

The research of the association between dyslipidemia and chronic kidney disease.

Xia Li, Yintao Chen, Shuang Chen, Guozhe Sun, Yingxian Sun*

Department of Cardiovascular Medicine, the First Hospital of China Medical University, Shenyang, Liaoning, PR China

Abstract

Background: Chronic Kidney Disease (CKD) has been a world-widely focused health problem and accompanied by a high risk of Cardiovascular Disease (CVD). The dysfunction of kidney due to hyperlipidemia is responsible for CKD. However, the association of dyslipidemia and CKD in rural area of China still remains to be investigated.

Methods: We selected 11197 (including 5189 men and 6008 women) as samples. The indexes chosen as variables included age, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), current smoking and drinking, Body Mass Index (BMI), exercise strength, Fasting Blood Glucose (FBG), and blood lipid. Estimated Glomerular Filtration Rate (eGFR) was selected to be the evaluation index of CKD. Finally, we acquired multiple logistic regression of eGFR and abnormal blood lipid levels in 3 models to evaluate the co-relationship between dyslipidemia and lowered eGFR.

Results: We established 3 models to evaluate the risk degree of mild CKD associating with dyslipidemia according to different co-variables combinations: high Triglyceride (TG), high Total Cholesterol (TC) and low High Density Lipoprotein-C (HDL-C), which are significant risk factors of mild CKD as they present intimate association with mild reduced eGFR (the OR (95% CI) and P value are: 1.224 (1.078-1.390), P=0.002; 1.560 (1.343-1.810), P<0.001; 1.391 (1.215-1.594), P<0.001 respectively). But high LDL-C only showed a suspect harmful property (OR=0.924 (0.773-1.105)) without ideal significance (P=0.389).

Conclusions: TG, TC, and HDL-C are all risk factors of mild reduced eGFR, indicating that dyslipidemia is closely related to the development of CKD.

Keywords: Dyslipidemia, Estimated glomerular filtration rate (eGFR), Chronic kidney disease (CKD), Cardiovascular disease (CVD).

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Introduction

For decades, dyslipidemia has been a significant cardiovascular risk factor worldwide that enables atherosclerosis of the coronary artery and peripheral arteries, including the renal arteries. Chronic Kidney Disease (CKD) is progressive loss of kidney function lasting for a period of months or years, which is more internationally recognized as a public health problem affecting about 5-10% of the world population [1,2].

Some clinical evidence has indicated that hypertriglyceridemia is an independent risk factor for CKD, and low High-Density Lipoprotein (HDL)-C levels can help predict CKD progression [3,4]. Therefore, patients with high triglyceride and low HDL levels have an increased risk of renal dysfunction [5]. According to recent research, patients with CKD and cardiovascular disease have a greater risk than patients with senile dyslipidemia and renal insufficiency [6]. It has been recognized that narrowed renal arteries (atherosclerosis) circulate less blood to the kidneys, causing a series of problems such as a reduced Glomerular Filtration Rate (GFR) [7]. A

cross-sectional study on CKD prevalence and risk factors in a Tibetan population (2010) indicated that high blood Total Cholesterol (TC) led to significantly reduced renal function (Estimated Glomerular Filtration Rate (eGFR), <60 mL/min/1.73 m², OR=3.5-4.5, (P=0.01)) [8]. Another recent cross-sectional study conducted in Shandong province demonstrated a more distinctive result: elevated Triglyceride (TG) levels (1.22-1.7 mmol/L) had a linear relationship with mildly reduced eGFRs (OR=1.98 (1.57-2.49), P<0.001) [9]. However, relevant studies related to these points have been rarely conducted in a general population in China, and the significance of low HDL-C has been rarely reported. Therefore, we aimed to investigate whether an abnormal lipid profile is a risk factor that affects eGFRs in a general population in China.

Methods

Liaoning province, which is located in North-East China, was selected as the region for the target population in this study. This study was designed to use a random-cluster sampling

scheme. Ethics approvals for entire target population were obtained before the study. Different indexes collected from the appropriate population were selected to characterize the prevalence and cardiovascular risk factors in rural areas of Liaoning province.

