47.2±1.8	47.0±2.0	<0.001	<0.001
Regular exerciser, %	45.2±2.0	40.9±1.9	42.6±2.0	35.9±1.9	<0.001	<0.001
Higher education, %	30.7±1.9	37.9±1.9	39.8±2.1	38.4±2.0	<0.001	<0.001
DM, %	10.3±1.1	10.2±1.1	12.7±1.3	14.8±1.3	<0.001	<0.001
Pre-menopausal women						
Ferritin levels	≤14.3	14.4-27.3	27.4-44.4	>44.4		
Age, y	35.5±0.5	35.1±0.5	34.8±0.5	36.1±0.5	0.231	0.530
BMI, kg/m²	22.0±0.2	22.6±0.2	22.8±0.2	23.1±0.2	0.001	<0.001
SBP, mmHg	108.4±0.6	107.4±0.6	107.9±0.6	109.7±0.7	0.064	0.105
DBP, mmHg	71.9±0.5	71.8±0.5	71.7±0.5	73.3±0.4	0.033	0.029
FPG, mg/dL	90.1±0.7	90.7±0.7	90.9±0.7	95.0±1.4	0.015	0.001
HbA1c, %	5.5±0.02	5.4±0.02	5.4±0.03	5.5±0.04	0.003	0.081
Hb, g/dL	13.0±0.03	13.3±0.03	13.4±0.04	13.5±0.04	<0.001	<0.001
Ferritin, ng/mL	8.7±0.2	20.5±0.2	35.4±0.2	72.1±1.8	<0.001	<0.001
Iron, μg/dL	96.4±2.3	111.2±2.2	115.4±2.1	120.1±2.2	<0.001	<0.001
TIBC, μg/dL	360.0±2.5	324.5±1.8	312.4±2.0	302.6±1.6	<0.001	<0.001
Cholesterol, mg/dL	181.3±1.6	179.0±1.6	177.9±1.6	185.2±1.8	0.011	0.168
Creatinine, mg/dL	0.72±0.01	0.71±0.00	0.71±0.01	0.71±0.00	0.548	0.160
WBC, $\times 10^9$/L	5.5±0.1	5.7±0.1	5.8±0.1	5.8±0.1	0.008	0.001
Regular drinker, %	11.1±1.4	11.6±1.8	11.8±1.6	17.6±1.9	<0.001	<0.001
Current smoker, %	7.1±1.6	8.2±1.4	8.3±1.5	10.6±1.6	<0.001	<0.001
Regular exerciser, %	37.3±2.6	37.0±2.3	36.5±2.4	38.1±2.5	<0.001	<0.001
Higher education, %	42.4±2.4	44.5±2.7	44.4±2.4	39.3±2.5	<0.001	<0.001
DM, %	2.0±0.6	2.8±0.7	2.8±0.7	6.4±1.2	<0.001	<0.001
Post-menopausal women						
Ferritin levels	≤36.5	36.6-57.7	57.8-87.3	>87.3		
Age, y	57.4±0.8	60.2±0.5	60.4±0.5	61.8±0.6	<0.001	<0.001
BMI, kg/m²	24.0±0.1	24.2±0.2	24.7±0.2	24.8±0.2	<0.001	<0.001
SBP, mmHg	123.6±1.0	123.4±0.8	126.1±0.9	124.5±0.7	0.089	0.163
DBP, mmHg	76.1±0.5	75.4±0.5	76.8±0.5	75.7±0.5	0.140	0.969
FPG, mg/dL	97.9±1.0	99.2±1.0	101.8±1. 4	107.2±1.5	<0.001	<0.001
HbA1c, %	5.9±0.04	6.0±0.04	6.0±0.05	6.1±0.05	0.005	<0.001
Hb, g/dL	13.3±0.04	13.5±0.04	13.5±0.04	13.5±0.04	<0.001	<0.001
Ferritin, ng/mL	24.4±0.4	46.9±0.3	71.4±0.40	134.2±2.6	<0.001	<0.001
Iron, μg/dL	101.5±1.5	105.5±1.3	103.0±1.4	110.8±1.7	<0.001	0.001
TIBC, μg/dL	336.8±1.9	314.6±1.7	307.2±1.8	300.3±1.9	<0.001	<0.001
Cholesterol, mg/dL	199.6±1.6	203.3±1.7	203.4±1.7	203.7±1.7	0.250	0.087
Creatinine, mg/dL	0.72±0.01	0.72±0.01	0.73±0.01	0.74±0.01	0.239	0.069
WBC, $\times 10^9$/L	5.6±0.1	5.6±0.1	5.6±0.1	5.7±0.1	0.614	0.270
Regular drinker, %	4.2±1.0	4.7±0.9	6.2±1.2	9.4±1.4	<0.001	<0.001
Current smoker, %	4.8±0.9	4.0±0.9	5.0±1.2	5.9±1.2	<0.001	<0.001
Regular exerciser, %	29.5±2.1	34.5±2.2	34.2±2.1	32.6±2.0	<0.001	<0.001
Higher education, %	15.0±1.9	9.4±1.6	7.6±1.3	9.9±1.6	<0.001	<0.001
DM, %	13.9±1.6	14.4±1.5	18.1±1.9	22.9±2.1	<0.001	<0.001

