ORIGINAL ARTICLE

High-density lipoprotein cholesterol, apolipoprotein E and atherogenic index of plasma are associated with risk of chronic kidney disease

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ABSTRACT

Aim To investigate the association of parameters of lipid profile and estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease (MDRD) in non-dialysis kidney patients.

Methods The observational, case-control study enrolled patients (n=117) recruited from the Nephrological Counselling Centre of the University Clinical Centre Sarajevo and divided into two groups: group 1 eGFR (15-59 mL/min/1.73 m^2), and group 2 (control) eGFR ≥ 60 mL/min/1.73 m^2. Concentration of lipids, lipoproteins and apolipoproteins was measured, and atherogenic index of plasma (AIP; log(TG/HDLc)) was calculated.

Results High density lipoprotein cholesterol (HDLc) and apolipoprotein E (APOE) concentrations in serum were reduced [(1.02 (0.94-1.29) vs 1.15 (1.1-1.4) mmol/L; p=0.009 and 0.035 (0.026-0.04) vs 0.041 (0.034-0.05) g/L; p=0.002, respectively)], while AIP was higher in group 1 than in group 2 (0.19±0.03 vs 0.09±0.04; p=0.013). Values less than 1.09 mmol/L and 0.038 g/L for HDLc and APOE, or higher than 0.165 for AIP (p<0.05) were associated with the eGFR below 60 ml/min/1.73 m^2. The age [OR = 1.1; 95% CI (1.05-1.17)] and AIP [OR = 8.7; 95% CI (1.18-65.0)] were independent positive predictors, while APOE was a negative predictor of eGFR reduction rate (OR=0.01; 95% CI (0.001-0.033; p<0.001).

Conclusion Changes in parameters such as HDLc, APOE and AIP are associated with CKD. The study results imply the need of the AIP calculation as routine laboratory work due to its role along with the age and APOE in the prediction of renal function decline.

Key words: kidney failure, estimated glomerular filtration rate, lipid profile

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. Characteristic lipid disturbances known as atherogenic dyslipidaemia are present in patients with CKD (1). Dyslipidaemia is one of the cardiovascular risk factors responsible for cardiovascular disease and rapid progression of chronic kidney disease to the end stage of renal disease. Early detection and management of dyslipidaemia will reduce cardiovascular burden and retard the progression of CKD (2). Traditionally, the risk of developing of cardiovascular disease is evaluated by determining lipid and lipoprotein parameters such as cholesterol, triglycerides, high-density lipoprotein cholesterol (HDLc) and low-density lipoprotein cholesterol (LDLc). Over time the statement that apolipoproteins such as apolipoprotein A-I (apo A-I), apolipoprotein B-100 (apo B-100), apolipoprotein E (APOE) are more significant parameters for risk assessment of developing cardiovascular disease than classical lipid parameters has become controversial (3-5). In order to attempt predictive capacity of lipids and an increase of the quality of their predictive capacity, lipid ratio known as atherogenic indices index was introduced as a reflection of the metabolic and clinical interactions between lipid fractions (6). Atherogenic index of plasma (AIP) as a logarithmically transformed ratio of molar concentrations of triglycerides (TG) to HDLc (logTG/HDL) and less susceptible to disease activity, explains the relationship between atherogenic and protective molecules (7). The lipid profile such as HDLc, TG with normal or even low total cholesterol (TC), and LDLc, frequently found in CKD, is strongly atherogenic (2). The degree of renal impairment, etiology of the primary disease, the presence of nephrotic syndrome and the method of dialysis affect concentrations of all lipoprotein classes showing variations of these abnormalities (8).

Besides the role of dyslipidaemia in the development of cardiovascular complications of CKD, confusion exists related to the role of major determinants of dyslipidemia in CKD patients as well. Some data suggest that dyslipidaemia causes a decrease in glomerular filtration rate (GFR) or reduced GFR leads to dyslipidaemia (9,10). Furthermore, other comorbidities in CKD such as diabetes or hypothyroidism additionally cause dyslipidaemia (11,12). In order to clarify the role of dyslipidaemia in CKD development, there is need to investigate the association of dyslipidaemia and GFR decline in kidney diseases. Among lipid profile parameters, there are limited data about their ability to differentiate and predict GFR decline below 60 mL/min/1.73m^2 assessed by the abbreviated Modification of Diet in Renal Disease (MDRD) formula (13).

