ORIGINAL ARTICLE
Nephrology

JKMS

http://dx.doi.org/10.3346/jkms.2012.27.6.630 • J Korean Med Sci 2012; 27: 630-635

Low-Grade Inflammation, Metabolic Syndrome and the Risk of Chronic Kidney Disease: the 2005 Korean National Health and Nutrition Examination Survey

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Received: 3 November 2011
Accepted: 13 March 2012

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Either chronic inflammation or metabolic syndrome (MetS) is associated with renal impairment. This cross-sectional study was designed to investigate the relationship between elevated white blood cell (WBC) counts and chronic kidney disease (CKD) stage 3 or more according to the presence of MetS in adult Koreans. In total, 5,291 subjects (≥ 20 yr-old) participating in the 2005 Korean National Health and Nutrition Examination were included. CKD stage 3 or more was defined as having an estimated glomerular filtration rate below 60 mL/min/1.73 m^2, as calculated using the formula from the Modification of Diet in Renal Disease study. The odds ratio (95% confidence interval) for CKD stage 3 or more in the highest WBC quartile (≥ 7,200 cells/μL) was 1.70 (1.17-2.39) after adjusting for MetS and other covariates, compared with the lowest WBC quartile (< 5,100 cells/μL). In subjects with MetS, the prevalence risk for CKD stage 3 or more in the highest WBC quartile was 2.25 (1.28-3.95) even after fully adjusting for confounding variables. In contrast, this positive association between WBC quartile and CKD stage 3 or more disappeared in subjects without MetS. Low-grade inflammation is significantly associated with CKD stage 3 or more in subjects with MetS but not in those without MetS.

Key Words: Kidney Failure, Chronic; Inflammation; Metabolic Syndrome; Leukocytes

INTRODUCTION

Chronic kidney disease (CKD) often progresses to end-stage renal disease (ESRD), necessitating renal replacement therapy, and the occurrence of which is steadily increasing. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of CKD stage 3 or more in the United States was 10.0% between 1994 and 1998, and it increased to 13.1% between 1999 and 2004 (1). CKD is known to be associated with cardiovascular morbidity and mortality (2). Thus, early identification and proper management of CKD can prevent ESRD and associated mortality.

Previous studies demonstrated that CKD may be a renal phenotype of MetS, which is associated with insulin resistance (3). Moreover, chronic low-grade inflammation plays a major role in the development of CKD (4). A higher level of C-reactive protein (CRP) is associated with endothelial injury, impaired vasodilation, and glomerulosclerosis (5). White blood cell (WBC) count is also readily available to clinicians as part of complete blood count. Recently, WBC count has been known as a useful predictor of certain diseases in addition to a marker of infection or inflammation. A higher level of WBC count, even within the normal range, has been associated with increased morbidity and mortality caused by atherosclerotic diseases (6, 7).

To date, little is known about whether low-grade inflammation is related to the risk of CKD, independent of MetS. In the present study, we investigated the association between WBC count as a nonspecific marker of inflammation and the prevalence risk of CKD stage 3 or more in Korean adults compiled in the 2005 Korean National Health and Nutrition Examination Survey (KNHANES). We further examined the predictive role of WBC count on the prevalence of CKD stage 3 or more according to the presence of MetS.

MATERIALS AND METHODS

Study sample

This study was based on data obtained from the 2005 Korean National Health and Nutrition Examination Survey (KNHANES), a cross-sectional and nationally representative survey that was conducted by the Ministry of Health and Welfare of the Republic of Korea in 2005. The target population of the survey was non-

pISSN 1011-8934
eISSN 1598-6357

institutionalized civilians in Korea of at least one year of age. Sampling units were households that were selected through a stratified, multistage, probability-sampling design that was based on geographic area, gender, and age from a database of household registries. There were 246,097 primary sampling units, each of which contained approximately 60 households. In total, 600 sampling frames, comprising 13,345 households from the primary sampling units, were randomly sampled. Of these, 12,001 households (89.9%) were included in the study. Weights indicating the probability of being sampled were assigned to each participant, enabling the results from this study to represent the entire Korean population. Participants completed four parts of a questionnaire, composed of a Health Interview Survey, Health Behavior Survey, Health Examination Survey, and Nutrition Survey.

The 2005 KNHANES had 34,145 initial participants. Of the 25,161 participants who were at least 20 yr old, we excluded subjects (n = 482) who had been diagnosed with any malignancies by doctors, as well as subjects (n = 19,326) who did not complete the health interview survey or undergo blood sampling. Participants with WBC counts higher than 10,000 cells/μL were excluded to rule out the possibility of current infection (n = 62). A total of 5,291 individuals (3,856 men and 1,435 women) were included in the final analysis.

