Total and LDL Cholesterol are Associated with Glomerular Filtration Rate in Normoalbuminuric Type 1 Diabetic Patients

Tomislav Bulum[1], Branko Kolarić[2,3], Ingrid Prkačin[4] and Lea Duvnjak[1]

[1] University of Zagreb, University Hospital Merkur, »Vuk Vrhovac« Clinic for Diabetes, Endocrinology and Metabolic Diseases, School of Medicine, Zagreb, Croatia
[2] University of Rijeka, School of Medicine, Rijeka, Croatia
[3] Zagreb County Institute of Public Health, Zagreb, Croatia
[4] University of Zagreb, University Hospital Merkur, School of Medicine, Department of Internal medicine, Zagreb, Croatia

ABSTRACT

Studies have generally suggested a positive association between dyslipidemia and chronic kidney disease, but sparse data are available on the relation of lipids and glomerular filtration rate in patients with normal renal function. We investigated the associations of serum lipids, including total, LDL, HDL, VLDL cholesterol, and triglyceride levels with estimated glomerular filtration rate (eGFR) in type 1 diabetic patients. Study included 313 normoalbuminuric type 1 diabetic patients with normal or mild decrease (eGFR > 60 mL/min per 1.73 m^2) renal function and before any interventions with statins, ACE inhibitors or angiotensin II receptor blockers. eGFR was significantly associated with total, LDL, and HDL cholesterol (r= –0.21, –0.18, and –0.17, respectively, for all p <0.05). Stratifying serum lipids for degree of eGFR, levels of total, LDL, and HDL cholesterol were inversely related to eGFR, but trends were significant only for total (5.1 vs 5.0 and 4.6 mmol/L) and LDL cholesterol (2.9 vs 2.8 and 2.4 mmol/L). We have detected an association between eGFR and lipid abnormalities in type 1 diabetes in early stages. The study was conducted in patients with no therapeutic intervention. This may suggest that lipid abnormalities may play a role in the pathogenesis of renal impairment in type 1 diabetic patients.

***Key words**: type 1 diabetes, serum lipids, renal function, glomerular filtration rate*

Introduction

Patients with type 1 diabetes have a 20–50% probability of developing end-stage renal disease[1], and identification of the determinants of the onset of early diabetic nephropathy is essential for reducing the morbidity and mortality associated with diabetes. In type 1 diabetic patients many studies have identified poor glycemic control as a most important risk factor for progression of diabetic kidney disease[2–4]. In addition, other important factors implicated in the development of nephropathy include duration of diabetes, smoking and hypertension[2,5,6]. Dyslipidemia has also been associated with the development and progression of nephropathy, and with mesangial, tubulointerstitial, and glomerular changes in the kidney[7–9]. Studies have suggested a positive association between dyslipidemia and advanced chronic kidney failure, but the relation between these markers and normal or mild renal dysfunction has not been well investigated. Moreover, it was postulated that lipids mainly act as late-stage accelerators or precipitators of nephropathy rather than underlying etiologic factor in type 1 diabetes[10].

In type 1 diabetic patients, although mortality from cardiovascular disease is three- to sixfold that of the general population[11], total, low density lipoprotein (LDL) cholesterol and triglyceride levels are usually within the normal range, and high density lipoprotein (HDL) cholesterol levels are also normal or even elevated[12,13]. However, multiple lipid abnormalities are present in early stages of diabetic nephropathy in type 1 diabetic pa-

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tients, even in state of normal or elevated glomerular filtration rate (GFR)[14,15]. In a number of studies, an increase in total and LDL cholesterol levels has been found to be a risk factor for nephropathy in type 1 diabetes[2,7,8,16–18]. Moreover, it was found that in those subjects with total cholesterol over 7 mmol/L the rate of decline in GFR was at least three times higher than in those with a level below 7 mmol/L[19]. In addition, in patients with diabetic nephropathy the diameter of LDL particles has been reported to be smaller as compared to diabetic patients without nephropathy[20].