Values are presented as mean±standard error.
Their *P* value and *P* for trend are determined by general linear model for continuous variables and chi square test for categorical variables.
Q indicates quartile.

pre-menopausal women, and 68.6 ng/mL in post-menopausal women. The prevalence of DM was 12.0% in men, 3.6% in pre-menopausal women, and 17.3% in post-menopausal women.

Table 2 shows participant characteristics according to ferritin quartile. Male mean BMI, fasting plasma glucose, and HbA1C level were greater with higher ferritin level (all *P* for trend <0.05). Male prevalence of DM was 10.3, 10.2, 12.7, and 14.8% for Q1 to Q4, respectively (*P* value <0.001 and *P* for trend <0.001). In pre-menopausal women, BMI and fasting plasma glucose level were greater with higher ferritin quartile, but HbA1C levels were similar. DM prevalence in pre-menopausal women was 2.0, 2.8, 2.8, and 6.4% for Q1 to Q4, respectively (*P* value <0.001 and *P* for trend <0.001). Like men, BMI, fasting plasma glucose, and HbA1C levels were greater with greater ferritin quartile (all *P* values for trends <0.001) in post-menopausal women. The percentage of DM in post-menopausal women was 13.9, 14.4, 18.1, and 22.9% for Q1 to Q4, respectively (*P* value <0.001 and *P* for trend <0.001).

We conducted logistic regression analyses in order to investigate the association between serum ferritin level and DM (Table 3). Compared with Q1, ORs (95% CIs) for DM of Q2, Q3, and Q4 were 0.99 (0.71-1.38), 1.27 (0.93-1.72), and 1.52 (1.14-2.03) in men; 1.41 (0.63-3.15), 1.41 (0.63-3.16), and 3.29 (1.55-7.00) in pre-menopausal women; and 1.04 (0.74-1.47), 1.36 (0.96-1.93), and 1.83 (1.29-2.60) in post-menopausal women, respectively, when unadjusted (Model 1). After adjusting for age, BMI, systolic blood pressure, total cholesterol, WBC count, alcohol habits, smoking status, physical activity, and education level, the ORs (95% CIs) for DM of Q2, Q3, and Q4 were 1.17 (0.81-1.19), 1.51 (1.08-2.13), and 1.67 (1.20-2.32) in men; 1.20 (0.50-2.87), 1.12 (0.45-2.81), and 2.06 (0.91-4.66) in pre-menopausal women, and 0.98 (0.67-1.45), 1.19 (0.83-1.72), and 1.60 (1.09-2.35) in post-menopausal women, respectively (Model 3).

DISCUSSION

In this cross-sectional study, we found that higher serum ferritin concentration was associated with higher DM prevalence in adult men and post-menopausal women in a representative sample of the Korean population after adjusting for age, BMI, systolic blood pressure, total cholesterol, WBC count, alcohol intake, smoking, physical activity, and education.