Data collection

At the time the 2005 KNHANES was conducted, citizens were informed that they had been randomly selected as a household to voluntarily participate in a nationally representative survey conducted by the Korean Government. All citizens were given the right to refuse to participate in accordance with the National Health Enhancement Act supported by the National Statistics Law of Korea. Physical examinations were performed by trained investigators following a standardized procedure. Body weight and height were measured in light indoor clothing without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Waist circumference was measured at the narrowest point between the lower border of the rib cage and the iliac crest. Body mass index (BMI) was calculated as the ratio of weight/height^2 (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the right arm using a standard mercury sphygmomanometer (Baumanometer, Baum, Copiague, NY, USA). The average of two systolic and diastolic blood pressure readings, which were recorded at an interval of five minutes, was used for analysis. Dietary intake was collected using the 24-hr recall method. All subjects were instructed to maintain their usual dietary habits. Daily calorie intake was calculated with Can-Pro 2.0, a nutrient intake assessment software program developed by the Korean Nutrition Society. After 12 hr of overnight fasting, blood samples were obtained from the antecubital veins of the study subjects. Fasting plasma glucose, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and creatinine levels were measured using a Hitachi 7600-110 chemistry analyzer (Hitachi, Tokyo, Japan). WBC counts were quantified by an automated blood cell counter (ADVIA 120, Bayer, New York, NY, USA).

Definitions of CKD stage 3 or more and metabolic syndrome

We defined CKD stage 3 or more as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2. The eGFR was calculated using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study: 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × 0.742 (if a woman) (8).

Previously, major organizations including International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute issued a harmonizing definition of MetS in 2009 (9). According to the harmonizing definition, MetS was defined as having three or more of the following criteria: waist circumference ≥ 90 cm in men and ≥ 85 cm in women; systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or taking antihypertensive medication; fasting plasma glucose ≥ 100 mg/dL or taking any anti-diabetic medication; TG level ≥ 150 mg/dL, or taking any lipid-lowering medication; HDL-C < 40 mg/dL in men and < 50 mg/dL in women or taking any lipid-lowering medication.

Statistical analysis

WBC quartiles were categorized as follows: Q1; < 5,100, Q2; 5,100-6,000, Q3; 6,100-7,100, and Q4; ≥ 7,200 cells/μL. With the exception of TG, the characteristics of the study sample were summarized using either the independent t-test or the one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. To compare the median values of nonparametric variables, such as TG, we used the Mann-Whitney U test and the Kruskal-Wallis test. We conducted linear regression analyses to verify trend analysis. To further evaluate the relationship between WBC quartile and CKD stage 3 or more in subjects with or without MetS, WBC quartiles were re-categorized as follows: Q1; < 5,100, Q2; 5,100-6,000, Q3; 6,100-7,000, Q4; ≥ 7,100 cells/μL in subjects without MetS, and Q1; < 5,600, Q2; 5,600-6,500, Q3; 6,600-8,000, Q4; ≥ 8,100 cells/μL in subjects with MetS. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for CKD stage 3 or more were calculated using multivariate logistic regression analyses after adjusting for confounding variables across WBC quartiles. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was determined at P values < 0.05.

Ethics statement

This study protocol was reviewed and approved by the institutional review board of Yonsei University College of Medicine,

Seoul, Korea (IRB No. 3-2010-0029). The participants and their parents (if applicable) provided written informed consent of their participation in the study. The Korea Centers for Disease Control and Prevention also obtained written informed consent to use blood samples from the participants for further analyses.

RESULTS

The overall prevalence of CKD stage 3 or more is 8.8% (5.6% in subjects without MetS versus 17.2% in subjects without MetS) after final exclusion. Table 1 lists the characteristics of the 5,291 subjects according to MetS. The mean or median value of BMI, waist circumference, SBP, DBP, fasting plasma glucose, TG, and creatinine are significantly higher in subjects with MetS than in those without MetS, while serum HDL-C levels and eGFR are higher in subjects without MetS than in those with MetS. The percentage of current smokers is higher in subjects with MetS, while that of regular drinkers is higher in subjects without MetS. The mean WBC count is higher in subjects with MetS (6,109 cells/μL in non-MetS group, 6,787 cells/μL in MetS group).

