What Do Very Low Plasma Concentrations of High-sensitivity C-reactive Protein (hs-CRP) Mean among Healthy Middle-aged Koreans?

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Background: Systemic low-grade inflammation (SLGI), as assessed by measurements of high-sensitivity C-reactive protein (hs-CRP), is a strong independent risk factor for cardiovascular diseases (CVD). Although individuals with hs-CRP ≤ 1 mg/L have been defined as being at low risk according to AHA/CDC guidelines, the value of very low hs-CRP levels (< 0.5 mg/L) for public health practices is unclear.

Methods: This cross-sectional cohort study assessed 104 healthy Koreans aged 34-60 years. Their anthropometric indices, results of computed tomography and bioelectrical impedance analysis, and biomarker concentrations in fasting venous blood samples were evaluated.

Results: Of 104 subjects, 88 (84.6%) had hs-CRP concentrations ≤ 1.0 mg/L. When this low risk group was subdivided into subjects with hs-CRP < 0.5 mg/L and hs-CRP levels between 0.5 and 1 mg/L, the former group showed better anthropometric profiles for central obesity and lipidemia.

Conclusion: Even in low risk subjects, higher serum concentrations of hs-CRP may be associated with increased central obesity. Lifestyle modifications to lower hs-CRP should be recommended in public health practice, with hs-CRP viewed not as a risk marker, but rather as a marker of wellness.

Key Words: High sensitivity C-reactive protein (hs-CRP), Biomarker, Anthropometry, Obesity

INTRODUCTION

Systemic low-grade inflammation (SLGI), as assessed by measuring serum concentrations of high-sensitivity C-reactive protein (hs-CRP), has been found to be an independent risk factor of future cardiovascular events [1].

Greater understanding of the relationship between SLGI and lifestyle factors would be useful in designing active lifestyle modifications that not only increase the wellness of the general population, but also prevent chronic diseases by reversing epigenetic mechanisms [2].

Primary prevention consists of health promotion and specific protection. Primary prevention should be a major goal of modern medicine, not only for cardiovascular diseases (CVD), but also for other chronic diseases, such as cancer and neurodegenerative diseases. The identification of population- and individual-level causes of CVD [3,4] has contributed to a 50% reduction in the mortality rate from coronary heart disease (CHD) between 1980 and 2000. This is

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due, in part, to changes in medical treatments after coronary events and in levels of risk factors in the population [5]. The public cholesterol-lowering campaign in the United States has significantly reduced mortality from CVD over the past 30 years. This decline was related to both primary (79%) and secondary (21%) prevention, with cholesterol lowering accounting for a 42.7% reduction in the death rate among asymptomatic individuals and 34% among patients with known CVD [6].

Some individuals, however, develop CVD without having traditional risk factors. Although efforts have been made to identify other causes or mechanisms of atherogenesis, novel etiologic and pathogenic factors of CVD have been difficult to determine. SLGI, however, has been found to be associated with atherosclerosis [7,8]. Indeed, hs-CRP is one of the most sensitive markers of systemic inflammation, particularly in the cardiovascular system [9].

Epigenetic factors may underlie the etiology and phenotypic variation of chronic diseases, including cancer and metabolic and inflammatory diseases. The epigenome results from interactions between a given developmental genetic asset, such as internal heterogeneity, and action of the environment over a lifetime [10]. Epigenetic mechanisms include DNA methylation, histone modification, and microRNA alterations, which collectively enable the cell to respond quickly to environmental changes. A number of CVD risk factors, such as nutrition, smoking, pollution, stress, and the circadian rhythm, have been associated with modification of epigenetic markers. Further examination of these mechanisms may lead to earlier prevention and novel therapies for CVD.

