Association between the Ratio of Triglycerides to High-Density Lipoprotein Cholesterol and Chronic Kidney Disease in Korean Adults: The 2005 Korean National Health and Nutrition Examination Survey

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Key Words

Chronic kidney disease • High-density lipoprotein cholesterol • Modification of Diet in Renal Disease study • Triglyceride

Abstract

Background: The ratio of triglycerides (TG, mg/dl) to high-density lipoprotein cholesterol (HDL-C, mg/dl) is a reliable indicator of insulin resistance and atherosclerotic diseases. The purpose of this study was to examine the association between TG/HDL-C and chronic kidney disease (CKD) in a nationally representative sample of Korean adults. **Methods:** This cross-sectional study included 5,503 subjects (≥ 19 years of age) who participated in the 2005 Korean National Health and Nutrition Examination Survey. CKD was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m² as calculated by the abbreviated formula from the Modification of Diet in Renal Disease study. **Results:** The overall prevalence of CKD in our sample was 9.0%. eGFR was negatively correlated with logarithm-transformed TG/HDL-C in Pearson's correlation. The prevalence of CKD in increasing TG/HDL-C quintiles was 4.4, 6.6, 9.5, 11.9, and 12.8%. In comparison with the lowest quintile of TG/HDL-C (< 1.38), the odds ratio (95% confidence interval) for CKD in the highest

quintile of TG/HDL-C (≥ 4.50) was 2.15 (1.38–3.37), after adjustment for multiple covariates (p value for trend = 0.036). **Conclusions:** TG/HDL-C was independently associated with increased prevalence of CKD in a sample of Korean adults.

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Introduction

Chronic kidney disease (CKD) often progresses to end-stage renal disease (ESRD), a cause of renal replacement therapy that is steadily increasing in frequency. CKD is also closely associated with cardiovascular morbidity and mortality [1, 2]. Early identification and proper management of CKD can prevent ESRD and its associated morbidities.

The most important risk factors for atherosclerotic cardiovascular disease (CVD), including hypertension and diabetes, play a major role in the development of CKD [1–3]. Dyslipidemia, which includes high triglyceride (TG) levels and low high-density lipoprotein chole-

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terol (HDL-C) levels, is considered both a cause and consequence of CKD, although the mechanisms underlying this relationship are not fully understood [4–7]. Dyslipidemia and abnormal lipoprotein levels induce mesangial cell damage as well as proliferation and atherosclerosis of renal arterioles, resulting in excessive glomerular basement membrane deposition and glomerulosclerosis [5]. These phenomena decrease renal function and further aggravate dyslipidemia.

The TG/HDL-C ratio is a better indicator of insulin resistance and cardiovascular events than other lipid parameters including TG, LDL-C, or the ratio of total cholesterol to HDL-C [8, 9]. In addition, TG/HDL-C correlates well with levels of small, dense LDL-C particles, which are easily oxidized and highly atherogenic [8]. Thus, it is conceivable that elevated TG/HDL-C may also indicate the development and progression of CKD, given the similar pathogenic mechanisms involved in atherosclerosis and glomerulosclerosis.

In the present study, we investigated the association between TG/HDL-C and CKD in a nationally representative sample of Korean adults.

Subjects and Methods

Study Subjects

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 Korean Ministry of Health and Welfare in 2005. The target population of the survey was non-institutionalized civilians in Korea 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. Six hundred sampling frames, consisting of 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 the Nutrition Survey.

The 2005 KNHANES had 34,145 initial participants. The Health Examination Survey was completed by 7,597 (70.2%) of the 10,816 selected individuals who had taken part in the Health Interview Survey. We excluded individuals younger than 19 years of age, without laboratory data such as creatinine and lipids, or who had not fasted for at least 12 h prior to blood sampling. A total of 5,503 (50.9%) individuals (2,345 men and 3,158 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 survey conducted by the Korean Ministry of Health and Welfare. 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. The participants and their parents (if applicable) provided written informed consent to participate in the study. The Korea Centers for Disease Control and Prevention also obtained written informed consent to use blood samples from participants for further analysis. This study was approved by the Institutional Review Board of Wonju Christian Hospital, Wonju College of Medicine, Yonsei University, Wonju, South Korea. Physical examinations were performed by trained medical staff 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/height² (kg/m²). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the right arm using a standard mercury sphygmomanometer (Baumanometer, USA). The average of 2 SBP and DBP readings, which were recorded at an interval of 5 min, was used for analysis. Dietary intake was collected using the 24-hour recall method. All subjects were instructed to maintain their usual dietary habits. Daily energy intake was calculated with Can-Pro 2.0, a nutrient intake assessment software program which was developed by the Korean Nutrition Society. After 12 h of overnight fasting, blood samples were obtained from the antecubital veins of the study subjects. Fasting plasma glucose, TG, HDL-C, and creatinine levels were measured using a Hitachi 7600-110 chemistry analyzer (Hitachi, Tokyo, Japan).

