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ORIGINAL RESEARCH

Relationship between dyslipidemia and albuminuria in hypertensive adults

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Abstract
This study aimed to estimate the relationship between various lipid abnormalities and albuminuria in hypertensive Korean adults. Data obtained from the Health and Nutrition Examination Survey in 2021 to 2022 were analyzed. The study included 2330 hypertensive participants. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured. Dyslipidemia parameters were defined as high TG ≥200 mg/dL, low HDL-C as HDL-C <40 mg/dL, high TC/HDL-C as TC/HDL-C ratio ≥4, high TG/HDL-C as TG/HDL-C ratio ≥3.8, and high LDL-C/HDL-C as LDL-C/HDL-C ratio ≥2.5. Albuminuria was defined as a urine albumin to creatinine ratio (ACR) ≥30 mg/g. Women with albuminuria showed significantly higher levels of TG, TC/HDL-C, and TG/HDL-C and a lower level of HDL-C than women without albuminuria (all $P<0.05$). LogTG, TC/HDL-C, and logTG/HDL-C were positively correlated with ACR in both men and women; however, HDL-C was negatively correlated with ACR in women and non-HDL-C was positively correlated with ACR in men. In men, there was no association between ACR and lipid parameters. However, in women, higher values for logTG, TC/HDL-C, and logTG/HDL-C were associated with an increased odds ratio (OR) for albuminuria (OR [95% confidence interval]: 1.53 [1.06–2.21], 1.21 [1.02–1.45], and 1.78 [1.21–2.63], respectively) and HDL-C with a decreased OR for albuminuria (0.78 [0.67–0.92]) after adjusting for all covariates. LogTG, TC/HDL-C, and logTG/HDL-C were associated with an increased prevalence of albuminuria in hypertensive women. Screening and treatment for dyslipidemia may be necessary for hypertensive women to address potential albuminuria.

Introduction
For decades, many countries have attempted to reduce cardiovascular risk factors such as hypertension (HTN), diabetes mellitus (DM), and dyslipidemia.[1–3] HTN is a major preventable risk factor for cardiovascular disease (CVD) and one of the leading causes of mortality and morbidity. Albuminuria is also a risk factor for CVD, and excess urinary albumin is related to increased all-cause mortality.[4,5] In patients with HTN, urinary albumin leakage has been used as a marker of cardiovascular complications and a reliable predictor of ischemic heart disease.[6,7]Many studies have shown a positive relationship between HTN and

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albuminuria.[8–13] High blood pressure seems to affect urinary albumin excretion via general vascular damage, such as endothelial dysfunction and atherosclerosis,[14] and directly via elevated glomerular pressure in the kidney.[15,16] Subsequently, HTN leads to an increase in the occurrence of CVD and accelerates the deterioration of renal function.[17,18] Dyslipidemia, which is associated with the atherosclerotic process, is also a major preventable risk factor for CVD.[19,20] It has generally been defined as elevated levels of total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), or low levels of high-density lipoprotein cholesterol (HDL-C).[21] Recently, fasting TG was found to independently predict both coronary artery calcification and incidental albuminuria in type 1 diabetes,[22] and nonhigh density lipoprotein cholesterol (non-HDL-C) levels and lipid-related ratios were found to be more predictive of CVD than an individual lipid profile.[23,24] Furthermore, abnormal lipid parameters are associated with albuminuria or reduced kidney function.[25] There was a Korean study on the relationship between TG/HDL-C and albuminuria in hypertensive subjects; however, they only included subjects who were >40 years and resided in rural areas.[26]We hypothesized that the comorbidity of dyslipidemia and HTN could exacerbate albuminuria. Therefore, we investigated the relationship between various dyslipidemia parameters and albuminuria in adults of Udaipur with HTN.