Little is known about the relationship between lipids and change in renal function among individuals with normal renal function, because most studies have focused on the progression of established renal disease. The objective of this study, therefore, was to evaluate the associations of serum lipids, including total, LDL, HDL, VLDL cholesterol and triglyceride levels with estimated GFR (eGFR) in normoalbuminuric type 1 diabetic patients with eGFR > 60 mL min^{-1} 1.73 m^{-2}.

Subjects, Materials And Methods

This study included 313 euthyroid patients with diabetes mellitus type 1. Type 1 diabetes was defined as an onset of diabetes before the age of 35 years, positive autoantibodies and permanent insulin treatment initiated within 1 year of diagnosis. The study included patients following characteristics: age of 18–65 years, minimum duration of type 1 diabetes of 1 year, no medical history of cardiovascular diseases or electrocardiogram (ECG) evidence of ischemic heart disease, absence of any systemic disease, and absence of any infections in the previous month. Patients with chronic renal disease or other chronic diseases likely to affect renal function were excluded. Patients were excluded from the study if they had taken any of the following: lipid-lowering therapy, antihypertensive therapy including ACE inhibitor or angiotensin II receptor blockers, medications that might affect glucose metabolism such as glucocorticoids as well as patients taking oral glucose-lowering medication. Acute and chronic inflammation was excluded on the basis of medical history, physical examination, and routine laboratory tests, including measurement of temperature and urinalysis.

All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed on all study subjects. Waist to hip ratio was calculated from the waist circumference (measured on bare skin as the narrowest circumference between the 10th rib and the iliac crest with tailor meter) and hip circumference (at the widest point of the gluteal muscles) and expressed in centimeters. Weight was measured by the physician using a balanced-beam scale with light clothing without shoes and expressed in kilograms (kg). Height was measured using a wall mounted stadiometer and expressed in centimeters (cm). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 minutes and expressed in mmHg. UAE was measured from at least two 24-h urine samples and determined as the mean of 24-h urine collections. Patients performed collections on two consecutive days to minimize variability. Normoalbuminuria was defined as a UAE <30 mg/24 h. Those with microalbuminuria (UAE ≥30<300 mg/24 h) and macroalbuminuria (UAE ≥300 mg/24 h) were excluded from the study. Serum creatinine was measured in fasting blood sample. From 2011 creatinine was measured by an enzymatic method that produced values traceable to the isotope dilution mass spectrometry (IDMS) values. We calibrated creatinine results generated before 2011 to the IDMS-traceable values obtained with the enzymatic method. Data on serum creatinine levels, age, sex and race were used to calculate the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and Modification of Diet in Renal Disease formula (MDRD)[21]. Renal function was further estimated using the Cockcroft-Gault formula for creatinine clearance adjusted for body surface area, which has been shown to be as accurate as creatinine clearance measured by 24 hour urine collections in diabetics[22]. Creatinine clearance >90 mL/min per 1.73 m^2 was considered normal, 60–90 mL/min per 1.73 m^2 was considered a mild decrease, and those with creatinine clearance <60 mL/min per 1.73 m^2, who has moderate to severe renal impairment, were excluded from the study[23].

Fasting venous blood samples were collected in the morning between 08:00 and 09:30 hours after an overnight fast for the determination of HbA1c, total, LDL, HDL, VLDL cholesterol, triglycerides and fasting glucose. Microalbumin and HbA1c was measured spectrophotometrically by turbidimetric immuno-inhibition (Olympus AU600, Beckman-Coulter, USA). Results of HbA1c (%) are expressed in the DCCT-equivalent. Glucose, cholesterol and triglycerides in serum were measured by an enzymatic colorimetric method, after precipitation with polyethylene glycol on an automatic spectrophotometer (Olympus AU600, Beckman-Coulter, USA). Complete blood count was determined on an automatic blood counter (Advia 120, Siemens Diagnostic Solutions, USA).