Although individuals with hs-CRP levels ≤ 1 mg/L have been defined as being at low risk for CVD according to AHA/CDC guidelines, the value of very low hs-CRP (<0.5

Table 1. Demographic and clinical characteristics of subjects

Variable (n = 88)	Mean $\pm$ SD	Median (Range)
Age (years)	46.16 $\pm$ 6.36	46.00 (34.00-60.00)
BMI (kg/m ²)	23.41 $\pm$ 2.84	22.85 (18.80-31.40)
WC (cm)	78.35 $\pm$ 8.70	76.75 (62.00-104.00)
WHR ¹⁾	0.86 $\pm$ 0.05	0.85 (0.70-0.99)
Mean SBP (mmHg)	118.44 $\pm$ 13.50	119.00 (98.00-159.00)
Mean DBP (mmHg)	73.57 $\pm$ 10.56	73.50 (51.00-100.00)
Glucose (mg/dL)	98.88 $\pm$ 16.08	95.50 (80.00-208.00)
Insulin ¹⁾ (μ U/mL)	5.67 $\pm$ 3.13	5.02 (0.20-18.04)
HOMA-IR ^{1),2)}	1.41 $\pm$ 0.93	1.19 (0.04-6.01)
TC (mg/dL)	184.94 $\pm$ 28.03	183.50 (129.00-259.00)
TG (mg/dL)	120.35 $\pm$ 64.53	101.00 (46.00-411.00)
LDL-C (mg/dL)	107.31 $\pm$ 24.81	109.00 (16.00-168.00)
HDL-C (mg/dL)	49.74 $\pm$ 12.03	48.00 (29.00-89.00)
apoA1 (mg/dL)	1.42 $\pm$ 0.23	1.40 (0.80-2.10)
apoB (mg/dL)	0.76 $\pm$ 0.15	0.80 (0.40-1.00)
apoB/apoA1 ratio	0.55 $\pm$ 0.16	0.52 (0.24-0.91)
Visceral fat (CT) (cm ²)	93.96 $\pm$ 56.18	81.95 (15.80-280.60)
VSR (CT)	0.94 $\pm$ 0.69	0.80 (0.20-3.40)
Creatinine (mg/dL)	0.75 $\pm$ 0.16	0.73 (0.39-1.10)
Uric acid (mg/dL)	4.80 $\pm$ 1.52	4.60 (2.00-9.00)
GGT (IU/L)	28.28 $\pm$ 21.33	20.00 (2.70-115.00)
PBF (BIA) (%)	25.49 $\pm$ 6.11	24.95 (13.20-39.00)
WHR (BIA)	0.88 $\pm$ 0.05	0.88 (0.77-0.98)

BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, VSR: visceral/subcutaneous fat ratio, GGT: gamma-glutamyl transferase, PBF: percentage body fat, BIA: bioelectrical impedance analysis.

1) n = 85.

2) HOMA-IR = [fasting glucose (mg/dL) $\times$ fasting insulin (μ U/mL)] / 405.

mg/L) in public health practice is unclear. This cross-sectional cohort study therefore assessed hs-CRP concentrations and the risk of CVD in 104 healthy Koreans aged 34-60 years.

MATERIALS AND METHODS

This study was approved by the local ethics committee. Written informed consent was obtained from all the participants prior to screening, and a detailed explanation of the study was provided. The study was conducted according to the principles of the Declaration of Helsinki for biomedical research involving human subjects and the Guideline for Good Clinical Practice.

1. Exclusion criteria

Subjects were excluded from this study if they had (1) hypertension (diastolic blood pressure (DBP) > 90 mmHg or systolic blood pressure (SBP) > 140 mmHg) with a history of cardiovascular events; (2) diabetes mellitus; (3) a history of cancer; (4) current renal, liver, digestive, rheumatic, or acute or chronic inflammatory disease; (5) a history of taking lipid-lowering medication; (6) previous use of steroids or non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin; or (7) a history of alcoholism or drug abuse. Subjects were also excluded if (8) they had participated in other clinical trials within the previous two months; (9) were pregnant and/or breastfeeding; or (10) if