The role of elevated serum ferritin concentration in type 2 diabetes has been investigated in several studies.[9,11-16] The results were inconsistent according to age, sex, and ethnic group in the study population. Some studies have reported an association between serum ferritin level and type 2 diabetes in the Asian population, and a few of these studies were in the Korean population.[13-16] Lee et al. reported that

Table 3. ORs (95% CI) for diabetes according to sex and menopausal specific ferritin quartiles

	Q1	Q2	Q3	Q4
Men				
Ferritin, ng/mL	≤68.3	68.4-104.6	104.7-158.5	>158.5
Model 1[a]	1	0.99 (0.71-1.38)	1.27 (0.93-1.72)	1.52 (1.14-2.03)
Model 2[b]	1	1.18 (0.82-1.69)	1.54 (1.10-2.16)	1.68 (1.22-2.31)
Model 3[c]	1	1.17 (0.81-1.69)	1.51 (1.08-2.13)	1.67 (1.20-2.32)
Pre-menopausal women				
Ferritin, ng/mL	≤14.3	14.4-27.3	27.4-44.4	>44.4
Model 1[a]	1	1.41 (0.63-3.15)	1.41 (0.63-3.16)	3.29 (1.55-7.00)
Model 2[b]	1	1.21 (0.51-2.86)	1.05 (0.43-2.57)	2.07 (0.94-4.56)
Model 3[c]	1	1.20 (0.50-2.87)	1.12 (0.45-2.81)	2.06 (0.91-4.66)
Post- menopausal women				
Ferritin, ng/mL	≤36.5	36.6-57.7	57.8-87.3	>87.3
Model 1[a]	1	1.04 (0.74-1.47)	1.36 (0.96-1.93)	1.83 (1.29-2.60)
Model 2[b]	1	1.00 (0.68-1.46)	1.21 (0.84-1.74)	1.57 (1.07-2.30)
Model 3[c]	1	0.98 (0.67-1.45)	1.19 (0.83-1.72)	1.60 (1.09-2.35)

Abbreviations: OR, odds ratios; CI, confidence interval.
The ORs were calculated using logistic regression analyses.
[a]Model 1 was not adjusted.
[b]Model 2 was adjusted for age, BMI, SBP, total cholesterol, WBC count.
[c]Model 3 was adjusted for age, BMI, SBP, total cholesterol, WBC count, alcohol habit, smoking status, physical activity and education level.

serum ferritin levels were associated with higher risk for diabetes in men and premenopausal women, but not in postmenopausal women.[13] Another previous study have shown a similar relationship between serum ferritin level and type 2 diabetes in Korean men; however, the participants, who were recruited while visiting the hospital for a regular health check-up, did not represent the general Korean population.[15] Our data supports the previous findings and extends them to include associations according to sex and menopausal status in a representative Korean population. We showed that higher serum ferritin concentration was positively associated with the prevalence of DM in men and post-menopausal women. The non-significant association in pre-menopausal women could be attributed to small sample size or markedly lower levels of mean serum ferritin in pre-menopausal women compared to men and post-menopausal women. Thus, iron plays less of a role in the production of oxidation stress and the development of diabetes. In pre-menopausal women, the menstrual cycle may affect ferritin level, yet this has not yet been considered as a confounding factor.[17]