The study protocol complies with the Declaration of Helsinki as well as with local institutional guidelines, and was approved by the local ethnics committees.

Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Correlations between parameters of renal function with anthropometric and metabolic variables were determined using Spearman rho test. To investigate the relation between serum lipids with GFR data were also stratified in different groups of GFR. Kruskal-Wallis test was used for calculating the significance of the trend for each variable among the different groups. Multiple logistic regression analysis was used to assess associations of serum lipids with risk of

lower eGFR. Level of statistical significance was chosen to $\alpha=0.05$. Statistical analysis was performed by statistical package STATA/IC ver.11.1.

Results

The characteristics of the study subjects are listed in Table 1. The average age was approximately 34 years, most were not overweight and 51% of subjects were female. Mean/median values of BMI, waist to hip ratio (WHR), systolic and diastolic blood pressure, fasting glucose, HDL cholesterol, and triglycerides were within the normal range for patients with diabetes with slightly elevated levels of HbA1c, total and LDL cholesterol. The majority of patients had high HDL cholesterol (for men ≥1.0 mmol/L, 96% of patients; for women ≥1.3 mmol/L, 95% of patients). The mean GFR estimated by the CKD-EPI was 106 mL min^{-1} 1.73 m^{-2}. The mean estimated GFR of 96 mL min^{-1} 1.73 m^{-2} estimated using MDRD formula and Cockcroft-Gault formula was significantly lower than when estimated using the CKD-EPI formula.

TABLE 1
CLINICAL AND METABOLIC CHARACTERISTICS OF ALL PATIENTS

Variable	mean ± SD	Interquartile range
Age (years)	35±10	18–65
Duration of diabetes (years)	13±9	1–42
Body mass index (kg/m^2)	24±3	15–37
Waist to hip ratio	0.81±0.07	0.6–1.0
Fasting glucose (mmol/L)	5.7±2.0	2.7–10.2
HbA1c (%)	7.43±1.63	4.5–14.2
Daily insulin dose (IU/d)	42±14	8–96
Systolic blood pressure (mmHg)	122±14	79–180
Diastolic blood pressure (mmHg)	78±9	50–100
Total cholesterol (mmol/L)	5.0±0.8	2.5–7.8
LDL cholesterol (mmol/L)	2.8±0.7	0.6–4.9
HDL cholesterol (mmol/L)	1.7±0.4	0.7–3.0
VLDL cholesterol (mmol/L)	0.48±0.29	0.16–1.9
Triglycerides (mmol/L)	1.07±0.6	0.3–4.1
Serum creatinine (μmol/L)	71±14	39–138
CKD-EPI (mL min^{-1} 1.73 m^{-2})	106±16	60–143
MDRD (mL min^{-1} 1.73 m^{-2})	96±20	52–171
Cockcroft-Gault (mL min^{-1} 1.73 m^{-2})	96±24	47–211
Urinary albumin excretion (mg/24 h)	12.5±7.2	1.7–29.8

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, MDRD – Modification of Diet in Renal Disease.

Associations of eGFR with anthropometric and metabolic variables are presented in Table 2. GFR estimated using the CKD-EPI formula was significantly associated with duration of diabetes, fasting glucose, daily insulin dose, HbA1c, total, LDL, and HDL cholesterol, with duration of diabetes, total and HDL cholesterol showing the strongest correlation (r= –0.29, –0.21, and –0.21, respectively, all $p<0.05$). Similar correlation results were found between anthropometric and metabolic variables and GFR estimated using the MDRD formula. GFR estimated using the Cockcroft-Gault formula was significantly correlated with even 10 parameters (duration of diabetes, BMI, WHR, fasting glucose, daily insulin dose, total, LDL, HDL, VLDL cholesterol and diastolic blood pressure) with BMI and WHR showing the strongest correlation (r=0.34, and –0.30, all $p<0.05$).