The aim of this study was to investigate the role of lipids, lipoproteins, apolipoproteins and atherogenic index of plasma in the differentiation of estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2 assessed by MDRD equation in predialysis, kidney disease patients. Additionally, we would like to define lipid parameter cut-off values for differentiation of CKD based on eGFR and to find the model for prediction of eGFR decline less than 60 mL/min/1.73m^2 in those patients.

PATIENTS AND METHODS

Patients and study design

The observational, case-control study enrolled 117 patients of both sexes, 35-60 years old, who were diagnosed with kidney disease persisting for at least three months. They attended the Nephrological Counseling Center of the University Clinical Center Sarajevo during the period December 2016-Septembar 2017. The participants were informed of all aspects of the research and gave written informed consents for inclusion in the study. The Ethics Committee approval of the University Clinical Center Sarajevo was obtained before the initiation of the study.

The data of the age, gender, current smoking, medical history including history of renal diseases and comorbidities were taken by medical interview, patient clinical examination and through evaluation of the patients' medical documentation.

Blood pressure measurements were done using a standardized protocol and calibrated sphygmomanometer. The inclusion criteria were: kidney disease that persists more than 3 months and eGFR more 15 mL/min/1.73m^2 (by definition, chronic kidney disease has reduced GFR less than 60 mL/min/1.73 m^2 for at least 3 months) (14). Patients treated with drugs such as hypolipi-

demics, corticosteroids and immunosuppressants (systemic diseases), transplant recipients, end stage renal disease patients treated with hemodialysis or peritoneal dialysis, patients diagnosed with nephrotic syndrome, diabetes, chronic alcoholism and diseases of the thyroid gland and liver, and those with triglyceride levels above 4.5 mmol/L were excluded from the study.

According to eGFR, patients were divided into two groups: group 1 - eGFR between 15 and 59 mL/min/1.73 m^2 (n=73) and group 2 (control) - eGFR ≥ 60 mL/min/1.73 m^2 (n=44).

Methods

The blood samples were collected after overnight fasting and the parameters were measured using standard laboratory assays; triglycerides (TG), total cholesterol (TC) and HDLc were measured by spectrophotometry (Clinical Chemistry Dimension analyzer SIMENS, Germany); ApoA-I, ApoB-100, APOE and lipoprotein (a) [(Lp (a)] were measured using immunoturbidimetric assays (Clinical Chemistry analyzer BN II, SIMENS, Germany). Creatinine and urea were measured in serum by kinetic colorimetric tests (Architect c8000i, ABBOT, Illinois, U.S.A.). Very low density lipoprotein (VLDLc) and LDLc were calculated according to commonly used formulas: VLDLc (mmol/L)=TG/ 2.2 mmol/L and LDLc (mmol/L)=TC- HDLc-VLDLc (15). Atherogenic index of plasma was calculated according to the formula: AIP= log TG / HDLc (16). All analyses were performed at the Organisational Unit Clinical Chemistry and Biochemistry, University Clinical Center Sarajevo. Estimated GFR was calculated from serum creatinine using revised MDRD formula: eGFR (mL/min/1.73 m2)=175 (serum creatinine inμmol/L × 0.011312)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American/ black) (13).

Statistical analysis

Kolmogorov-Smirnov test was used to test the normal distribution of the variables.The data were expressed as the mean with standard deviation or median with interquartile interval depending on normality of data distribution. To test the difference between groups, parametric/non-parametric tests (Student t-test or Mann-Whitney test, respectively) were used. The differences between categorical variables were tested by χ^2 test. The Receiver Operating Characteristics (ROC) curve was used to identify variables and their cut-off values for differentiation of patients with eGFR less than 60 mL/min/1.73/m^2. It was followed by calculations of specificity, sensitivity, positive and negative predictive values according to formulas: sensitivity=A/(A+C)x100; specificity=D/(D+B)x100; positive predicitive value (PPV)=A/(A+B)x100; negative predictive value (NPV)= D/(D+C)x100; A-true positive; B-false positive; C-false negative; D-true negative. Multivariable logistic regression analysis was conducted to test the predictive model for eGFR less than 60 mL/min/1.73/m^2. Probabilty was set at $p<0.05$ and considered significant.

RESULTS

Patients of eGFR group 1 were significantly older compared to those in eGFR group 2 ($p<0.001$). Furthermore, urea, creatinine and blood pressure were significantly higher in group 1 patients (Table 1).