Methods

Survey overview and study participants

This study used the data obtained from the Health and Nutrition Examination Survey (HANES) of 2021 to 2012, which was conducted by American International Institute of Medical Sciences, Bedwas, Udaipur, Rajasthan. The survey was designed to evaluate health and nutrition status, and it comprised a health interview, nutritional assessment, and health examination. A stratified, multistage, cluster-sampling design with proportional allocation based on geographic area, sex, and age from the National Census Registry was used for the selection of survey participants to represent the entire noninstitutionalized civilian population in Udaipur. A total of 16,576 participants were included in the HANES of 2021 to 2022. Of these, 14,246 individuals were excluded for the following reasons: <19 years of age (3717), missing data (2423), cancer (53), estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (133), DM (808), or lacking HTN (7112). Finally, 2330 patients who had HTN or take antihypertensive medications were included in this study. All participants provided written informed consent, and the Institutional Review Board of the Division of Chronic Disease Surveillance under the Centers for Disease Control and Prevention approved the study protocol.

Lifestyle Variables

The sociodemographic and lifestyle factors were considered confounding variables, including age, smoking, alcohol drinking, physical activity, and menopause status. Self-report questionnaires were adapted to survey smoking, alcohol consumption, and physical activity. Heavy drinkers were defined as those who drank >30 g/day of alcohol according to the amount of alcohol consumption per day up to 1 month before the interview. Current smokers were defined as those who currently smoked and had smoked >100 cigarettes. We assessed physical activity by means of the modified short form of International Physical Activity Questionnaire for the population.[27] Regular physical exercise was defined as moderate exercise for >30 minutes per session more than 5 times/week or vigorous exercise for >20 minutes per session more than 3 times/week.

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Anthropometric and Biochemical Measurements

We measured body weight, height, and waist circumference (WC) to the nearest 0.1 kg, 0.1 cm, and 0.1 cm, respectively. Body mass index was estimated as follows: body weight/height^2 (kg/m^2). WC was measured on the mid-axillary line between the upper margin of the iliac crest and the lower border of the rib cage during expiration. We used a standard mercury sphygmomanometer (Baumanometer, WA Baum Co., NY) to measure blood pressure (BP) and checked BP 3 times in 5-minute intervals in a sitting position. The mean of the 2nd and 3rd BP was used in final analyses. HTN was defined by systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or use of anti-HTN drugs. Blood samples were acquired after fasting for at least 8 hours. A Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan) was used to measure serum levels of creatinine, TC, HDL-C, LDL-C, and TG. A 1470 Wizard gamma-counter (Perkin-Elmer, Turku, Finland) with an immunoradiometric assay using an INS-IRMA kit (Biosource Europe SA, Nivelles, Belgium) was adapted to assess fasting serum insulin levels.

Nutritional Assessment

Daily food intake was evaluated using the 24-hour recall method and a food frequency questionnaire. Daily intake of total energy and fat were estimated using a food database developed for the HANES and the food composition table published by the National Rural Living Science Institute.

Definition of Albuminuria and eGFR

The urine albumin to creatinine ratio (ACR) was used as the index of urinary albumin excretion. A urine sample was collected during the first morning voiding. Conventionally, subjects with ACR<30 mg/g were defined as having normal albuminuria. Microalbuminuria was defined as 30≤ACR<300 mg/g and macroalbuminuria as ACR≥300 mg/g.[28,29] According to this definition of albuminuria, hypertensive subjects with urinary ACR less than 30 mg/g were considered the normal group and subjects with a urinary ACR of 30 mg/g or more as the albuminuria group. We calculated eGFR by Modification of Diet in Renal Disease (MDRD) equation.[30]

Definition of Dyslipidemia Parameters

We defined the dyslipidemia parameters according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III:[31] high TC, TC level ≥240 mg/dL, or the use of lipid-lowering drugs; high TG, TG levels ≥200 mg/dL; and low HDL-C, HDL-C level <40 mg/dL. Additionally, we defined high non-HDL-C (non-HDL-C≥160 mg/dL), high TC to HDL-C ratio (TC/HDL-C≥4), high TG to HDL-C ratio (TG/HDL-C≥3.8), and high LDL-C to HDL-C ratio (LDL-C/HDL-C≥2.5) as abnormal dyslipidemia parameters.[32,33]