TABLE 2
SPEARMAN CORRELATION ANALYSIS OF ASSOCIATIONS OF EGFR WITH METABOLIC AND ANTHROPOMETRIC VARIABLES

Variable	CKD-EPI	MDRD	Cockcroft--Gault
Age	–0.60*	–0.42*	–0.52*
Duration of diabetes	–0.29*	–0.21*	–0.27*
Body mass index	–0.10	–0.13*	0.34*
Waist to hip ratio	0.01	0.01	0.30*
Fasting glucose	–0.13*	–0.12*	–0.11*
HbA1c	0.15*	0.18*	0.10
Daily insulin dose	0.13*	0.11*	0.25*
Total cholesterol	–0.21*	–0.18*	–0.17*
LDL cholesterol	–0.18*	–0.15*	–0.12*
HDL cholesterol	–0.17*	–0.16*	–0.28*
VLDL cholesterol	0.06	0.06	0.15*
Triglycerides	0.06	0.06	0.15*
Systolic blood pressure	–0.08	–0.07	0.07
Diastolic blood pressure	–0.01	–0.01	0.12*

* $p<0.05$, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, MDRD – Modification of Diet in Renal Disease.

Relationship between eGFR among patients with a mild decrease of renal function, normal renal function and hyperfiltrating patients are presented in Table 3. Stratifying serum lipids for degree of GFR, estimated using the CKD-EPI formula, levels of total, LDL, and HDL cholesterol were inversely related to eGFR, but trends were significant only for total and LDL cholesterol. In addition, those patients with eGFR ≤ 90 mL/min/1.73 m^2 were older, had longer duration of diabetes and higher daily insulin dose, but lower HbA1c.

In logistic regression analysis, higher total, LDL and HDL cholesterol was significantly associated with risk of lower eGFR estimated with CKD-EPI formula (OR= 0.49–0.65, p=0.001) (Table 4, Model A). However, after adjustment for age, sex and duration of diabetes serum lipids were not associated with eGFR in our normoalbuminuric subjects (Table 4, Model B).

Discussion

Serum lipids may play a significant independent role in the development of diabetic nephropathy and decline in renal function and progression of albuminuria[2,7–9,

TABLE 3
LEVELS OF SERUM LIPIDS DEPENDING ON LEVEL OF EGFR (ESTIMATED WITH THE CKD-EPI FORMULA)

Variable	eGFR 60–89	eGFR 90–120 mL min^{-1} 1.73 m^{-2}	eGFR ≥120	P
N	55/313	220/313	38/313	
Sex (m/f)	19/36	116/104	17/21	0.04
Age (years)	45 (19–60)	35 (19–65)	22 (18–34)	<0.001
Duration of diabetes (years)	16 (2–42)	12 (1–42)	7 (1–25)	<0.001
Body mass index (kg/m^2)	24 (17–33)	24 (17–37)	24 (15–34)	0.4
Waist to hip ratio	0.81±0.07	0.81±0.06	0.81±0.06	0.7
HbA1c (%)	7.1±1.2	7.3±1.6	8.4±1.9	0.002
Fasting glucosae (mmol/L)	5.5 (2.4–12.6)	5.4 (2.2–12.5)	4.7 (2.1–9.1)	0.1
Daily insulin dose (IU/d)	47±15	42±14	39±11	0.02
Systolic blood pressure (mmHg)	120 (79–170)	120 (90–180)	120 (90–140)	0.3
Diastolic blood pressure (mmHg)	80 (65–110)	80 (60–110)	80 (50–90)	0.7
Total cholesterol (mmol/L)	5.1±0.7	5.0±0.9	4.6±0.7	0.02
LDL cholesterol (mmol/L)	2.9±0.7	2.8±0.7	2.4±0.7	0.006
HDL cholesterol (mmol/L)	1.8±0.4	1.6±0.3	1.6±0.3	0.1
VLDL cholesterol (mmol/L)	0.41 (0.2–1.15)	0.40 (0.16–1.9)	0.43 (0.2–1.89)	0.3
Triglycerides (mmol/L)	0.91 (0.4–2.5)	0.8 (0.3–4.1)	0.95 (0.4–4.1)	0.3

