Increased Triglycerides and High Density Lipoprotein Ratio Associated with Progression of Chronic Kidney Disease in Patients with Type 2 Diabetes Mellitus

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Abstract

Dyslipidemia is a common occurrence in type 2 diabetes mellitus (T2DM) patients and plays the major role in accelerated risk of cardiovascular disease (CVD) and possible causes chronic kidney disease (CKD), the progression of which leads to end-stage renal disease. A total of 266 T2DM patients were categorized into 2 groups according to their TG/HDL-C ratio of ≥2.5 and <2.5. The comparison of the clinical characteristics in these 2 groups demonstrated that Glucose, HbA1c, total Cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) levels, TG/HDL-C ratio were significantly higher, while high density lipoprotein cholesterol (HDL-C) and estimated glomerular filtration rate (eGFR) were significantly lower in the group with TG/HDL-C ratio ≥2.5 ($p<0.05$). Multiple logistic regressions demonstrated elevated TG/HDL-C ratio associated with CKD and increased HbA1c. The ORs and 95 % CIs were 4.94 (2.45, 9.96), 2.29 (1.13, 4.65) after adjusting for their covariates. Elevated TG/HDL-C ratio was associated with CKD and HbA1c and may increase the rate of disease progression and predict decline in kidney function and structural damage in these T2DM patients.

Keywords: Type 2 Diabetes Mellitus; Estimated Glomerular Filtration Rate; Chronic Kidney Disease; Hypertriglyceridemia; Reduced High Density Lipoprotein Cholesterol

Introduction

Dyslipidemia is common in patients with type 2 diabetes mellitus (T2DM) and it plays the major role in the accelerated risk of cardiovascular disease (CVD) in those patients [1-3]. Elevated triglycerides (TG) reduced high density lipoprotein cholesterol (HDL-C) and small dense low density lipoprotein (LDL)-particles (independent of LDL-cholesterol (LDL-C)), elevated triglyceride-rich remnant lipoprotein (TGRLs), and hyperinsulinemia [1-3] are the major clinical characteristics of dyslipidemia in T2DM patients. Lower HDL-C level is associated with insulin resistance for mediated glucose disposal and compensation of hyperinsulinemia, with high levels of fasting glucose and insulin [4].

Chronic kidney disease (CKD) is defined as the insufficiency or reduction in the glomerular filtration rate (GFR) as well as the abnormalities of structure and/or function of the kidneys as evidenced by urinalysis, biopsy or imaging [5,6]. CKD is the one of the global public health concerns and the major risk factor of cardiovascular disease. CKD in T2DM patients

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contributes the morbidity, mortality and excessive health care [7]. Moreover, cardiovascular death in T2DM patients has been shown to be associated with the development of CKD and progression to end-stage renal disease (ESRD) [8-10]. CKD progression leads to ESRD that needs treatment with dialysis and causes accelerated morbidity and mortality in T2DM patients [11-13].

Dyslipidemia has been implicated as a possible cause of CKD [14,15]. Many researchers have demonstrated the association of moderate CKD with elevated levels of triglycerides (TG) and a decreased level of high density lipoprotein cholesterol (HDL-C) ratio [14-17]. Among others, our recent studies have also demonstrated that TG/HDL-C ratio was associated with insulin resistance [13,18-20]. The TG/HDL-C ratio was a better predictor of both cardiovascular events and the LDL particle size [18-20]. However, there is little knowledge about the association of TG/HDL-C ratio and CKD. In the present study, we aim to evaluate the association of TG/HDL-C with CKD in T2DM patients.

Materials and Methods

Subjects

A total of 266 T2DM patients were randomized from the Diabetes Care Clinic of Ladyao Hospital, Nakornsawan Province during December 2013 to July 2014. All T2DM patients had overt diabetes for more than 5 years. They were receiving regular treatment with glycemic lowering, lipid lowering and anti-hypertensive medication. The exclusion criteria were sustained heart failure, recent myocardial infarction, unstable angina, stroke, ESRD, acute or chronic infection, cancer, hepatic disease and acute illness. They had good history of control over their blood glucose levels at time of recruitment. All participants gave written informed consent. Our study protocol was approved by the Ethic committees of Naresuan University.

Physical and Biochemical Examination

Blood pressure (BP) measurement, height, weight and waist circumference (WC) were measured and body mass index (BMI) was calculated for all T2DM patients. WC was measured at the midpoint between the rib cage and the top of lateral border of iliac crest at minimum respiration. BP was measured after the participants had been seated and rested for 5 minutes and the mean value of at least two measurements was used. Venous blood samples were collected in the seated position from all participants without stasis after 8–12 hour fast. Blood specimens were processed and assayed in the clinical laboratory of Ladyao Hospital, Nakornsawan Province, Thailand. Plasma glucose (Glu), blood urea

nitrogen (BUN), creatinine (CT), total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C) and hemoglobin A1c (HbA1c) were measured by with standard enzymatic method (Thermo Scientific, KONELAB Prime 60i, Finland). TG/HDL-C ratio was calculated by TG divided by HDL-C concentrations (expressed as mg/dl).