Table 1. Basic characteristics of the patients relative to the estimated glomerular filtration rate

Parameters	eGFR Group 1* (n=73)	eGFR Group 2* (n=44)	p
Age (years) median (25th-75th percentile)	56.0 (52.2-59.0)	48.0 (35.5-57.0)	<0.001
Duration of illness (years) median (25th-75th percentile)	5.0 (2.0-15.0)	3.0 (1.0-10.0)	0.22
Gender (males) (%)	33 (45.2)	21 (47.7)	0.85
Smoking (yes) (%)	22 (30.1)	17 (38.6)	0.42
Creatinine (μmol/L) median (25th-75th percentile)	168.0 (1250-229.5)	81.5 (69.3-93.0)	<0.001
Urea (mmol/L) median (25th-75th percentile)	9.8 (7.2-15.2)	5.0 (4.13-5.58)	<0.001
SBP (mmHg) median (25th-75th percentile)	130.0 (120-142.0)	120 (112.5-130.0)	0.002
DBP (mmHg) median (25th-75th percentile)	80 (80.0-90.0)	80.0 (70.0-80.0)	0.003

Median, median with 25th-75th percentile; *eGFR Group 1: estimated glomerular filtration rate between 15-59 mL/min/1.73 m^2; eGFR Group 2: estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73 m^2; SBP, systolic blood pressure; DBP, diastolic blood pressure

Among tested parameters, median values of HDLc and APOE were significantly lower (p=0.009 and p=0.002, respectively) in patients of eGFR group 1 compared to eGFR group 2 patients. However, AIP value was higher in group 1 than in group 2 of the patients (p=0.013). The level of other lipids, lipoproteins and apolipoproteins did not differ significantly between the groups (Table 2).

Table 2. Lipids, lipoproteins, apoproteins and atherogenic index of plasma relative to estimated glomerular filtration rate (eGFR)

Parameters	Mean±standard deviation (median with 25th-75th percentile)		p
	eGFR Group 1* (n=73)	eGFR Group 2* (n=44)	
TC (mmol/L)	5.37 (4.6-5.8)	5.52 (5.1-6.2)	0.2
TG (mmol/L)	1.74 (1.3-2.3)	1.38 (1.0-2.3)	0.095
VLDLc (mmol/L)	0.79 (0.6-1.0)	0.63 (0.5-1.0)	0.095
LDLc (mmol/L)	3.3±0.11	3.57±0.14	0.35
HDLc (mmol/L)	1.02 (0.94-1.29)	1.15 (1.1-1.4)	0.009
Lp(a) (mmol/L)	0.09 (0.03-0.2)	0.07 (0.02-0.18)	0.21
Apo B-100 (mmol/L)	0.85±0.03	0.91±0.04	0.12
Apo A-I (mmol/L)	1.23±0.03	1.24±0.03	0.29
APOE (g/L)	0.035 (0.026-0.04)	0.041 (0.034-0.05)	0.002
AIP	0.19±0.03	0.09±0.04	0.013

*eGFR Group 1: estimated glomerular filtration rate between 15-59 mL/min/1.73 m^2; eGFR Group 2: estimated glomerular filtration rate greater than or equal to 60 mL/min/1.73 m^2; TC, total cholesterol; TG, triglycerides; VLDL, very low density lipoprotein cholesterol; LDLc, low density lipoprotein cholesterol; HDLc, high density lipoprotein cholesterol; Lp(a), lipoprotein (a); Apo B-100, apolipoprotein B; ApoA-I, apolipoprotein A-I; APOE, apolipoprotein E; AIP, atherogenic index of plasma

ROC analysis showed that HDLc, APOE and AIP in patients with eGFR less than 60 mL/min/1.73/m^2 were less than 1.09mmol/L (p=0.002) and 0.038 g/L (p=0.002) for HDLc and APOE, but higher than 0.165 for AIP (p=0.019) (Table 3).

Multiple logistic regression analysis was used to test the model for prediction of eGFR less than 60 mL/min/1.73/m^2. A univariate regression analysis included dependent variables such as age, sex, history of kidney disease, smoking habit, concentration in serum of parameters such as lipids, lipoproteins, apolipoproteins, and value of AIP as independent predictors in the model. Among them, age, AIP and APOE were associated with eGFR less than 60 mL/min/1.73/m^2. Therefore, predictors associated with eGFR less than 60 mL/min/1.73/m^2 in the univariate regression analysis were included in the model of multivariable regression analysis. It was found that age [OR = 1.1; 95% CI (1.05-1.17)] and AIP [OR = 8.7; 95% CI (1.18-65.0)] were independent positive predictors, while APOE was a negative predictor [OR = 0.01; 95% CI (0.001-0.033)] of eGFR less than 60 mL/min/1.73/m^2. The model was statistically significant (p <0.001) and could explain between 35.0% (R^2 Cox and Snell) and 47.4% (R^2 Nagelkerkea) variance results and accurately classified 77.0% of cases (Table 4).