To guarantee the preciseness of the results, we excluded patients who had mental disorders or malignant tumors and who were pregnant, as well as those who were diagnosed with kidney disease. Finally, we selected a sample that included 11197 patients (including 5189 men and 6008 women). We evaluated patients with the following characteristics: age, ≥ 40 y (as compared with other calculation formulas, the formula to calculate the CKD-EPI is more accurate for estimating GFRs, especially for those aged ≥ 40 y); Systolic Blood Pressure (SBP, ≥ 140 mmHg); Diastolic Blood Pressure (DBP, ≥ 90

mmHg); current smoking and drinking; Body Mass Index (BMI, >25 kg/m²); exercise strength; fasting blood glucose (FBG, ≥ 7 mmol/L) and abnormal blood lipid (TG, TC, LDL-C, and HDL-C). These variables were analyzed enzymatically on an auto-Analyzer (Olympus AU640; Olympus, Kobe, Japan, or Bayer RA-XT; Bayer Diagnostics, Tarrytown, NY, USA) using kits (Bayer Diagnostics). The laboratory measurements were calibrated and verified following analysis of biochemical indices and the results met the national standards of measurement (CNAS certificate of accreditation No.L0467, quality index $U=0.006$ ($k=2$)). These variables were used to compare characteristics among different eGFR groups (eGFR, >90 mL/min/1.73 m² or 60-90 mL/min/1.73 m²) based on gender (men and women have different GFRs) (Table 1).

Table 1. The instruments, kits and methods used for the analysis of various parameters.

Variables	Instruments	Kits	Methods
TG	ROCHE COBAS 8000	Triglyceride Quantification Kit, Kyowa Hakko Kirin Co., Ltd.	Free glycerol elimination method
TC	ROCHE COBAS 8000	Total Cholesterol Assay Kit, Kyowa Hakko Kirin Co., Ltd.	Cholesterol oxidase method
LDL-C	ROCHE COBAS 8000	LDL Cholesterol Assay Kit, Kyowa Hakko Kirin Co., Ltd.	Selective solubilization method
HDL-C	ROCHE COBAS 8000	HDL Cholesterol Assay Kit, Kyowa Hakko Kirin Co., Ltd.	Chemical modification enzymic method
FBG	ROCHE COBAS 8000	Blood Glucose Monitor Kit, Kyowa Hakko Kirin Co., Ltd.	Hexokinase method

A multiple logistic regression analysis was conducted using both a single factor and multiple factors, with 2 classification variables (eGFR, 60-90 and >90). eGFR was a dependent variable used to analyze the risk correlation between blood lipid levels and eGFR, and the remaining were covariates. The multivariate analysis was used to eliminate covariate interference on the results. Therefore, we set the abovementioned indexes (except blood lipids) as co-variables and established 3 different combinations to obtain a multiple logistic regression involving different eGFR levels and lipid data: model 1, data analyzed without co-variables; model 2, data analyzed, including age and gender; and model 3, data analysis included age, gender, blood pressure, current smoking, current drinking, BMI, and blood glucose. Finally, the logistic regression for eGFR and dyslipidemia in the 3 models was critically analyzed (processed using SPSS).

Data collection

Data were collected by cardiologists and trained nurses using a standard questionnaire in a face-to-face interview during a single visit to the Department of Laboratory Testing, the First Affiliated Hospital of China Medical University. Before the survey was performed, we invited all eligible investigators (students at the First Affiliated Hospital of China Medical University) to attend an organized training session, in which they were informed of the purpose of this study, how to administer the questionnaire, the standard measurement method, the importance of standardization, and the study

procedures. Only those who were deemed qualified after passing a post-training test could conduct the research. During data collection, our inspectors were given additional instructions and support.

The study was guided by a central steering committee, along with a subcommittee for quality control. Educational level was assessed as follows: completion of primary school (or less), middle school, high school, or a higher-level of education. Self-reported sleep duration (including nocturnal and nap duration) was also obtained.

According to the American Heart Association protocol, Blood Pressure (BP) was measured 3 times at 2 min intervals after ≥ 5 min of rest using a standardized automatic electronic sphygmomanometer (HEM-907; Omron). The participants were advised to avoid caffeinated and alcoholic beverages and exercise for at least 30 min before the measurement. During the measurement, participants were seated with their arms supported at the level of their heart, with a cuff tied at moderate tension on their arm (2.5 cm above the elbow joint). The mean of 3 blood pressure measurements was calculated and used in all analyses.

Weight and height were measured within 0.1 kg and 0.1 cm, respectively, with the participants wearing lightweight clothing, but without their shoes. Waist Circumference (WC) was measured at the umbilicus using a non-elastic tape (to the nearest 0.1 cm), with the participants standing while maintaining the end of normal expiration. BMI was calculated as weight (kilogram) divided by height squared (meters).