Table 1. Characteristics of the study subjects

Parameters	Non-MetS	MetS	*P* value
No. (men, %)	3,856 (40.4)	1,435 (49.8)	< 0.001
Age (yr)	43.8 ± 14.6	55.2 ± 13.5	< 0.001
BMI (m/kg^2)	22.9 ± 2.9	26.1 ± 3.0	< 0.001
WC (cm)	77.8 ± 8.3	89.5 ± 7.6	< 0.001
WBC (cells/μL)	6,109 ± 1,763	6,787 ± 1,936	< 0.001
SBP (mmHg)	114.5 ± 15.6	131.5 ± 17.2	< 0.001
DBP (mmHg)	74.9 ± 9.8	83.9 ± 10.5	< 0.001
FPG (mg/dL)	90.2 ± 16.7	108.6 ± 30.7	< 0.001
TG (mg/dL)*	91.0 (67.0, 123.0)	177.0 (129.0, 240.0)	< 0.001
HDL-C (mg/dL)	47.4 ± 10.9	38.8 ± 7.6	< 0.001
Creatinine (mg/dL)	0.97 ± 0.17	1.02 ± 0.23	< 0.001
Current smoker (%)†	21.3	24.6	< 0.001
Regular drinker (%)†	75.4	67.4	< 0.001
Energy intake (kcal)	2012.0 ± 829.2	1974.3 ± 849.6	0.174
eGFR (mL/min/1.73 m^2)	77.4 ± 11.8	72.3 ± 12.6	0.002

All data except TG, smoking status, and drinking status are represented as mean ± standard deviation (SD). Smoking status and drinking status are represented as percentages. TG is represented as the median (lower, higher quartile). **P* value as determined by Mann-Whitney U test; †*P* value as determined by chi square test. BMI, body mass index; WC, waist circumference; WBC, white blood cell; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rates.

Table 2 shows the subject characteristics according to WBC count quartile. The mean or median values of BMI, waist circumference, WBC, SBP, DBP, fasting plasma glucose, TG, and creatinine increase as WBC quartile increases, while HDL-C decreases in accordance with WBC quartile.

Table 3 shows the results of the logistic regression analyses designed to investigate the relationship between WBC quartile, MetS, and CKD stage 3 or more. In comparison with participants who are categorized in the first WBC quartile (< 5,100 cells/μL), the OR for CKD stage 3 or more of participants who are categorized in the highest WBC quartile (≥ 7,200 cells/μL) is 1.70 (95% CI, 1.17-2.39) after adjusting for age, gender, SBP, fasting plasma glucose, energy intake, smoking status, alcohol-drinking status, BMI, and MetS. Although the OR of MetS for CKD stage 3 or more is significant in Model 2, which is fully adjusted except for WBC quartile, its significance disappears in Model 4, which is fully adjusted including WBC quartile.

To further evaluate the relationship between WBC quartile and CKD stage 3 or more in subjects with or without MetS, we conducted multivariate logistic regression analyses that were stratified according to MetS (Fig. 1). In subjects with MetS, the

Table 2. Characteristics according to WBC quartile (cells/μL)

Parameters	Q1 < 5,100 cells/μL	Q2 5,100-6,000 cells/μL	Q3 6,100-7,100 cells/μL	Q4 ≥ 7,200 cells/μL	*P* value
No. (men, %)	1,520 (25.5)	1,272 (41.0)	1,185 (46.4)	1,314 (61.7)	
Age (yr)	48.2 ± 15.3	47.0 ± 14.8	46.2 ± 15.4	46.0 ± 15.0	< 0.001
BMI (m/kg^2)	23.1 ± 3.0	23.7 ± 3.3	23.9 ± 3.4	24.3 ± 3.3	< 0.001
WC (cm)	78.2 ± 9.1	80.7 ± 9.5	81.6 ± 9.7	83.9 ± 9.4	< 0.001
WBC (cells/μL)	4,410 ± 610	5,670 ± 310	6,660 ± 330	8,740 ± 1,530	< 0.001
SBP (mmHg)	116.5 ± 17.6	119.2 ± 17.8	119.8 ± 17.2	121.6 ± 17.8	< 0.001
DBP (mmHg)	75.3 ± 10.3	77.3 ± 10.6	77.7 ± 10.6	79.4 ± 11.2	< 0.001
FPG (mg/dL)	91.4 ± 15.3	94.7 ± 21.8	96.8 ± 27.2	98.6 ± 26.0	< 0.001
TG (mg/dL)*	85.0 (62.0, 121.0)	105.0 (76.0, 147.8)	115.0 (80.0, 175.0)	129.0 (90.0, 199.0)	< 0.001
HDL-C (mg/dL)	47.7 ± 11.6	45.2 ± 10.3	44.3 ± 10.2	42.7 ± 10.3	< 0.001
Creatinine (mg/dL)	0.95 ± 0.13	0.98 ± 0.14	1.00 ± 0.24	1.02 ± 0.23	< 0.001
Current smoker (%)†	10.1	19.5	21.9	39.2	< 0.001
Regular drinker (%)†	70.9	72.3	73.7	76.5	< 0.001
Energy intake (kcal)	1,919.7 ± 798.6	2,003.8 ± 830.5	1,981.0 ± 787.6	2,115.8 ± 907.9	< 0.001
eGFR (mL/min/1.73 m^2)	74.4 ± 11.6	76.0 ± 11.8	76.2 ± 12.4	77.5 ± 13.0	< 0.001