Table 4. Multivariable logistic regression model of independent risk factors for predicting estimated glomerular filtration rate (eGFR) less than 60 mL per minute per 1.73 m^2

Model	Regression Coefficient	Standard error	p	OR	95% CI for OR	
					Lower limit	Upper limit
Age	0.1	0.03	0.001	1.1	1.05	1.17
AIP	2.17	1.0	0.034	8.7	1.18	65.0
APOE	-7.2	1.9	0.001	0.01	0.001	0.033

AIP, atherogenic index of plasma; APOE, apolipoprotein E; OR, odds ratio; CI, confidence interval

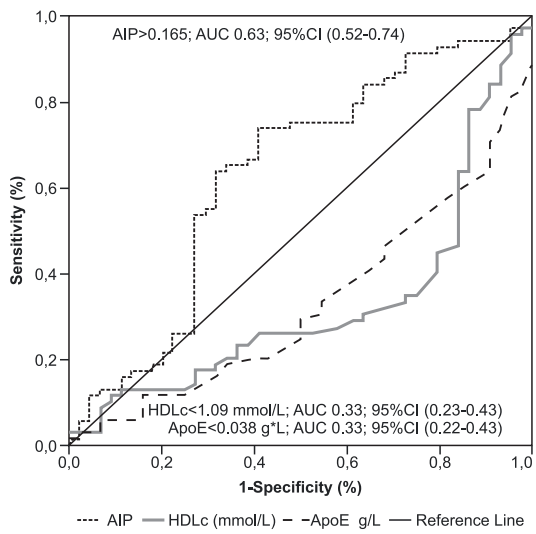

Figure 1. Receiver operating characteristics (ROC) curve of high density lipoprotein cholesterol (HDLc), apolipoprotein E (APOE) and atherogenic index of plasma (AIP) in differentiation of estimated glomerular filtration rate (eGFR) of more or less than 60 mL/min/1.73 m^2
AUC, area under curve; CI, confidence interval;

DISCUSSION

Up to now dyslipidaemia, has been associated with rapid decline in renal function and commencement of renal replacement therapy in CKD patients. The precise mechanism is unknown; however, abnormalities in plasma lipids and lipoproteins are well documented (1). However,

Table 3. Sensitivity and specificity of high density lipoprotein cholesterol (HDLc), apolipoprotein E (APOE) and atherogenic index of plasma (AIP) in differentiation of patients with estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73/m^2

Variables	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	95% CI	p
HDLc (mmol/L)	1.09	0.33	64.4	68.2	77	53.6	0.23-0.43	0.002
APOE (g/L)	0.038	0.33	66.7	54.5	69.7	51.1	0.22-0.43	0.002
AIP	0.165	0.63	61.6	64.4	75	50.9	0.52-0.74	0.019

AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval

dyslipidaemia, as a predictor or mediator of decline in renal function of CKD patients is not completely clear (9,10) pointing out the need of its analysis based on the method of GFR assessment and proper selection of patients. Various comorbidities as causes of secondary dyslipidaemia, ways of studied groups comparison and finally, methods of GFR assessment resulted in controversial data regarding lipids and their role in CKD (9-12). Up to now very few data have been published on association of pre-dialysis CKD patients (classified into groups below and greater/ equal to 60 mL/min/1.73m^2) and dyslipidaemia based on MDRD assessment of GFR.

In this study we tried to clarify which parameters of lipid profile are able to differentiate and predict decline in eGFR below 60 mL/min/1.73m^2. Values of HDLc, APOE were lower and AIP was significantly higher in patients with eGFR between 15 and 59 mL/min/1.73 m^2. The results of ROC analysis revealed that values of HDLc lower than 1.09 mmol/L, APOE lower than 0.038 g/L and AIP higher than 0.165 could differentiate patients with decline in eGFR values less than 60mL/min/1.73 m^2. Although these three parameters could be used as a marker for differentiation of patients with eGFR below 60 ml/min/1.73 m^2 since areas under the curve were statistically significant, relatively low sensitivities and specificities do not warrant their clinical use as markers of CKD. However, we believe that these markers have importance for the differentiation of CKD patients if they are combined with other biomarkers requiring further elucidation.