Fasting blood samples were collected in the morning after fasting at least 12 h. Blood samples were obtained from an antecubital vein and collected in vacutainer tubes containing a coagulation accelerator. Each vacutainer tube was kept stationary for 30 min before centrifugation (3000 r/min, 10 min), and the serum samples were collected. Fasting Plasma Glucose (FPG), TC, low-density lipoprotein cholesterol (LDL-C), HDL-C, TGs, Creatinine (Cr), and other routine blood biochemical indexes were analyzed enzymatically using an auto-analyzer. All laboratory equipment was calibrated, and blinded duplicate samples were used for these analyses.

Definitions and standard settings

High blood pressure (hypertension): This index was classified according to American Heart Association (AHA) standards (http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/GettheFactsAboutHighBloodPressure/TheFactsAboutHighBloodPressure_UCM_002050_Article.jsp#.WX9GVzO77Vo): SBP>140 mmHg and DBP>90 mmHg (SBP>140 mmHg; DBP<90 mmHg terms to isolated systolic hypertension).

Current smoking: Smoking was classified as follows: (1) Frequent smoking (smoke>1 cigarette per d, persistent or cumulative use for >6 months); (2) Occasional smoking (smoke>4 cigarettes per week but not to exceed 1 cigarette per d); (3) No smoking. Current smoking was defined as smoking within the past 30 d and satisfied one of the 3 above mentioned items (WHO standard, <http://www.who.int/topics/tobacco/en/>).

Current drinking: Drinking of alcohol is classified as mild (1.3-20 g/d), moderate (20-50 g/d), or severe (>50 g/d) in China (alcohol consumption in terms of ethanol equivalent weight). Current drinking refers to patients who drank alcohol within the past 30 d according to one of the 3 above mentioned classifications.

Physical exercise strength: We divided exercise strength into low, moderate, and high levels secondary to occupational and leisure-time physical activity. Occupational and leisure-time physical activity were merged and regrouped into the following 3 categories: (1) Low exercise strength (low levels of both occupational and leisure-time physical activity); (2) Moderate exercise strength (moderate or high levels of either occupational or leisure-time physical activity); (3) High exercise strength (moderate or high levels of both occupational and leisure-time physical activity).

FBG: The normal FBG range is 3.9-6.1 mmol/L, and impaired FBG levels are considered to be 6.1-7.0 mmol/L (normal oral glucose tolerance test, 2 h). The diagnostic criteria for diabetes mellitus (American Diabetes Association, ADA, <http://www.diabetes.org/are-you-at-risk/prediabetes/>) include FBG levels of >7 mmol/L.

BMI: Patients with a BMI of >25 kg/m² are considered overweight, implying an abnormal physical appearance (BMI, 25-29.9 kg/m² is pre-obese, 30-34.9 kg/m² is obese class I, 35-40 kg/m² is obese class II, and >40 kg/m² is obese class III)

according to WHO criteria (<http://www.who.int/mediacentre/factsheets/fs311/en/>).

eGFR: This index is defined depending on different eGFR levels (<http://www.renal.org/information-resources/the-uk-eckd-guide/about-egfr#sthash.1fDqe9Ms.dpbs>): eGFR>90 mL/min/1.73 m², normal; 60-90 mL/min/1.73 m², mild renal failure; and <60 mL/min/1.73 m², severe renal failure.

Results

Table 2 shows the ages of mild reduced eGFR groups mainly at or above 40 y old: 97.6% men and 97.8% women.

Table 2. Variables from the different eGFR groups. Note: Each denominator indicates the number of patients in each eGFR group.