Table 2. Comparison of variables between subjects with hs-CRP <0.5 mg/L and hs-CRP 0.5 to ≤1 mg/L

Variable	Overall (n = 88)	hs-CRP <0.5 mg/L (n = 53)	hs-CRP 0.5 to ≤1 mg/L (n = 35)	p-value
Age (years)	46.16 ± 6.36	45.47 ± 5.92	47.20 ± 6.93	0.2141
Gender				
Male	42 (47.73%)	17 (32.08%)	25 (71.43%)	0.0003
Female	46 (52.27%)	36 (67.92%)	10 (28.57%)	
BMI (kg/m ²)	23.41 ± 2.84	22.47 ± 2.33	24.84 ± 2.96	<.0001
WC (cm)	78.35 ± 8.70	75.34 ± 7.27	82.91 ± 8.79	<.0001
WHR ¹⁾	0.86 ± 0.05	0.84 ± 0.05	0.88 ± 0.05	0.001
Mean SBP (mmHg)	118.44 ± 13.50	115.45 ± 13.39	122.97 ± 12.53	0.0097
Mean DBP (mmHg)	73.57 ± 10.56	70.85 ± 9.99	77.69 ± 10.19	0.0025
Glucose (mg/dL)	98.88 ± 16.08	97.15 ± 18.07	101.49 ± 12.26	0.1836
Insulin ¹⁾ (μU/mL)	5.67 ± 3.13	5.12 ± 2.42	6.55 ± 3.88	0.0642
HOMA-IR ^{1),2)}	1.41 ± 0.93	1.24 ± 0.64	1.69 ± 1.21	0.0578
TC (mg/dL)	184.94 ± 28.03	180.51 ± 29.09	191.66 ± 25.28	0.0676
TG (mg/dL)	120.35 ± 64.53	96.89 ± 36.84	155.89 ± 80.14	0.0002
LDL-C (mg/dL)	107.31 ± 24.81	105.19 ± 22.13	110.51 ± 28.42	0.3271
HDL-C (mg/dL)	49.74 ± 12.03	52.26 ± 12.91	45.91 ± 9.51	0.0145
apoA1 (mg/dL)	1.42 ± 0.23	1.42 ± 0.24	1.41 ± 0.22	0.7341
apoB (mg/dL)	0.76 ± 0.15	0.72 ± 0.15	0.82 ± 0.13	0.0026
apoB/apoA1 ratio	0.55 ± 0.16	0.52 ± 0.16	0.60 ± 0.15	0.0265
Visceral fat (CT) (cm ²)	93.96 ± 56.18	70.78 ± 44.60	129.06 ± 54.12	<.0001
VSR (CT)	0.94 ± 0.69	0.73 ± 0.57	1.26 ± 0.73	0.0003
Creatinine (mg/dL)	0.75 ± 0.16	0.71 ± 0.15	0.81 ± 0.17	0.0041
Uric acid (mg/dL)	4.80 ± 1.52	4.35 ± 1.24	5.48 ± 1.66	0.0005
GGT (IU/L)	28.28 ± 21.33	21.30 ± 16.39	38.86 ± 23.71	0.0003
PBF (BIA) (%)	25.49 ± 6.11	25.20 ± 6.27	25.93 ± 5.91	0.5833
WHR (BIA)	0.88 ± 0.05	0.86 ± 0.04	0.90 ± 0.04	<.0001

BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, VSR: visceral/subcutaneous fat ratio, GGT: gamma-glutamyl transferase, PBF: percentage body fat, BIA: bioelectrical impedance analysis.

1) n = 85 (no data for one subject with hs-CRP <0.5 mg/L and 2 with hs-CRP 0.5 to ≤1 mg/L).

2) HOMA-IR = [fasting glucose (mg/dL) x fasting insulin (μU/mL)] / 405.

they had received hormone-replacement therapy. Finally, a total of 104 adults were enrolled.