TABLE 4
MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF SERUM LIPIDS WITH DEVELOPMENT OF LOWER EGFR (ESTIMATED WITH THE CKD-EPI FORMULA)

Independent variable	Model A	Model B
Total cholesterol	0.65 (0.50–0.84)*	1.01 (0.73–1.38)
LDL cholesterol	0.60 (0.44–0.82)*	0.93 (0.64–1.35)
HDL cholesterol	0.49 (0.28–0.87)*	0.96 (0.46–1.99)
VLDL cholesterol	1.53 (0.71–3.29)	1.52 (0.60–3.83)
Triglycerides	1.20 (0.85–1.70)	1.20 (0.79–1.82)

Data are OR (95% CI) from separate models. Model A crude; model B adjusted for age, sex and duration of diabetes.
* $p<0.05$.

[14–18,24,25]. In a number of studies, an increase in total and LDL cholesterol levels has been found to be a risk factor for nephropathy in type 1 diabetes[2,7,8,16–18]. In this cross-sectional study of 313 normoalbuminuric type 1 diabetic patients with normal renal function we demonstrated that lipid profiles of patients with type 1 diabetes are not only closely related to albuminuria, but also to estimated GFR.

It has been argued that in type 1 diabetes increased HbA1c as a marker of chronic hyperglycemia is the most important risk factor for progression of diabetic kidney disease[2–4,26]. Hyperglycemia also leads to glycation of lipids and lipoproteins in diabetic patients that may slow down the catabolism of atherogenic LDL-cholesterol[27]. However, mean HbA1c levels (7.4%) in our subjects was significantly lower than in most previous studies and our subjects with mild decrease of renal function and higher LDL cholesterol had, surprisingly, significantly lower levels of HbA1c compared to subjects with higher eGFR.

Hyperlipidemia contributes not only to cardiovascular disease but also to renal disease progression[28]. In both type 1 and type 2 diabetes an unfavorable lipid profile is present at a very early stage of albuminuria, even when GFR is normal or elevated[29,30]. It was also demonstrated that both total and LDL cholesterol measured at baseline were associated with significantly higher incidence of microalbuminuria, end stage renal disease as well as of cardiovascular events in patients with type 2 diabetes[18,31,32]. Our patients with estimated GFR 60–90 mL min^{-1} 1.73 m^{-2} display an atherogenic lipid profile with high total cholesterol and LDL cholesterol. Circulating lipoproteins play a direct role in the pathogenesis of glomerulosclerosis and tubulointerstitial changes[7–9,33]. Animal models suggest that dyslipidemia plays an important role not only in the progression of chronic renal disease but also in its development[34]. In addition, a decline in renal function has been reported to be associated with advanced glomerular lesions even in normoalbuminuric type 1 diabetic patients with reduced GFR[35]. Combined angiotensin-converting enzyme inhibitor and statin therapy limited glomerulosclerosis, tubular damage, and interstitial inflammation with a significant improvement in renal function[36,37]. Our study included patients before any interventions with statins, ACE inhibitors or angiotensin II receptor blockers that may allows purer physiological examination of the association between GFR and serum lipids because ACE-inhibitors can elevate serum creatinine and statins lower serum lipids. However, it should be stressed that associations between lipid abnormalities and renal function in our study is weak, and that associations were lost in multivariate analysis.

It is also possible that insulin resistance syndrome may underlie or mediate the association between lipids and a loss of renal function because insulin resistance in patients with type 1 diabetes underlies many of the alterations of diabetic nephropathy including serum lipids[38,39]. Our patients with mild decrease of renal function have higher daily insulin dose in contrast to subjects who had normal or elevated renal function suggesting that insulin resistance through associated dyslipidemia may play a role in the diabetic nephropathy.