	eGFR (mL/min/1.73 m ²)		
	<60	60-90	≥ 90
Male			
Age (≥ 40 y) (n/%)	83 (100%)	1642 (97.6%)	2999 (87.6%)
SBP (≥ 140 mmHg) (n/%)	64 (77.1%)	992 (59%)	1494 (43.6%)
DBP (≥ 90 mmHg) (n/%)	36 (43.4%)	482 (28.7%)	860 (25.1%)
BMI (≥ 25 kg/m ²) (n/%)	40 (48.2%)	791 (47.0%)	1430 (41.8%)
FBG (≥ 7.0 mmol/L) (n/%)	17 (20.5%)	176 (10.5%)	292 (8.5%)
Current drinking (n/%)	12 (14.5%)	608 (36.1%)	1751 (51.1%)
Current smoking (n/%)	26 (31.3%)	844 (50.2%)	2102 (61.4%)
Low exercise strength (n/%)	48 (57.8%)	514 (30.6%)	598 (17.5%)
Moderate exercise strength (n/%)	33 (39.8%)	1060 (63.1%)	2648 (77.3%)
High exercise strength (n/%)	2 (2.4%)	107 (6.4%)	178 (5.2%)
Female			
Age (≥ 40 y) (n/%)	142 (100%)	2435 (97.8%)	2864 (84.9%)
SBP (≥ 140 mmHg) (n/%)	96 (67.6%)	1182 (47.5%)	1308 (38.8%)
DBP (≥ 90 mmHg) (n/%)	39 (27.5%)	547 (22%)	588 (17.4%)
BMI (≥ 25 kg/m ²) (n/%)	66 (46.5%)	1139 (45.7%)	1538 (45.6%)
FBG (≥ 7.0 mmol/L) (n/%)	35 (24.6%)	277 (11.1%)	268 (7.9%)
Current drinking (n/%)	3 (2.1%)	64 (2.6%)	108 (3.2%)
Current smoking (n/%)	43 (30.3%)	461 (18.5%)	489 (14.5%)
Low exercise strength (n/%)	90 (63.5%)	1059 (42.5%)	1003 (29.7%)
Moderate exercise strength (n/%)	39 (27.5%)	1278 (51.3%)	2197 (65.1%)
High exercise strength (n/%)	13 (9.2%)	154 (6.2%)	175 (5.2%)

Both men and women who had high SBP and DBP demonstrated increasing blood pressure values with decreasing eGFRs, so as to abnormal BMI and FBG shown in the study.

High current drinking and smoking rates were observed in the normal male eGFR group (51.1% and 61.4%, respectively) but

were lower in the decreased eGFR group (36.147% and 50.178%, respectively). Women tended to have lower current drinking levels, and the trend was similar. However, the trend of current smoking in the women's group was opposite that of the men's group.

People with low exercise strength demonstrated an even lower exercise tolerance as their eGFR decreased, and fewer patients in both the male and female groups had moderate exercise strength. Furthermore, in all groups, very few patients had high exercise strength.

These data demonstrated that BP, BMI and FEG were all positively related to decreased eGFRs, which might imply that they were risk factors for CKD.

Multiple logistic regression analysis

The sample from the third group was not adequate for comparison. Patients in the group with an eGFR of >90 were normal, and an eGFR of 60-90 represented a pathological condition, so the multiple logistic regression for the 2 eGFR groups was analyzed in the 3 models and is shown in Table 3. In model 1, the data are shown without any co-variables; a high

TG, high TC, and low HDL-C demonstrated a positive association with a mild decline in eGFR, and the risk significance was simultaneously apparent, with an OR value (expressed as OR (95% CI, P value)) of 1.184 (1.064-1.316; P=0.0019), 1.894 (1.665-2.155; P<0.001), and 1.274 (1.135-1.429; P<0.001), respectively. In model 2, the data were revised to assess age and gender, and in model 3, the data were revised to assess age, gender, BP, current smoking, current drinking, BMI, and blood glucose. The 3 indexes demonstrated a positive association and significance, indicating that they were vital risk factors for mildly decreased eGFRs. High LDL-C levels did not demonstrate a risk, with or without the co-variables (LDL-C, model 3, OR=0.744 (0.607-0.913), P=0.389). The logistic regression results did not reveal a pervasive conclusion as other similar studies had: high LDL-C levels have been shown to be a significant vascular risk factor in dyslipidemia and CKD but probably does not have a relationship with kidney dysfunction. However, in contrast to nearly all other research, low HDL-C levels played an important role in mild CKD (in model 3; OR: 1.391 (1.215-1.594); P<0.001).

Table 3. Logistic regression of the 2 eGFR groups (eGFR was a dependent variable). Note: A multiple logistic regression analysis was performed using both a single factor and multiple factors, with 2 classification variables (eGFR: 60-90 and >90). eGFR was a dependent variable used to analyze the risk correlation between blood lipids and eGFR, and the remaining were covariates. The multivariate analysis was used to eliminate covariate interference on the results.