Definitions of CKD and TG/HDL-C

We defined CKD as an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m². The eGFR was calculated using the abbreviated equation from the Modification of Diet in Renal Disease (MDRD) study: $186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742$ (if female) [9].

TG/HDL-C was calculated as TG (mg/dl) divided by HDL-C (mg/dl). We classified TG/HDL-C into 5 quintile groups. These groups were categorized as follows: Q₁ <1.38, Q₂ 1.38–2.01, Q₃ 2.02–2.88, Q₄ 2.89–4.49, Q₅ ≥4.50.

Statistical Analyses

With the exception of TG and TG/HDL-C, the characteristics of the study sample were summarized using either the independent two-sample t test or the one-way ANOVA test for continuous variables and the χ^2 test for categorical variables. To compare the median values of TG and TG/HDL-C, we used the Mann-Whitney U test and the Kruskal-Wallis test. We conducted linear regression analysis to verify trend analysis. We investigated the relationship between eGFR and other continuous variables using Pearson's correlation analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for CKD were calculated using multivariate logistic regression analysis after adjustment for other covariates across quintiles of TG/HDL-C. To identify the clinical utility of TG/HDL-C in CKD, we calculated the area under the

Table 1. Basic characteristics of the study subjects

	Men (n = 2,345)	Women (n = 3,158)	p value
Age, years	46.9 ± 14.9	46.8 ± 15.9	0.848
BMI	24.0 ± 3.1	23.5 ± 3.4	<0.001
WC, cm	84.2 ± 8.8	78.4 ± 9.6	<0.001
SBP, mm Hg	122.8 ± 16.0	116.5 ± 18.6	<0.001
DBP, mm Hg	80.7 ± 10.5	74.7 ± 10.4	<0.001
FPG, mg/dl	98.0 ± 26.0	93.1 ± 19.9	<0.001
TG, mg/dl	125.0 (87.0, 187.0)	93.0 (68.0, 134.0)	<0.001 ^a
HDL-C, mg/dl	42.4 ± 10.2	47.1 ± 10.9	<0.001
TG/HDL-C	3.04 (1.96, 4.90)	2.02 (1.36, 3.19)	<0.001 ^a
Creatinine, mg/dl	1.07 ± 0.19	0.92 ± 0.16	<0.001
Smoking status, %			<0.001 ^b
Never smoker	20.2	91.5	
Former smoker	34.2	4.1	
Current smoker	45.6	4.4	
Drinking status, %			<0.001 ^b
Non-drinker	31.9	67.3	
Current drinker	68.1	32.7	
Regular exercise, %			<0.001 ^b
None	47.4	56.9	
1–2 times/week	15.7	9.8	
≥3 times/week	36.9	33.3	
Energy intake, kcal	2,311.0 ± 925.6	1,767.7 ± 679.3	<0.001
eGFR, ml/min/1.73 m ²	80.8 ± 11.1	72.5 ± 12.1	<0.001
CKD, %	3.9	12.9	<0.001 ^b

WC = Waist circumference; FPG = fasting plasma glucose. All data except smoking status, drinking status, regular exercise, TG, and TG/HDL-C are represented as mean ± standard deviation. TG and TG/HDL-C are represented as median (lower, higher quartile). Smoking status was categorized as current smoker (a person who smokes cigarettes daily), former smoker (a person

who smoked in the past but does not smoke cigarettes currently), and never smoker (a person who has never smoked a cigarette). CKD was defined as an eGFR <60 ml/min/1.73 m². ^a p value as determined by Mann-Whitney U test. ^b p value as determined by χ^2 test.

receiver-operating characteristic (ROC) curve which we had constructed for this analysis. All analyses were conducted using SPSS for Windows (version 12.0; SPSS Inc., Chicago, Ill., USA). All statistical tests were two-sided, and statistical significance was determined at p value <0.05.

Results

Table 1 shows the characteristics of the 5,503 adult subjects (2,345 men and 3,158 women). The mean age of men and women was 46.9 and 46.8 years, respectively. The mean or median values of BMI, waist circumference, SBP, DBP, fasting plasma glucose, TG, TG/HDL-C, creatinine, daily energy intake, and eGFR were significantly higher in men than in women, while serum HDL-C levels were higher in women than in men. The percentage of subjects who were current smokers, current alcohol

drinkers, or engaged in regular exercise was higher in men, while the percentage of subjects with CKD was higher in women (3.9% in men vs. 12.9% in women).