Statistical Analysis

Statistical analysis was performed using the SAS survey procedure using sampling weights to provide nationally representative estimates. *P* values <0.05 were considered statistically significant. The SAS software package version 9.2 for Windows (SAS institute, Cary, NC) was used. To assess the differences in the baseline clinical and biochemical characteristics between the normal and the albuminuria groups, Student *t* tests were used to compare continuous variables and Chi-squared tests were used to compare categorical variables. Since the variables such as TG and TG/HDL-C were right-skewed, we used the natural log transformation on TG/HDL-C after evaluating for normality by Q–Q plot. Pearson correlation analysis was performed to assess the correlation between urinary ACR and various dyslipidemia parameters. Age- and multivariable-adjusted logistic regression analyses were

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conducted to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) for albuminuria according to increases in dyslipidemia parameters. Age, body mass index, alcohol consumption, smoking status, physical activity, total energy intake, fat intake, use of lipid or BP-lowering drugs, and menopause status (in analyses of women) were considered confounding factors[34–36] in the multivariate analyses.

Results

Baseline characteristics of the subjects

Men with albuminuria were older and had an increased proportion of subjects with a lower income (Q1) than men without albuminuria. In men, all lipid parameters did not differ between the 2 groups. WC, systolic blood pressure, TG, TC/HDL-C, and TG/HDL-C were significantly higher in women with albuminuria than women without albuminuria. However, HDL-C and current smoking were lower in women with albuminuria compared to women without albuminuria (Table (Table11).

Table 1

General Characteristics of Subjects With and Without Albuminuria

	Men			Women		
	ACR < 30 mg/g	ACR ≥ 30 mg/g	*P* Value*	ACR < 30 mg/g	ACR ≥ 30 mg/g	*P* Value*
N	1,024	97		1,042	167	
Age, year	49.8 ± 0.6	54.7 ± 1.9	0.016	60.2 ± 0.5	62.4 ± 1.3	0.118
BMI, kg/m^2	25.2 ± 0.2	25.9 ± 0.7	0.274	24.8 ± 0.1	25.2 ± 0.3	0.184
WC, cm	87.2 ± 0.5	89.8 ± 1.8	0.167	83.0 ± 0.4	84.9 ± 0.8	0.040
SBP, mm Hg	133.6 ± 0.5	136 ± 2.1	0.271	135.2 ± 0.7	139.8 ± 1.7	0.010
DBP, mm Hg	88.9 ± 0.4	88.6 ± 1.7	0.864	81.7 ± 0.5	83.3 ± 1	0.126
TC, mg/dL	191.3 ± 1.4	196.4 ± 4	0.261	201 ± 1.4	202.2 ± 3.6	0.771
HDL-C, mg/dL	49 ± 0.5	51.8 ± 2.1	0.208	53.3 ± 0.5	49.8 ± 0.9	0.001
LDL-C, mg/dL	110 ± 1.4	107.1 ± 3.7	0.467	120.7 ± 1.3	121.7 ± 3.2	0.786
TG, mg/dL†	146.6 (140.1–153.5)	163.3 (146.6–182.0)	0.057	118.1 (113.5–122.9)	133.5 (119.7–149.0)	0.037
Non-HDL, mg/dL	142.3 ± 1.5	144.6 ± 4.1	0.616	147.7 ± 1.4	152.4 ± 3.4	0.188
TC/HDL-C	4.1 ± 0.1	4.1 ± 0.2	0.850	3.9 ± 0	4.2 ± 0.1	0.010
TG/HDL-C†	4.3 (4.1–4.5)	4.5 (4.0–5.0)	0.461	3.4 (3.3–3.5)	3.9 (3.6–4.3)	0.008
LDL-C/HDL-C	2.4 ± 0	2.2 ± 0.1	0.380	2.4 ± 0	2.5 ± 0.1	0.109
eGFR, mL/min/1.73 m^2	90.4 ± 0.6	89.8 ± 2.1	0.754	90.2 ± 0.6	88.7 ± 1.7	0.439
Heavy alcohol intake (yes, %)	45.4 (2.1)	45 (6.4)	0.951	3.7 (0.8)	2.0 (0.9)	0.233
Current smoking (yes, %)	39.7 (2.1)	41.5 (6.3)	0.796	5.5 (1.0)	1.6 (0.8)	0.007
Regular exercise (yes, %)	19.9 (1.5)	21.1 (5.2)	0.820	14.7 (1.5)	15.5 (3.8)	0.846
Menopause (yes, %)				74.8 (2.2)	81.5 (4.4)	0.204
Dyslipidemia medication (yes, %)	7.2 (0.9)	10.1 (3.7)	0.382	13.1 (1.3)	11.9 (2.7)	0.684
HTN medication (yes, %)	37.6 (1.9)	48.2 (6.3)	0.108	64.0 (2.0)	67.5 (4.4)	0.467