2. Anthropometric examinations and measurements

Weight and height were measured by trained clinical trial center staff while participants wore lightweight clothing without shoes. Weight was measured to the nearest 0.1 kg and height to the nearest millimeter. Body mass index (BMI) was calculated as the ratio of weight to the square of the height. Waist circumference (WC) was measured at the midpoint between the lower edge of the costal arch and the top of the iliac crest. After five minutes of rest, SBP and DBP were measured (in mmHg) in a seated position with a patient monitor (IntelliVue MP70, Phillips Medical Systems, Eindhoven, Netherlands). All participants underwent body composition analysis. Body composition, including percentage body fat (PBF) and waist-to-hip ratio (WHR), was also assessed by bioelectrical impedance analysis (BIA), with a commercially available body analyzer (InBody 3.0, Biospace, Seoul, Korea). Participants were scanned in the supine position using a Siemens CT scanner (Somatom Plus 4). Visceral and subcutaneous fat were analyzed in a single 10 mm thick slice at the L4 vertebral level.

3. Biomarkers

Venous blood samples were collected after a 12 h fast. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were assayed by routine laboratory methods, while glucose, insulin, and HbA1c were measured using the Hitachi-7600 analyzer (Hitachi Ltd., Tokyo, Japan). The concentrations of apoB, apoA1, and hs-CRP were measured by turbidometry and ELISA methods. The homeostasis model assessment of insulin resistance (HOMA-IR) was defined as the product of fasting plasma insulin ($\mu\text{U/mL}$) and glucose (mg/dL) divided by 405. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), albumin, blood urea nitrogen (BUN), and creatinine were measured using an auto-analyzer (Variant, Bio-Rad, Hercules, CA, USA).

4. Statistical analysis

Data is expressed as mean $\pm$ standard deviation (SD) or

median (range). The means of variables in two groups were compared by t-tests. Comparisons between combinations of groups were made using the Bonferroni t-test. The associations between hs-CRP and other variables were examined by Pearson's correlation analysis. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using SAS[®] (Version 9.3, SAS Institute Inc., Cary, NC, USA) or R version 3.0.1.

RESULTS

Of the 104 initially recruited subjects, 16 were excluded,

Table 3. Pearson correlation analysis between hs-CRP and other factors

Variable (n = 88)	r*	p-value
Age (years)	0.095	0.3786
BMI (kg/m ²)	0.525	<.0001
WC (cm)	0.507	<.0001
Waist Hip Ratio ¹⁾	0.436	<.0001
Mean SBP (mmHg)	0.286	0.0070
Mean DBP (mmHg)	0.313	0.0030
Glucose (mg/dL)	0.209	0.0503
Insulin ¹⁾ ($\mu\text{U/mL}$)	0.317	0.0031
HOMA-IR ^{1),2)}	0.348	0.0011
TC (mg/dL)	0.147	0.1706
TG (mg/dL)	0.461	<.0001
LDL-C (mg/dL)	0.092	0.3916
HDL-C (mg/dL)	-0.255	0.0163
apoA1 (mg/dL)	-0.013	0.9032
apoB (mg/dL)	0.282	0.0077
apoB/apoA1 ratio	0.200	0.0618
Visceral fat (CT) (cm ²)	0.558	<.0001
VSR (CT)	0.398	0.0001
Creatinine (mg/dL)	0.325	0.0020
Uric acid (mg/dL)	0.434	<.0001
GGT (IU/L)	0.420	<.0001
PBF (BIA) (%)	0.110	0.3092
WHR (BIA)	0.507	<.0001

BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, VSR: visceral/subcutaneous fat ratio, GGT: gamma-glutamyl transferase, PBF: percentage body fat, BIA: bioelectrical impedance analysis.

*r = Correlation coefficient.

1) n = 85.