Table 2 shows Pearson's correlations among eGFR, age, SBP, fasting plasma glucose, daily energy intake, waist circumference, BMI, and logarithm-transformed TG/HDL-C (logTG/HDL-C). Age, SBP, fasting plasma glucose, waist circumference, BMI, and logTG/HDL-C were negatively correlated with eGFR, while daily energy intake was positively associated with eGFR. All values were statistically significant (p < 0.05), except for the correlation between daily energy intake and fasting plasma glucose.

Table 3 shows subjects' characteristics according to TG/HDL-C quintile. The mean or median values of age, BMI, waist circumference, SBP, DBP, fasting plasma glucose, TG, TG/HDL-C, and creatinine increased as TG/HDL-C quintile increased. Conversely, HDL-C and eGFR

Table 2. Pearson's correlation among eGFR and other continuous variables

	eGFR	Age	SBP	FPG	Energy intake	WC	BMI	logTG/HDL-C
eGFR	1							
Age	-0.502**	1						
SBP	-0.205**	0.504**	1					
FPG	-0.119**	0.253**	0.218**	1				
Energy intake	0.206**	-0.189**	-0.032*	-0.019	1			
WC	-0.089**	0.299**	0.383**	0.234**	0.098*	1		
BMI	-0.099**	0.135**	0.273**	0.152**	0.050**	0.822**	1	
logTG/HDL-C	-0.077**	0.211**	0.279**	0.267**	0.060**	0.460**	0.352**	1

FPG = Fasting plasma glucose; WC = waist circumference. * $p < 0.05$; ** $p < 0.01$.

Table 3. Subjects' characteristics according to TG/HDL-C quintile

	TG/HDL-C-Q ₁ <1.38	TG/HDL-C-Q ₂ 1.38–2.01	TG/HDL-C-Q ₃ 2.02–2.88	TG/HDL-C-Q ₄ 2.89–4.49	TG/HDL-C-Q ₅ ≥4.50	p value
Men	1,095 (25.3%)	1,099 (30.7%)	1,112 (43.4%)	1,095 (51.8%)	1,102 (61.8%)	<0.001 ^a
Age, years	41.3 ± 15.3	44.3 ± 15.2	47.6 ± 15.7	50.2 ± 15.2	50.8 ± 13.8	<0.001
BMI	21.9 ± 2.9	23.0 ± 3.1	23.8 ± 3.1	24.5 ± 3.1	25.3 ± 3.1	<0.001
WC, cm	74.3 ± 8.3	77.7 ± 8.8	81.1 ± 8.9	84.3 ± 8.6	87.0 ± 8.2	<0.001
SBP, mm Hg	112.1 ± 16.0	114.8 ± 16.7	119.7 ± 17.5	123.4 ± 17.7	125.6 ± 17.6	<0.001
DBP, mm Hg	73.2 ± 9.8	74.6 ± 10.1	77.3 ± 10.3	79.4 ± 10.5	81.8 ± 11.1	<0.001
FPG, mg/dl	88.1 ± 11.0	91.1 ± 17.4	94.8 ± 19.7	97.5 ± 22.7	104.4 ± 33.5	<0.001
TG, mg/dl	57.0 (48.0, 66.0)	81.0 (71.0, 91.0)	104.0 (93.0, 117.0)	141.0 (124.0, 161.3)	232.0 (191.0, 306.0)	<0.001 ^b
HDL-C, mg/dl	56.3 ± 10.8	48.9 ± 8.6	43.8 ± 7.5	40.8 ± 7.2	35.8 ± 6.5	<0.001
TG/HDL-C	1.06 (0.90, 1.23)	1.68 (1.53, 1.84)	2.43 (2.21, 2.64)	3.50 (3.16, 3.97)	6.40 (5.18, 8.53)	<0.001 ^b
Creatinine, mg/dl	0.94 ± 0.12	0.95 ± 0.13	0.98 ± 0.14	1.01 ± 0.25	1.04 ± 0.24	<0.001
Smoking status, %						<0.001 ^a
Never smoker	76.7	71.2	60.7	53.1	43.6	
Former smoker	11.9	13.4	17.9	19.7	21.9	
Current smoker	11.4	15.4	21.4	27.1	34.5	
Drinking status, %						0.012 ^a
Non-drinker	52.8	53.9	53.6	53.4	47.5	
Current drinker	47.2	46.1	46.4	46.6	52.5	
Regular exercise, %						0.076 ^a
None	50.8	53.0	50.4	52.8	57.3	
1–2 times/week	12.5	12.6	12.3	12.2	11.7	
≥3 times/week	36.7	34.4	37.3	35.0	31.0	
Energy intake, kcal	1,931.9 ± 760.1	1,990.2 ± 848.4	1,962.3 ± 830.2	2,005.3 ± 822.0	2,091.3 ± 907.8	0.001
eGFR, ml/min/1.73 m ²	77.5 ± 11.9	77.0 ± 12.0	76.3 ± 12.3	75.1 ± 12.7	74.5 ± 12.7	<0.001
CKD, %	4.4	6.6	9.5	11.9	12.8	<0.001 ^a