All data except TG, smoking status, and drinking status are represented as mean ± standard deviation (SD). Smoking status and drinking status are represented as percentages. TG is represented as the median (lower, higher quartile). **P* value as determined by Kruskal Wallis test; †*P* value as determined by chi square test. BMI, body mass index; WC, waist circumference; WBC, white blood cell; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rates.

http://dx.doi.org/10.3346/jkms.2012.27.6.630

Table 3. Odds ratio and 95% confidence intervals for chronic kidney disease stage 3 or more according to WBC quartile and metabolic syndrome

Model	WBC counts				MetS	
	Q1 < 5,100 cells/μL	Q2 5,100-6,000 cells/μL	Q3 6,100-7,100 cells/μL	Q4 ≥ 7,200 cells/μL	Non-MetS	MetS
Model 1	1	1.32 (0.97-1.80)	1.43 (1.04-1.97)	1.72 (1.25-2.38)	1	1.62 (1.29-2.04)
Model 2	1	1.41 (1.01-1.97)	1.37 (0.96-1.94)	1.73 (1.22-2.47)	1	1.35 (1.00-1.82)
Model 3	1	1.40 (1.00-1.95)	1.34 (0.94-1.90)	1.70 (1.17-2.39)		
Model 4					1	1.28 (0.95-1.73)

Model 1, adjusted for age and gender; Model 2, adjusted for SBP, fasting plasma glucose, energy intake, smoking status, alcohol-drinking status, and BMI, additionally to Model 1; Model 3, adjusted for metabolic syndrome, additionally to Model 2; Model 4, adjusted for WBC count, additionally to Model.

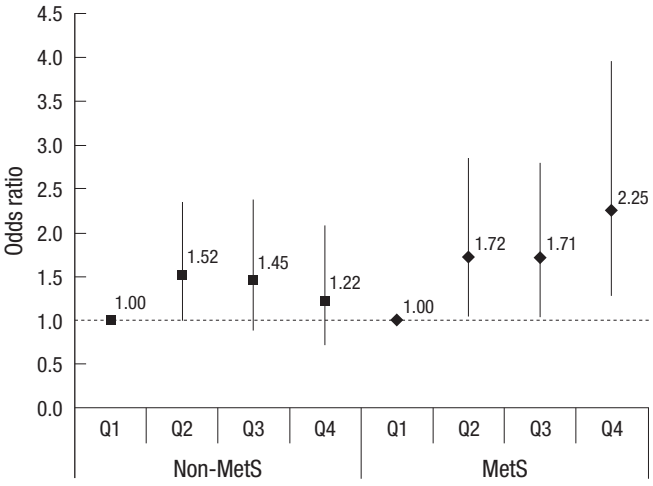

Fig. 1. Odds ratio for chronic kidney disease stage 3 or more of individuals with or without metabolic syndrome, according to WBC quartile. Logistic regression analysis model was adjusted for age, gender, SBP, fasting plasma glucose, energy intake, smoking status, alcohol-drinking status, and BMI.

risk for CKD stage 3 or more in the highest WBC quartile is 2.25 (1.28-3.95), even after fully adjusting for confounding variables. In contrast, this positive association between CKD stage 3 or more and WBC quartile are not found in subjects without MetS.

DISCUSSION

The major finding in this study is that a higher level of WBC count in Korean adults with MetS is strongly associated with the prevalence of CKD stage 3 or more, but not in Korean adults without MetS.

Each component of MetS is strongly associated with the development of CKD (10). Abdominal obesity is one of the most common risk factors for ESRD and CVD through insulin resistance and inflammatory cytokines secreted by adipose tissue (11). High blood pressure and insulin resistance are well-established risk factors for CKD in previous studies (12, 13). Dyslipidemia also contributes to accelerated development of renal insufficiency (14). Mesangial cells exposed to lipids are stimulated to secrete pro-inflammatory cytokines, such as interleukin-6, tumor necrosis factor-α, and transforming growth factor-β, resulting in excessive glomerular basement membrane material and glomerulosclerosis (14, 15). Particularly, individuals with high TG and low HDL-C levels have a higher risk of renal dysfunction (16).