2) HOMA-IR = [fasting glucose (mg/dL) $\times$ fasting insulin ($\mu\text{U/mL}$)] / 405.

including four with high-risk hs-CRP concentrations (>3.0 mg/L) and 12 with intermediate-risk hs-CRP concentrations (1.0 to <3.0 mg/L). The baseline characteristics of the 88 included subjects are presented in Table 1. The 88 subjects included 42 males and 46 females, with a mean age of 46.16 ± 6.36 years, with 53 having hs-CRP concentrations <0.5 mg/L and 35 having hs-CRP concentrations of 0.5 to ≤ 1 mg/L. When factors were compared in these two groups, we found that BMI, WC, SBP, DBP, TG, apoB, visceral fat, visceral/subcutaneous fat ratio (VSR), creatinine, uric acid, GGT, and WHR were significantly higher ($p < 0.01$ each) in subjects with hs-CRP concentrations of 0.5 to ≤ 1 mg/L (Table 2). Interestingly, HDL-C concentrations were significantly lower ($p < 0.05$). There was no difference in TC concentration ($p = 0.0676$) between groups.

Pearson's correlation analysis showed that hs-CRP con-

centration correlated positively with BMI, WC, WHR, BP, TG, visceral fat, VSR, uric acid, GGT, and WHR (BIA) ($p < 0.0001$ each) and negatively with HDL-C ($p < 0.01$), but did not correlate with TC or LDL-C (Table 3). It should be noted, however, that subjects with hs-CRP <0.5 mg/L were predominantly female (68%), suggesting that gender was a potential confounding factor. To avoid this effect, we compared all variables between males in the two groups of participants. In this setting BMI, WC, WHR, TG, visceral fat, GGT, PBF (BIA) and WHR (BIA) still showed positive correlations with hs-CRP (Tables 4 and 5).

DISCUSSION

We observed significantly higher BMI, WC, TG, apoB, visceral fat, VSR, creatinine, uric acid, GGT, and WHR (BIA)

Table 4. Comparison of variables in male subjects ($n = 42$) with hs-CRP <0.5 mg/L and hs-CRP 0.5 to ≤ 1 mg/L

Variable	Overall ($n = 42$)	hs-CRP <0.5 mg/L ($n = 17$)	hs-CRP 0.5 to ≤ 1 mg/L ($n = 25$)	p-value
Age (years)	47.07 ± 6.52	46.94 ± 5.92	47.16 ± 7.02	0.9165
BMI (kg/m^2)	24.51 ± 2.75	23.26 ± 1.62	25.36 ± 3.06	0.0065
WC (cm)	83.60 ± 8.47	80.94 ± 7.09	85.40 ± 8.98	0.0944
WHR ¹⁾	0.89 ± 0.05	0.88 ± 0.05	0.89 ± 0.05	0.3003
Mean SBP (mmHg)	124.48 ± 10.65	121.82 ± 9.75	126.28 ± 11.05	0.1866
Mean DBP (mmHg)	79.74 ± 8.34	77.59 ± 7.48	81.20 ± 8.72	0.1712
Glucose (mg/dL)	105.67 ± 20.31	107.24 ± 28.47	104.60 ± 12.70	0.7239
Insulin ¹⁾ ($\mu\text{U}/\text{mL}$)	6.53 ± 3.68	5.39 ± 2.29	7.33 ± 4.26	0.0757
HOMA-IR ^{1),2)}	1.74 ± 1.15	1.45 ± 0.72	1.95 ± 1.35	0.1416
TC (mg/dL)	190.38 ± 23.54	188.35 ± 30.81	191.76 ± 17.58	0.6837
TG (mg/dL)	153.00 ± 75.33	119.29 ± 40.80	175.92 ± 85.05	0.0066
LDL-C (mg/dL)	110.90 ± 25.15	114.53 ± 23.69	108.44 ± 26.28	0.4480
HDL-C (mg/dL)	45.50 ± 10.76	47.35 ± 11.55	44.24 ± 10.24	0.3640
apoA1 (mg/dL)	1.37 ± 0.23	1.36 ± 0.24	1.38 ± 0.23	0.8374
apoB (mg/dL)	0.82 ± 0.12	0.81 ± 0.16	0.83 ± 0.09	0.5520
apoB/apoA1 ratio	0.62 ± 0.15	0.61 ± 0.17	0.62 ± 0.14	0.7956
Visceral fat (CT) (cm^2)	131.19 ± 56.68	101.79 ± 58.99	151.18 ± 46.27	0.0042
VSR (CT)	1.45 ± 0.65	1.29 ± 0.67	1.56 ± 0.63	0.2064
Creatinine (mg/dL)	0.88 ± 0.13	0.86 ± 0.14	0.90 ± 0.11	0.3785
Uric acid (mg/dL)	5.96 ± 1.21	5.62 ± 1.00	6.20 ± 1.30	0.1343
GGT (IU/L)	40.38 ± 24.53	31.24 ± 23.46	46.60 ± 23.69	0.0449
PBF (BIA) (%)	21.72 ± 4.85	18.94 ± 3.26	23.62 ± 4.88	0.0013
WHR (BIA)	0.89 ± 0.04	0.87 ± 0.03	0.91 ± 0.04	0.0031

BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, VSR: visceral/subcutaneous fat ratio, GGT: gamma-glutamyl transferase, PBF: percentage body fat, BIA: bioelectrical impedance analysis.

1) $n = 39$ (no data for one subject with hs-CRP <0.5 mg/L and 2 with hs-CRP 0.5 to ≤ 1 mg/L).

2) $\text{HOMA-IR} = [\text{fasting glucose (mg/dL)} \times \text{fasting insulin } (\mu\text{U/mL})] / 405$.

Table 5. Pearson correlation analysis between hs-CRP and other factors in male subjects

Variable (n = 42)	r*	p-value
Age (years)	-0.103	0.5153
BMI (kg/m ²)	0.563	0.0001
WC (cm)	0.418	0.0059
WHR ¹⁾	0.370	0.0205
Mean SBP (mmHg)	0.221	0.1602
Mean DBP (mmHg)	0.229	0.1438
Glucose (mg/dL)	0.036	0.8200
Insulin ¹⁾ (μU/mL)	0.350	0.0287
HOMA-IR ^{1),2)}	0.335	0.0371
TC (mg/dL)	0.097	0.5392
TG (mg/dL)	0.395	0.0096
LDL-C (mg/dL)	-0.012	0.9393
HDL-C (mg/dL)	-0.118	0.4580
apoA1 (mg/dL)	0.102	0.5197
apoB (mg/dL)	0.158	0.3167
apoB/apoA1 ratio	0.024	0.8818
Visceral fat (CT) (cm ²)	0.485	0.0011
VSR (CT)	0.207	0.1876
Creatinine (mg/dL)	0.099	0.5343
Uric acid (mg/dL)	0.348	0.0241
GGT (IU/L)	0.308	0.0474
PBF (BIA) (%)	0.650	<.0001
WHR (BIA)	0.571	<.0001

BMI: body mass index, WC: waist circumference, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, VSR: visceral/subcutaneous fat ratio, GGT: gamma-glutamyl transferase, PBF: percentage body fat, BIA: bioelectrical impedance analysis.

*r=Correlation coefficient.

1) n = 39.

2) HOMA-IR = [fasting glucose (mg/dL) × fasting insulin (μU/mL)] / 405.

(p < 0.01 each) and significantly lower HDL-C (p < 0.05) in subjects with hs-CRP concentrations of 0.5 to ≤1 mg/L compared to those with hs-CRP <0.5 mg/L. However, multivariate logistic analyses showed that higher hs-CRP levels were largely seen in those of the female gender [11]. Pearson's correlation analysis in the 42 male subjects showed that BMI, TG, visceral fat, and WHR (BIA) were significantly higher (p < 0.001) in subjects with hs-CRP 0.5 to ≤1 mg/L.