FPG = Fasting plasma glucose; WC = waist circumference. All data except smoking status, drinking status, regular exercise, TG, and TG/HDL-C are represented as mean ± standard deviation. TG and TG/HDL-C are represented as median (lower, higher quartile). Smoking status was categorized as current smoker (a person who smokes cigarettes daily), former

smoker (a person who smoked in the past but does not smoke cigarettes currently), and never smoker (a person who has never smoked a cigarette). CKD was defined as eGFR <60 ml/min/1.73 m².

^a p value as determined by χ^2 test. ^b p value as determined by Kruskal-Wallis test.

Fig. 1. Prevalence of CKD according to TG/HDL-C quintile. p value <0.001, χ^2 test. p value for trend = 0.002.

Fig. 2. ROC curve for TG/HDL-C in CKD. Area under the ROC curve = 0.608. Sensitivity = 75.3%, specificity = 42.6%.

Table 4. OR for CKD according to TG/HDL-C quintile

	TG/HDL-C-Q ₁ <1.38	TG/HDL-C-Q ₂ 1.38–2.01	TG/HDL-C-Q ₃ 2.02–2.88	TG/HDL-C-Q ₄ 2.89–4.49	TG/HDL-C-Q ₅ ≥4.50	p value for trend
Model 1	1	1.53 1.05–2.23	2.30 1.62–3.27	2.94 2.09–4.14	3.20 2.28–4.49	0.001
Model 2	1	1.23 0.80–1.90	1.45 0.96–2.18	1.81 1.21–2.69	2.42 1.63–3.60	0.005
Model 3	1	1.13 0.71–1.79	1.30 0.84–2.03	1.39 0.89–2.16	2.15 1.38–3.37	0.036

Model 1: not adjusted; model 2: adjusted for age and gender; model 3: adjusted for SBP, fasting plasma glucose, energy intake, smoking status (never smoker, former smoker, current smoker), alcohol drinking status (non-drinker, current drinker), exercise status (no exercise, 1–2 times/week, ≥3 times/week), and waist circumference, in addition to the covariates included in model 2.

decreased as TG/HDL-C quintile increased. The percentage of subjects who currently smoke, currently drink, or have CKD increased with TG/HDL-C quintiles, while the percentage of subjects engaging in regular exercise did not differ among quintile groups.

Figure 1 shows the prevalence of CKD according to TG/HDL-C quintile. The overall prevalence of CKD was 9.0%. The percentage of subjects with CKD increased with increasing quintile group (p value for trend = 0.002).

The ROC curve analysis was examined to determine the degree of the association between TG/HDL-C and CKD (fig. 2). The area under the ROC curve for TG/HDL-C of CKD is 0.608 (sensitivity 75.3% and specificity 42.6%).

Table 4 shows the results of the logistic regression analysis designed to investigate the relationship between TG/HDL-C quintile and CKD. In comparison with participants who were categorized in the TG/HDL-C-Q₁ (<1.38), the OR for CKD of participants who were categorized in the TG/HDL-C-Q₅ (≥4.50) was 3.20 (95% CI, 2.28–4.49) when not adjusted. Model 2 shows that the OR (95% CI) for CKD was 2.42 (1.63–3.60), after adjustment for age and gender. We then conducted multivariate logistic regression analysis after adjusting for SBP, fasting plasma glucose, daily energy intake, smoking status, alcohol drinking status, exercise status, and waist circumference in model 3, in addition to the covariates included

in model 2. The OR (95% CI) for CKD in TG/HDL-C-Q₅ was 2.15 (1.38–3.37) in model 3. Trend analyses were statistically significant in all models (*p* values for trend = 0.001 in model 1, 0.005 in model 2, and 0.036 in model 3).

Discussion

The major finding in this study was that TG/HDL-C was significantly associated with CKD in a nationally representative sample of Korean adults.