The present study has a number of potential limitations. First, we did not measured GFR directly. However, there is no optimal non-invasive method to estimate early changes in renal function and radio-isotope clearance GFR measurements are impractical for this number of patients. The MDRD formula tends to overestimate the number of patients with impaired renal function[21], Cockcroft-Gault formula overestimates the actual renal function, while CKD-EPI formula has been shown to be accurate in determining renal function in diabetic patients with normal renal function[40]. Second, our study was cross-sectional, which limited our ability to infer a causal relation between serum lipids and risk of nephropathy. Third, our analyses were based on measurement of traditional lipoprotein markers. However, it is likely that in clinical practice the measurement of conventional lipoprotein parameters is sufficient to assess the risk of microvascular complications in type 1 diabetes, in contrast to additional parameters which make little predictive impact[16]. Fourth, our analyses were based on measurement of serum creatinine, eGFR and urinary albumin excretion on two consecutive days that may not reflect the relation over time. Prospective studies are needed to evaluate whether the observed lipid abnormalities play a role in the progression of renal function in type 1 diabetic patients.

In conclusion, we have detected an association between eGFR and lipid abnormalities in type 1 diabetes in early stages. The study was conducted in patients with no therapeutic intervention. This may suggest that lipid abnormalities may play a role in the pathogenesis of renal impairment in type 1 diabetic patients.

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T. Bulum

University of Zagreb, University Hospital Merkur, »Vuk Vrhovac« Clinic for Diabetes, Endocrinology and Metabolic Diseases, School of Medicine, Zagreb, Croatia
e-mail: tbulum@idb.hr

UKUPNI I LDL KOLESTEROL SU POVEZANI S GLOMERULARNOM FILTRACIJOM U NORMOALBUMINURIČNIH BOLESNIKA SA TIPOM 1 ŠEĆERNE BOLESTI

S A Ž E T A K

Mnoga istraživanja su potvrdila značaj dislipidemije u kroničnoj bubrežnoj bolesti, ali malo toga je poznato o utjecaju serumskih lipida na glomerularnu filtraciju u osoba sa normalnom bubrežnom funkcijom. Istraživali smo povezanost serumskih lipida (ukupnog, LDL, HDL, HDL2, HDL3, VLDL kolesterola i triglicerida) te glomerularne filtracije (GF) u bolesnika sa tipom 1 šećerne bolesti. Istraživanje je obuhvatilo 313 normoalbuminuričnih bolesnika sa tipom 1 šećerne bolesti s urednom ili blago sniženom bubrežnom funkcijom (GF >60 mL/min/ 1.73 m^2) i prije terapije statinima, ACE-inhibitorima ili blokatorima angiotenzinskih receptora. GF procijenjena CKD-EPI i MDRD formulom bila je statistički značajno povezana s ukupnim, LDL, HDL, HDL2, i HDL3 kolesterolom (r= –0.21, –0.18, –0.17, –0.21, i –0.14, za sve $p<0.05$). Nakon podjele bolesnika prema stupnju GF, razina ukupnog, LDL, HDL i HDL2 kolesterola je bila u negativnoj povezanosti s razinom GF, ali je statistički značajna povezanost dokazana samo za razinu ukupnog (5.1 prema 5.0 i 4.6 mmol/L) i LDL kolesterola (2.9 prema 2.8 i 2.4 mmol/L). Rezultati istraživanja ukazuju da je lipidni poremećaj prisutan već u stanju normalne bubrežne funkcije u normoalbuminuričnih bolesnika sa tipom 1 šećerne bolesti i da je viša razina ukupnog i LDL kolesterola povezana s pogoršanjem GF. Prospektivne studije će pokazati da li navedeni lipidni poremećaji doprinose progresiji bubrežne bolesti u bolesnika sa tipom 1 šećerne bolesti.