Data are presented as the mean ± SE or percentage (SE). ACR = albumin to creatinine ratio, BMI = body mass index, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = nonhigh density lipoprotein cholesterol, SBP = systolic blood pressure, SE = standard error, TC = total cholesterol, TG = triglycerides, WC = waist circumference.

*P values were obtained using a Chi-squared test or Student t test.

†Log transformation and data are presented as geometric mean ± SE.

Correlation Between ACR and Dyslipidemia Parameters

In men, ACR had a significant positive correlation with logTG, non-HDL-C, TC/HDL-C, and logTG/HDL-C. In women, ACR also had a positive correlation with logTG, TC/HDL-C, and logTG/HDL-C. However, HDL-C was negatively correlated with ACR in women (Table (Table22).

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Table 2
The Correlation Between ACR and Dyslipidemia Parameters in Men and Women

	Men		Women	
	γ	*P* Value*	γ	*P* Value*
TC, mg/dL	0.07	0.063	0.02	0.706
HDL-C, mg/dL	−0.03	0.564	−0.10	0.009
LDL-C, mg/dL	−0.01	0.762	0.01	0.866
LogTG, mg/dL†	0.15	<0.001	0.10	0.009
Non-HDL-C, mg/dL	0.08	0.038	0.05	0.177
TC/HDL-C	0.09	0.030	0.08	0.035
LogTG/HDL-C†	0.13	<0.001	0.12	0.004
LDL-C/HDL-C	0.03	0.447	0.06	0.151

ACR = albumin to creatinine ratio, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, non-HDL-C = nonhigh density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides.

*P values were obtained by Pearson correlation analysis.

†Log transformation.

Prevalence of Dyslipidemia Parameters and Urinary Albumin Excretion

Figure Figure11 shows the proportion of subjects who satisfied the diagnostic criteria for each dyslipidemia parameter in men and women, categorized by ACR. In men, the prevalence of all dyslipidemia parameters did not differ significantly between the 2 groups (Figure (Figure1A).1A). However, in women, the prevalence of low HDL-C, high TG, high TC/HDL-C, high TG/HDL-C, and high LDL-C/HDL-C were significantly elevated in women with albuminuria compared to women without albuminuria (Figure (Figure11B).