As is the case in Westernized countries, there has been a recent dramatic increase in the prevalence of CKD and ESRD requiring renal replacement therapy [10, 11]. Increasing numbers of people with advanced age, hypertension, diabetes, or metabolic syndrome contribute to the high prevalence of renal dysfunction [11, 12].

Previous studies have shown that dyslipidemia is associated with both the development of CKD and its mortality. Dyslipidemia is a consequence of renal impairment, and also a mediator of CKD exacerbation. TG/HDL-C has been identified as an indicator of insulin resistance and atherosclerosis, as well as their comorbidities. Increased TG/HDL-C can be associated with glomerulosclerosis, which is related to the development of CKD. Participants in the fifth quintile of TG/HDL-C were associated with increased risk of CKD, even after adjustment for multiple covariates (age, gender, SBP, fasting plasma glucose, daily energy intake, smoking status, alcohol drinking status, exercise status, and waist circumference). The adjusted covariates in table 4 are considered common risk factors for CKD and CVD.

Although the mechanism of CKD development is not clearly understood, CKD shares many risk factors with CVD. In addition to the traditional risk factors for CKD, chronic inflammation, oxidative stress, and obesity are also indicators for the development of renal dysfunction [13, 14]. On a cellular level, it has been shown that 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 [15]. Molecular similarities between glomerular mesangial cells and vascular smooth muscle cells point to a common underlying pathophysiology in the development of atherosclerosis and glomerulosclerosis [16, 17].

As Muntner et al. [18] demonstrated that high TG and low HDL-C were associated with an increased risk of renal dysfunction, we now know that dyslipidemia may exacerbate preexisting renal impairment and that lipid-lowering medications such as statin can reduce renal dys-

function and proteinuria [19]. In addition, developed CKD accelerates lipid permeability and excretion in glomerulus, resulting in further exacerbation of dyslipidemia. Having activated a vicious cycle between chronic renal dysfunction and dyslipidemia, many individuals with CKD suffer from and die of CVD [20]. Statin treatment potentially slows progressive renal dysfunction and disconnects this cycle through pleiotrophic renoprotective effects, such as improving endothelial function as well as anti-inflammatory, antithrombotic, antioxidant, and immunomodulatory properties [21].

Insulin resistance mediates diabetes, obesity, hypertension, lipid abnormalities, and atherosclerosis, all of which are risk factors of CVD and CKD [22, 23]. Insulin resistance is also a significant risk factor for the progression of renal dysfunction in nondiabetic subjects [24]. TG/HDL-C is a useful marker of insulin resistance and a predictor of cardiovascular mortality [25, 26]. Elevated TG/HDL-C is associated with increased levels of small, dense LDL-C particles, which are highly atherogenic [27, 28]. These findings suggest that increased TG/HDL-C may be associated with glomerulosclerosis and CKD.

This study is the first to explore the association between CKD and TG/HDL-C. Laboratory examination of these parameters is commonly available and inexpensive. Although Schaeffner et al. [6] showed that elevated total cholesterol, non-HDL-C, total cholesterol/HDL-C ratio, and reduced HDL-C were associated with the development of renal dysfunction in men, they did not show whether increased TG/HDL-C, a reliable marker of insulin resistance, was correlated with CKD. Furthermore, our study of 2005 KNHANES participants is nationally representative of Korean adults.

There are some study limitations which should be considered when the findings of present work are interpreted. First, it is difficult to determine a causal relationship between lipid ratio and an increased risk of CKD using a cross-sectional study design. Although increased TG/HDL-C induced by renal dysfunction can aggravate the progression of CKD through lipid nephrotoxicity [5], CKD can itself affect the metabolism of lipoprotein and change TG/HDL-C. Second, we defined CKD as an eGFR <60 ml/min/1.73 m² using the MDRD formula. The eGFR may not accurately estimate actual GFR. Furthermore, because the MDRD formula was developed using study samples of primarily European descents, the formula may not apply as precisely to Koreans. Finally, we did not include individuals with proteinuria, which may constitute a phenotype of CKD. However, because urine samples, collected by KNHANES, were not the first void-

ed urine in the morning, it is difficult to obtain a quantitative measurement and to control for selection bias.

In conclusion, the results of this study suggest that TG/HDL-C is significantly associated with CKD in a nationally representative sample of Korean adults after controlling for major and minor risk factors. Because increases in TG/HDL-C begin during the early stages of renal dysfunction, it is a useful parameter to identify subjects susceptible to CKD and prevent its development before the appearance of renal impairment.

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Disclosure Statement

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