Statistically significant associations between hs-CRP and measures of generalized and central obesity have been reported previously [12-14]. Our results are consistent with

the established importance of BMI and central obesity as risk factors for SLGI [15]. Excess body fat, particularly abdominal obesity, is associated with SLGI. In males, BIA evaluations, including percent body fat (r = 0.650) and WHR (r = 0.571), showed stronger correlations with hs-CRP increments than did the anthropometric indices, WC (r = 0.418), WHR (r = 0.370), and visceral fat analysis by CT (r = 0.485). Accordingly, it is important to choose simple and reliable methods of measuring body fat composition in clinical and public health practice.

High levels of hs-CRP have been shown to be an independent predictor of CVD and metabolic syndrome [16]. To our knowledge, this is the first study of healthy middle-aged Korean adults showing that very low hs-CRP levels are inversely associated with other traditional risk factors of chronic diseases.

Very low hs-CRP may be achieved by lifestyle modifications, including increased physical activity and dietary interventions. This may enhance the wellness of the general population, reducing both fat aggregation in the abdomen and vascular inflammation, thereby preventing chronic diseases.

This study had several limitations. First, as in any cross-sectional study, we could analyze only the correlation between hs-CRP and other variables, but could not determine causality or mechanisms. Second, since the cohort in this study included only healthy workers at a hospital, the data cannot be extrapolated to the entire population. Third, the small sample size of the cohort in this study may not have provided the power necessary to detect variability in some of the biomarkers. Additional studies are needed to corroborate our findings and extend them to other biomarkers.

Very low levels of hs-CRP and traditional risk factors for chronic diseases correlated well with each other in middle-aged Korean adults. Periodic measurements of abdominal obesity may also be used to assess systemic inflammation in individuals.

In conclusion, we found a significant association between SLGI and indices of central obesity in healthy middle-aged Koreans. Although causality could not be established, these findings suggest the need for chronic disease prevention programs, employing very low levels of hs-CRP as a marker of wellness.

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REFERENCES

1. Pearson TA, Mensah GA, Hong Y, Smith SC, Jr., Cdc, Aha. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: overview. *Circulation* 2004;110:e543-4.
2. Napoli C, Crudele V, Soricelli A, Al-Omran M, Vitale N, Infante T, Mancini FP. Primary prevention of atherosclerosis: a clinical challenge for the reversal of epigenetic mechanisms? *Circulation* 2012;125:2363-73.
3. Blackburn H. Introduction to Ancel Keys Lecture. Ancel Keys, pioneer. *Circulation* 1991;84:1402-4.
4. Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, Djordjevic BS, Dontas AS, Fidanza F, Keys MH, et al. The diet and 15-year death rate in the seven countries study. *Am J Epidemiol* 1986;124:903-15.
5. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007;356:2388-98.
6. Young F, Capewell S, Ford ES, Critchley JA. Coronary mortality declines in the U.S. between 1980 and 2000 quantifying the contributions from primary and secondary prevention. *Am J Prev Med* 2010;39:228-34.
7. Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999;340:115-26.
8. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007-11.
9. Silva D, Pais de Lacerda A. High-sensitivity C-reactive protein as a biomarker of risk in coronary artery disease. *Rev Port Cardiol* 2012;31:733-45.
10. Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS. Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 2009;5:401-8.
11. Albert MA, Ridker PM. C-reactive protein as a risk predictor: do race/ethnicity and gender make a difference? *Circulation* 2006;114:e67-74.
12. Vikram NK, Misra A, Pandey RM, Dwivedi M, Luthra K, Dhingra V, Talwar KK. Association between sub-clinical inflammation & fasting insulin in urban young adult north Indian males. *Indian J Med Res* 2006;124:677-82.
13. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. *Am J Cardiol* 2010;106:56-61.
14. McDade TW, Rutherford JN, Adair L, Kuzawa C. Adiposity and pathogen exposure predict C-reactive protein in Filipino women. *J Nutr* 2008;138:2442-7.
15. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract* 2005;69:29-35.
16. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003;107:391-7.