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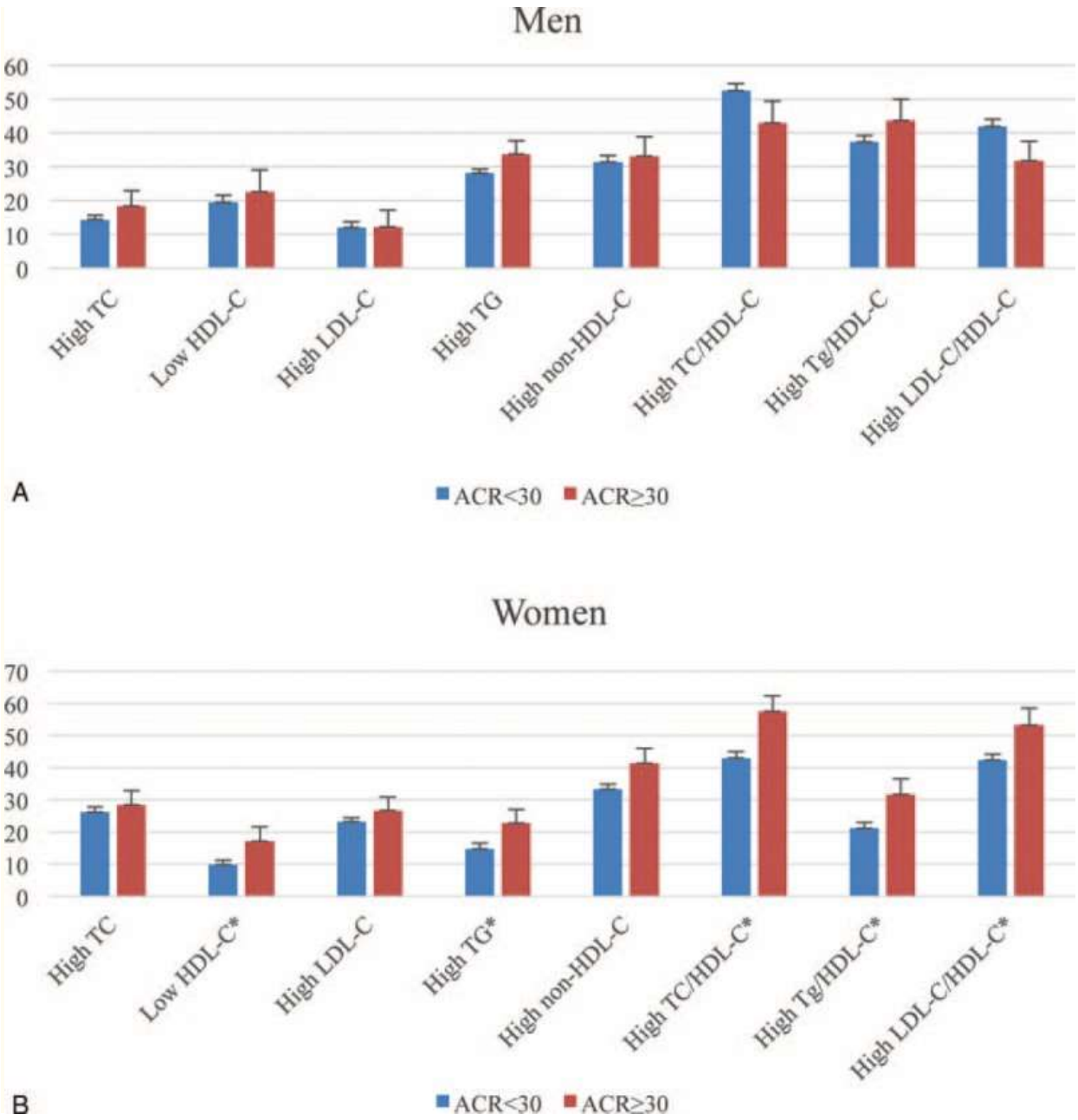

Figure 1

The prevalence of dyslipidemia parameters in hypertensive adults with ACR<30mg/g or ACR≥30mg/g. *P value<0.05. ACR=albumin to creatinine ratio, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, non-HDL-C=nonhigh density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides.

Multivariable-Adjusted ORs and 95% CIs for Albuminuria According to the Increase in the Dyslipidemia Parameters

In men, ACR was not associated with any lipid parameters after adjusting for all covariates. In women, increases in logTG, TC/HDL-C, and logTG/HDL-C were associated with elevated ORs for albuminuria after adjusting for all covariates (OR [95% CI]: 1.53 [1.06–2.21], 1.21 [1.02–1.45], and 1.78 [1.21–2.63], respectively). However, HDL-C was associated with a decreased OR for albuminuria in women after adjusting for all covariates (0.78 [0.67–0.92]) (Table33).