Rahman et al. (17) reported that total cholesterol, triglycerides, Lp (a), VLDLc, LDLc, HDLc, apoA-I, and apo-B were not independently associated with progression of kidney disease in the large cohort of CKD patients. In addition, they stated that lipid-lowering agents have not shown a consistent benefit on the progression of kidney disease. Investigating the role of dyslipidaemia in the prediction of cardiovascular disease and staging of CKD in diabetic pre-dialysis and dialysis patients Corsetti et al. (18) emphasized the antiatherogenic properties of HDL derived from apolipoproteins and enzymes such as APOE and the value of APOE in the prediction of cardiovascular risk in women. In apparently healthy individuals, Malarkodi et al. (19) found a significant negative correlation of LDL, total cholesterol, non-high density cholesterol (non-HDLc) and a positive correlation of HDL with eGFR. The results of our study regarding HDLc were concordant with the results of Baragetti et al. (20), who reported that low HDLc levels, diabetes and hypertension were associated with reduced GFR; additionally, in their study, low HDLc levels were associated with earlier initiation of dialysis, or doubling of the plasma creatinine level. High density lipoprotein cholesterol was the only lipid parameter associated with the increased risk of eGFR below 60 ml/min/1.73 m^2 (hazard ratio 0.951; 95% confidence interval (CI) 0.917-0.986, p= 0.007), independently of the presence of diabetes. In the study of Bowe et al. (21), HDLc lower than 30 mg/dL was associated with the increased risk of eGFR below 60 ml/min/1.73 m^2 and CKD progression. In our study, HDLc could not predict eGFR below 60 ml/min/1.73 m^2, while APOE and AIP along with age were independent predictors of decline in eGFR below 60 ml/min/1.73 m^2. The model provided 77% chance of a correct classification of patients. Specific abnormalities in the lipoprotein metabolism result from an inappropriate activity of key enzymes developed in the early stage of kidney function decline leading to dyslipidaemia (1,22,23). Penn Diabetes Heart Study conducted on type 2 diabetics without cardiovascular or renal complications showed that Lp (a) may play a role in renal impairment; twofold increase in Lp (a) was associated with decline in eGFR (24). Contrary to the Penn Diabetes Heart Study, but similar to our study, Rahman et al. (17) did not find any significant association between plasma Lp (a) levels and decline in eGFR, stating that Lp (a) plays a role in the early development of cardiovascular disease especially, whereas other pathologies such as hyperfiltration and fibrosis may drive subsequent eGFR decline. Lipoprotein (a) concentrations vary considerably between individuals due to genetic and non-genetic factors (25). The current study did not enrol CKD patients with type 2 diabetes, pointing the possible additional role of diabetes on Lp(a) association with eGFR decline in the Penn Diabetes Heart Study (24). It is known that the of role Lp (a) in affecting CVD risk among diabetic patients is complicated by the presence of various metabolic abnormalities and a clear role of Lp(a) in diabetic patients is yet to be demonstrated (26).

Atherogenic index of plasma was found to be correlated with cardiovascular risk, lipoprotein particle size, insulin resistance and metabolic syndrome (27-29). The study of Lee et al. (30) showed the significant association of the highest and the lowest AIP groups with increased risk of all-cause mortality, showing a U-shaped association. Data regarding association of AIP and decline in eGFR are scarce especially in predialysis chronic kidney disease patients. The study of Adejumo et al. (31) tested the role of AIP across CKD stages in Nigeria and found significant increase in AIP in the CKD patients with renal function decline emphasizing the need to test the atherogenic risk of CKD patients by using lipid ratio such as AIP instead of evaluating each component separately. It is similar to the present study where we found that elevated AIP along with age and APOE predicted the eGFR less than 60 mL/min/1.73 m^2.

The major limitation of the study was the small sample size due to highly limited inclusion criteria, so low specificity and sensitivity of HDLc, APOE, and AIP for differentiation of patients with eGFR less than 60 mL/min/1.73 m^2 should be elucidated on a larger study group and combined with other parameters to test their possible clinical application.

In conclusion, the study has revealed that changes in parameters such as HDLc, APOE and AIP are associated with CKD but further elucidation is needed. The results of our study also imply the need for the AIP calculation as routine laboratory work due to its role along with age and APOE in the prediction of renal function decline. In addition, the results stressed the role of atherogenic index of plasma as the important parameter that should be used for prediction but also in monitoring of patients with mild and moderate eGFR reduction. Methods of patient selection and assessing of eGFR should be taken into consideration when the association of dyslipidaemia and renal function decline are investigated.

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