Chronic low-grade inflammation is a common risk factor of MetS and CKD, as well as CVD (17, 18). Higher levels of inflammatory markers such as WBC count and CRP are associated with the morbidity and mortality of CKD (18, 19). Chronic low-grade inflammation has been identified as an integral part of the pathogenesis of vascular diseases such as hypertension (20). Vascular inflammation plays a crucial role in the development of hypertension through endothelial dysfunction, mediated by a reduced availability of nitric oxide (NO) and increased activity of the renin-angiotensin system (21). Also, a deficiency of the endogenous vasodilator, NO, occurs in various stages of CKD and may contribute to the progression of CKD (22, 23). Moreover, various inflammatory cytokines are related to the initiation and progression of CKD (24).

We show that higher WBC count is associated with the prevalence of CKD stage 3 or more, even after adjustment for MetS, in addition to the traditional risk factors of CKD. Our results are in agreement with previous studies that showed chronic low-grade inflammation to be a risk factor of CKD (4, 18, 24). In this study, MetS is associated with the prevalence of CKD stage 3 or more (OR [95% CI] 1.35 [1.00-1.82]) when adjusted only for age, gender, SBP, fasting plasma glucose, energy intake, smoking status, alcohol-drinking status, and BMI; while the association between MetS and CKD stage 3 or more disappears when additionally adjusted for WBC count. We stratified individuals according to the presence of MetS in order to investigate the independent effect of WBC count on the prevalence risk of CKD stage 3 or more after controlling for MetS. Among individuals without MetS, WBC count is not associated with the prevalence of CKD stage 3 or more. However, in individuals with MetS, the association between elevated WBC count and CKD stage 3 or more is enhanced (OR [95% CI] 2.25 [1.28-3.95]). In our study, the relationship between elevated WBC count and CKD stage 3 or more is observed only for individuals with MetS for some reason, but not for those without MetS. Some studies have shown that inflammation is significantly associated with MetS and its diagnostic parameters (11, 17). Probably, after chronic low-grade inflammation initiates subclinical abnormalities of cardiometabolic risk factors, leading to MetS, a phenotype of renal impairment

appears to subsequently develop. Also, co-existence of low-grade inflammation and MetS could synergistically affect the deterioration of renal dysfunction. Fakhrzadeh et al. (25) also reported that the risk of CKD is increased in subjects with both elevated CRP and MetS in an elderly Iranian sample. In that study, subjects with MetS and elevated CRP levels, another inflammatory marker, have a 1.71-fold greater risk of CKD stage 3 or more compared to those without MetS and low CRP levels. Our study confirms that the co-existence of MetS and chronic low-grade inflammation measured according to WBC count is associated with the prevalence risk of CKD stage 3 or more.

There are some study limitations that should be considered when interpreting the findings of the present work. First, it is difficult to determine a causal relationship between a higher WBC count and increased risk of CKD stage 3 or more using a cross-sectional study design. Further prospective research is warranted to better understand its causal relationship. Second, we used a definition of CKD stage 3 or more as eGFR less than 60 mL per min per 1.73 m^2 using the MDRD formula. This eGFR may not accurately estimate actual GFR. Furthermore, because the MDRD formula was developed using study samples of primarily European descent, an additional estimation of GFR in Koreans may be necessary. Third, we did not include individuals with proteinuria, which may be a phenotype of CKD. However, because the urine samples of the 2005 KNHANES were not collected at the first void in the morning, it is difficult to obtain quantitative measurements and to control for selection bias. Fourth, the prevalence of CKD stage 3 or more seems to be higher than the prevalence reported in other studies (26). We could not fully control for selection bias in the process of selecting the cases. The mean ages of the 5,440 selected participants were significantly older than those of the 19,721 excluded participants (47.2 yr vs 45.3 yr). Thus, the inclusion of relatively older subjects during the selection process could have contributed to this higher prevalence of CKD stage 3 or more in this study. Finally, because WBC count in this study was only measured once, it was not possible to determine whether an acute episode of infection or chronic inflammation was responsible for the correlation observed. In order to minimize the possibility of including participants with active infections, we excluded participants with WBC $\geq$ 10,000 cells/μL.

In conclusion, low-grade inflammation is significantly associated with CKD stage 3 or more in subjects with MetS but not in those without MetS.

ACKNOWLEDGMENTS

The 2005 KNHANES was conducted by the Korea Ministry of Health and Welfare in 2005. We thank all members who conducted the 2005 KNHANES and the civilians who participated in this survey.

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