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Table 3
Multivariable-Adjusted ORs and 95% CIs for Albuminuria According to the Increase in Dyslipidemia Parameters in Men and Women

	Men		Women	
	Model 1	Model 2	Model 1	Model 2
TC*	1.05 (0.98–1.13)	1.05 (0.98–1.12)	1.01 (0.96–1.06)	1.03 (0.95–1.06)
HDL-C*	1.18 (0.93–1.50)	1.20 (0.91–1.58)	0.79 (0.67–0.92)	0.78 (0.67–0.92)
LDL-C*	0.98 (0.90–1.06)	0.97 (0.90–1.04)	1.01 (0.94–1.07)	1.00 (0.93–1.08)
LogTG	1.52 (1.11–2.08)	1.48 (0.99–2.21)	1.54 (1.04–2.28)	1.53 (1.06–2.21)
Non-HDL-C*	1.03 (0.96–1.11)	1.02 (0.96–1.10)	1.03 (0.98–1.09)	1.03 (0.97–1.10)
TC/HDL-C	1.01 (0.77–1.33)	0.98 (0.74–1.30)	1.22 (1.04–1.43)	1.21 (1.02–1.45)
LogTG/HDL-C	1.29 (0.87–1.90)	1.22 (0.77–1.94)	1.80 (1.20–2.71)	1.78 (1.21–2.63)
LDL-C/HDL-C	0.88 (0.62–1.25)	0.86 (0.62–1.21)	1.19 (0.94–1.49)	1.19 (0.92–1.54)

Model 1 adjusted for age. Model 2 adjusted for age, BMI, alcohol consumption, smoking status, physical activity, total energy intake, fat intake, use of lipid or BP lowering drugs, menopause, and eGFR. ACR = albumin to creatinine ratio, BMI = body mass index, BP = blood pressure, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglycerides.
*Every increment of 10 mg/dL for the dyslipidemia parameters.

Discussion

In this study, logTG, TC/HDL-C, and logTG/HDL-C were weak, but positively correlated with ACR in men and women. However, non-HDL-C was also weak, but positively correlated with ACR in men and HDL-C was negatively correlated with ACR in women. The prevalence of high TG, high TG/HDL-C, high TC/HDL-C, and high LDL-C/HDL-C were significantly elevated in women with albuminuria compared to women without albuminuria. LogTG, TC/HDL-C, and logTG/HDL-C were associated with elevated ORs for albuminuria, and HDL-C was associated with a decreased OR for albuminuria only in women.

Although abnormal lipid values predicted the progression of kidney function in some cohort studies,[37–39] the relationship between dyslipidemia and albuminuria is controversial. Some studies found that high TG was associated with ACR in patients with DM.[40–42] In the Framingham Offspring cohort study, HDL-C was negatively associated with ACR.[43] In a community-based Korean population study, microalbuminuria was also associated with high TG and low HDL-C, but not with TC and LDL-C.[44] However, in the Third National Health and Nutrition Examination Survey (NHANES III), microalbuminuria was associated with increased TC and LDL-C, but not HDL-C.[45] Aside from these conventional lipid parameters, recent studies have found that high TG/HDL-C, or the atherogenic index, is associated with the presence of small dense LDL-C,[46] which is associated with an increased risk for cardiovascular events in many studies.[47–49] Small dense LDL-C can penetrate the arterial wall more easily and is susceptible to oxidization compared to large LDL-C.[50,51] Some Asian studies have found a relationship between the TG/HDL-C and nephropathy in prediabetic patients or those with DM.[52,53] High TG and low HDL-C were also associated with ACR, and small dense LDL-C was associated with increased ACR in the general population.[54]

TG/HDL-C reflects not only atherogenic dyslipidemia, but also insulin resistance,[55] which is also associated with abdominal obesity.[56] Since albuminuria itself is also associated with abdominal obesity,[57] insulin resistance may explain the association between TG/HDL-C and albuminuria.