Serum ferritin is a highly sensitive and reliable parameter used to evaluate body iron stores,[18] and it also reflects systemic inflammatory status and oxidative stress-mediated cellular damage.[5] Although the exact mechanism underlying the association between elevated serum ferritin concentration and DM is not clearly understood, it is thought that higher serum iron contributes to the development of diabetes by causing chronic low grade inflammation and oxidative stress. Under conditions of oxidative stress, a higher serum ferritin level may lead to iron-catalyzed formation of hydroxyl radicals and subsequent cellular or tissue damage, leading to insulin dysfunction, such as insulin resistance and abnormal pancreatic β-cell function.[13,19] Insulin receptors and insulin receptor substrates (IRS) tend to be abnormally phosphorylated on serine or threonine residues instead of the typical tyrosine residue through stress-sensitive serine (Ser)/threonine (Thr) kinase signaling pathways such as Iκβ kinase B.[20] Ser/Thr phosphorylation of IRS proteins inhibits their function and interferes with insulin signaling, thus leading to the development of an insulin resistant state. Furthermore, hyperinsulinemia stimulates cellular iron uptake through transferrin receptor externalization and gene expression of ferritin.[21] The onset of insulin resistance and hyperinsulinemia by iron excess enhances intracellular translocation of iron and aggravates iron toxicity. This vicious cycle may induce mitochondrial and pancreatic dysfunction, finally resulting in a deterioration of insulin production to an insufficient level.

There are some limitations to be considered. First, it is not possible to identify a causal relationship between higher ferritin concentration and increased risk of DM using a cross-sectional study design. Although there are some longitudinal studies addressing this relationship, the participants comprised Koreans who were visiting the hospital for a regular health check-up and did not represent the general Korean population. Thus, the cohorts that comprised previous and the present studies were slightly different and may account for the observed differences. Further prospective research based on representative Korean data is warranted to better understand this causal relationship. Second, serum ferritin is an acute phase protein and may increase under inflammatory circumstances or infections. We excluded individuals with a WBC count of 10,000 cells/μL or greater in order to minimize the possibility of including individuals with active infection. In addition, we adjusted for WBC count to control for the potential confounding factor; however, we were unable to adjust for CRP as another inflammatory marker because it was not tested in the 2010-2012 KNHANES. Third, subjects with hemochromatosis were not investigated in the 2010-2012 KNHANES and thus were not excluded in our study, although hemochromatosis is rare in the Korean population. Therefore, including subjects with hemochromatosis would have negligible effects on the result, if any. Fourth, it is possible that our population included subjects with undiagnosed diabetes at baseline; a two-hour oral glucose tolerance test would be useful to directly evaluate a person's insulin response in the KNHANES.

In conclusion, elevated serum ferritin concentration was associated with an increased risk of DM in a representative sample of the general South Korean population. Prospective studies are needed to determine whether elevated iron stores precede the development of DM and whether a threshold exists above which ferritin level is associated with increased risk of DM.

요 약

연구배경: 한국 성인을 대상으로 당뇨와 혈청 페리틴의

상관관계를 알아보고자 하였다.

방법: 국민건강영양조사 제5기(2010-2012년) 자료에서 19세 이상의 한국 성인 9,576명(남자 4,264명, 폐경 전 여성 2,394명, 폐경 후 여성 2,918명)을 대상으로 연구를 시행하였다. 당뇨는 공복 혈당 ≥126 mg/dL이거나 당화혈색소 ≥ 6.5%, 또는 경구혈당강하제를 복용하거나 인슐린 치료를 받고 있는 경우로 정의하였다.

결과: 당뇨 유병률은 남성, 폐경 전 여성, 폐경 후 여성에서 각각 12.0%, 3.6%, 17.3%로 나타났다. 혈청 페리틴 사분위가 증가할수록 당뇨 유병률은 증가하는 것으로 나타났다. 제1사분위에서 제4사분위로 갈수록 유병률이 남자에서는 10.3%, 10.2%, 12.7%, 14.8%; 폐경 전 여성에서는 2.0%, 2.8%, 2.8%, 6.4%; 폐경 후 여성에서는 13.9%, 14.4%, 18.1%, 22.9%로 나타났다. 제1사분위에 비해 제4사분위 교차비(95% 신뢰구간)가 연령 등을 보정한 후, 남성에서는 1.67 (1.20-2.32), 폐경 전 여성에서는 2.06 (0.91-4.66), 폐경 후 여성에서는 1.60 (1.09-2.35)로 나타났다.

결론: 한국 남성 및 폐경 후 여성에서 혈청 페리틴 수치는 당뇨 증가와 연관이 있었다.

중심 단어: 당뇨병, 혈청 페리틴, 인슐린 저항성

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