Logistic regression of the eGFR \geq 90 mL/min/1.73 m ² group						
Independent variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
TG (\geq 92.26)	0.831 (0.748-0.992)	0.001	0.790 (0.701-0.891)	<0.001	0.808 (0.712-0.917)	0.001
TC (\geq 96.21)	0.518 (0.456-0.588)	<0.001	0.626 (0.542-0.723)	<0.001	0.632 (0.545-0.733)	<0.001
LDL-C (\geq 94.16)	1.056 (0.894-1.270)	0.479	1.366 (1.120-1.667)	0.002	1.343 (1.097-1.645)	0.004
HDL-C (\geq 91.03)	0.771 (0.689-0.863)	<0.001	0.636 (0.558-0.725)	<0.001	0.716 (0.626-0.819)	<0.001
Logistic regression of the eGFR 60-90 mL/min/1.73 m ² group						
Independent variables	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
TG (\geq 92.26)	1.184 (1.064-1.316)	0.002	1.244 (1.102-1.404)	<0.001	1.224 (1.078-1.390)	0.002
TC (\geq 96.21)	1.894 (1.6665-2.155)	<0.001	1.576 (1.363-1.822)	<0.001	1.560 (1.343-1.810)	<0.001
LDL-C (\geq 94.16)	0.924 (0.733-1.105)	0.389	0.727 (0.595-0.889)	0.002	0.744 (0.607-0.913)	0.005
HDL-C (\geq 91.03)	1.274 (1.135-1.429)	<0.001	1.561 (1.368-1.780)	<0.001	1.391 (1.215-1.594)	<0.001

Conclusions

Dyslipidemia and hypertension have been proven to be individual risk factors for CKD. Some medical literature has already reported on their correlation [10]. Renal insufficiency without albuminuria was found to be significantly associated with abnormal lipid metabolism, mainly secondary to atherosclerosis-related renal artery occlusion and abnormal renal hemodynamics, postulated to be associated with

macrophage-derived foam cells (because of lipid precipitation in the extracellular matrix) [11,12]. In this study, strictly controlled data collection from a wide range of patients was conducted in North-East China, an area that has been rarely investigated in recent decades. We showed that hypertriglyceridemia had an association and significance in a mild renal dysfunction group that was similar to other studies. A cross-sectional study was conducted in Zhuhai from June to

October 2012, and TG was significantly associated with CKD, with an OR for CKD of 2.65 (95% CI: 1.65-4.26; $P < 0.001$). After adjusting for diabetes and hypertension, the association was still significant (OR=2.09; 95% CI: 1.26-3.45; $P = 0.004$) (data analyzed using SSPS). Age, gender, hypertension, diabetes, overweight, smoking, and drinking are traditional risk factors for CKD [13]. Thus, this modification proved that TG is a more pertinent risk factor for CKD as it excluded the two main generally accepted individual risk factors. However, we obtained a similar conclusion using a similar co-variable revision method.

In this study, we did not expect that no correlation between CKD and high LDL-C levels would be demonstrated, even revised without any co-variables (OR=0.924 (0.773-1.105); $P = 0.389$). Research on correlations between LDL-C and CKD has shown that LDL-C levels are related to preclinical renal insufficiency in Japanese men. Blood LDL-C levels were higher in patients with CKD than male patients who did not have CKD.

High blood TC and low HDL-C levels can be confirmed as risk factors for mild renal insufficiency, as significance was demonstrated in this study even after revising the co-variables. According to a cohort study with a mean 10 y follow-up (840 subjects with CKD stages 3-4), a significant association existed between CKD and TC (hazard ratio, 95% CI=1.03; 1.0-1.06), but it disappeared after modifying the co-variables. However, our study did not demonstrate the same conclusions, and thus, we could consider TC as a risk factor for CKD. Correlation between decreased HDL-C levels and declining eGFRs is still unclear according to recent research. In this study, we performed a data analysis and obtained results from large sample sizes. The mechanism involved with low HDL-C levels inducing decreased eGFRs is sophisticated. Scavenger receptor class B member 1-mediated serum cholesterol efflux is significantly reduced in patients with CKD, and impaired HDL is also observed in patients with renal dysfunction [14]. Therefore, patients with low HDL-C levels should be considered in clinical dyslipidemia therapy.

In conclusion, our research aimed to explore the correlation between dyslipidemia and mild CKD in a rural area of northeast China. However, we did not evaluate albuminuria, another independent diagnostic criterion for CKD that helps in the prediction of cardiovascular disease [15]. Moreover, the selected population and region determined the application limitation. We measured abnormal blood lipid levels according to the world standard; however, additional classification of dyslipidemia levels was not adopted in our study so we could investigate the association of different blood lipid ranges and CKD. Therefore, additional study of these aspects is necessitated to confirm a correlation between dyslipidemia and mild CKD.

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Conflict of Interest

None.

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***Correspondence to**

Yingxian Sun

Department of Cardiovascular Medicine

The First Hospital of China Medical University

Shenyang

Liaoning

PR China