Previous studies have already found the association between dyslipidemia, especially TG/HDL-C, and albuminuria in Asian subjects.[26,58] In both studies, the subjects were limited to ages more than 40 and living in rural area, whereas our representative sample of Korean population were aged more than 18 and had HTN. Unlike aforementioned studies, Japanese population study showed that TG/HDL-C was associated with albuminuria not only in the

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subjects with HTN but also without HTN.[59] These results indicate that dyslipidemic features such as high TG/HDL-C level may deteriorate kidney function by means of eGFR and albuminuria.

Moreover, the association between the TG/HDL-C ratio and the risk of mortality was abolished after additional adjustment for renal function measures (eGFR and albuminuria) in an Italian cohort study.[60] This indicates that the prediction of cardiovascular and all-cause mortality by TG/HDL-C might be largely influenced by the status of kidney dysfunction in type 2 DM.

Abnormal lipid profiles, such as high TC and high TG, could cause tubulointerstitial damage via the infiltration and deposition of fat in the renal tubules[25] and may also develop in association with inflammation in the vessel walls.[61–63] Additionally, abnormal lipid metabolism could cause increased urine albumin excretion and renal dysfunction via the acceleration of renovascular atherosclerosis. In hypertensive patients, the direct transmission of pulsatile stress to the glomeruli contributes to glomerular damage and arterial atherosclerotic changes.[15,64,65] Therefore, hypertensive patients with dyslipidemia may have a higher ACR than those without dyslipidemia.

Similar to the current study, some studies have shown gender differences in the relationship between albuminuria and dyslipidemia.[53,54] Although the reason for this is not clear, some studies suggest that the gender differences are due to the favorable lipoprotein profile more commonly seen in women, including less small dense LDL-C and higher HDL-C, compared with men.[66,67] As other factors such as testosterone levels and visceral fat are less dominant in women compared to men, abnormalities in the lipid profile due to hormonal or metabolic changes could have a greater influence on the development of albuminuria in women than in men.[54]

There are some limitations in this study. First, this is a cross-sectional study, so it does not show causal relationships. Second, only the morning urine sample was measured to evaluate albuminuria. Indeed, a 24-hour urine collection is the most exact urine sampling method for evaluating albuminuria. However, a single morning urine sample is known to correlate with the 24-hour urine albumin excretion ratio.[68] Since the morning urine sample after fasting is more concentrated than other urine samples collected at other times, it could mislead the diagnosis of microalbuminuria. Third, the specific types of antihypertensive medication that may influence albuminuria or renal function, such as angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, were not considered because a self-report questionnaire was used to assess drug use. Forth, the adjustment of lipid lowering drugs remains controversial. We adjusted the use of lipid lowering drug in model 2 of Table Table3,3, based on the result of a meta-analysis that there was a modest reduction of proteinuria in the subjects with statin therapy.[69] However, in the 2 recent meta-analyses, the lipid-lowering therapy with statin did not improve kidney outcomes such as proteinuria in the subjects with chronic kidney disease.[70,71]

Despite these limitations, this study has several strengths. This study showed epidemiological evidence from a large population-based study using nationally representative data reflecting a single ethnicity. To the best of our knowledge, this is the study to examine the relationship between albuminuria and dyslipidemia in hypertensive subjects using a traditional lipid profile and an atherogenic lipid profile including TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and non-HDL-C in Asian individuals.

In conclusion, higher levels of TG, TG/HDL-C, and TC/HDL-C and lower levels of HDL-C were significantly associated with increased adjusted ORs for albuminuria in hypertensive women. Physicians should consider the lipid profile of patients with albuminuria, especially hypertensive women. Further prospective studies are needed to evaluate the causal

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relationship and mechanism of the association between dyslipidemia and albuminuria in hypertensive patients.

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Footnotes
Abbreviations: ACR = albumin to creatinine ratio, CI = confidence interval, CVD = cardiovascular disease, DM = diabetes mellitus, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, HANES = National Health and Nutrition Examination Survey, LDL-C = low-density lipoprotein cholesterol, Non-HDL-C = nonhigh density lipoprotein cholesterol, OR = odds ratio, TC = total cholesterol, TG = triglyceride, WC = waist circumference.
D HK and Y-HK contributed equally to this work.
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