Estimated Glomerular Filtration Rate (Egfr)

Estimated glomerular filtration rate was calculated by the Cockroft–Gault formula which incorporates age, body weight, and sex [21]. The formula is: eGFR = [(140 - age) * weight (kg) *constant]/[serum creatinine (μmol/L)] where 1.23 and 1.04 are constants for men and women, respectively. Five eGFR stages were used: Stage I was normal eGFR ($\geq$90ml/min/1.73 m2); Stage II was mild eGFR (60-89 mL/min/1.73 m2); Stage III was moderate eGFR (30-59 ml/min/1.73 m2); Stage IV was severe eGFR (<30 ml/min/ 1.73 m2), and Stage V was end-stage renal disease: eGFR (<15 ml/min/1.73 m2). An eGFR lower than 60 ml/min/1.73 m2 (moderately eGFR) was defined as chronic kidney disease (CKD) [12].

Statistical Analysis

All data are presented as median and inter quartile range for non-normally distributed data and tested with Shapiro-Wilk test. These T2DM patients were stratified to 2 groups according to TG/HDL-C ratio $\geq$2.5 and <2.5 as in our recent study [17]. We compared all clinical characteristics of these 2 groups of T2DM patients by using Mann-Whitney U-test. Bivariate correlation of these clinical variables was analyzed by using Spearman rank correlation test. Clinical variables that correlated with TG/HDL-C ratio in these T2DM patients were tested as independent variables in multivariate analysis. Odds ratios (OR) from logistic regression analyses were used to estimate the risk of CKD. Elevated TG/HDL-C ratio was associated with CKD and elevated HbA1c after adjusting with their covariate. The results of all statistical analyses were evaluated for statistical significance using p-value <0.05 and the 95% confidence intervals (CI). All analysis was performed using the SPSS computer program version 13.0 (SPSS, Chicago, IL).

Results

The comparison results of these two groups demonstrated that T2DM patients with higher TG/HDL-C ratio group was significantly higher Glu, HbA1c, TC, TG, LDL-C levels and lower HDL-C, eGFR levels (p<0.05) as shown in Table 1. The medication of glycemic lowering and lipid lowering are also listed in Table 1. The bivariate correlation of TG/HDL-C ratio with eGFR

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(r= -0.496, p<0.001), HbA1c (r= 0.138, p=0.024), Glu (r= 0.194, p=0.002), TC (r= 0.178, p=0.004), and SystBP (r= 0.201, p=0.014), while the bivariate correlation of the other variables are shown in Table 2. By multiple logistic regression analysis, elevated TG/HDL-C ratio was associated with risk of CKD, OR 4.21 (95 % CI 2.13-8.33) and elevated HbA1c, OR 2.47 (95 % CI 1.23-4.95) after adjusting for covariates in these T2DM patients, as demonstrated in Table 3.

Variables	TG/HDL-C ≥ 2.4 (n=193)	TG/HDL-C <2.4 (n=73)	p-value
Age (yrs)	63.0* (55.0-72.0)*	63.0 (51.5-71.0)	0.370
Glu (mmol/l)	7.12 (6.07-8.91)	6.60 (5.39-7.92)	0.013
HbA1c	54.70 (49.15-61.72)	51.74 (45.83-60.24)	0.022
BUN (mmol/l)	4.99 (3.92-6.78)	4.99 (3.92-6.78)	0.966
CT (μmol/l)	76.91 (60.11-99.45)	73.37 (56.58-97.59)	0.167
TC (mmol/l)	4.64 (4.02-5.39)	4.26 (3.65-4.82)	0.003
TG (mmol/l)	1.93 (1.54-2.64)	1.01 (0.83-1.19)	<0.001
HDL-C (mmol/l)	1.01 (0.88-1.22)	1.53 (1.32-1.83)	<0.001
LDL-C (mmol/l)	2.56 (2.09-3.28)	2.19 (1.69-2.88)	0.002
TG/HDL-C ratio	4.10 (3.15-6.60)	1.60 (1.10-2.00)	<0.001
eGFR (ml/min/1.73 m²)	59.0 (50.24-82.27)	83.80 (62.94-98.39)	<0.001
Metformin	138(71.5%)	50(68.5%)	
Triglycerides level (≥1.70 mmol/l)	130(67.4%)	-	
Triglycerides level (<1.70 mmol/l)	63(32.6%)	73(100%)	
HDL-C levels (≤1.04 mmol/l men, ≤1.30 mmol/l women)	143(74.1%)	14(19.2%)	
HDL-C levels (>1.04 mmol/l men, >1.30 mmol/l women)	50(25.9%)	59(80.8%)	
Glipizide	90(46.6%)	35(47.9%)	
Pioglitazone	19(9.8%)	6(8.2%)	
Glibencamide	6(3.1%)	-	
Mixtard	7(3.6%)	2(2.7%)	
Simvastratin	123(63.7%)	35(47.9%)	
Gemfibrozil	36(18.7%)	4(5.5%)	
Atovastatin	3(1.6%)	1(1.4%)	

Table 1: Comparison of the clinical characteristics of both TG/HDL-C ratio ≥2.4 and <2.4 groups of type 2 diabetes mellitus patients by using Mann-Whitney U-test.

Correlation between parameters		Correlation coefficient		Correlation between parameters		Correlation coefficient	
		r	p- value			r	p- value
Age	BUN	-0.498	<0.001	TG	HDL-C	-0.460	<0.001
	CT	-0.347	<0.001		LDL-C	0.134	0.032
	eGFR	-0.222	0.006		WC	0.212	0.018
Glu	CT	-0.199	0.001	HDL-C	HbA1c	-0.144	0.018
	TG	0.177	0.004	TG/HDL-C	eGFR	-0.496	<0.001
	HDL-C	-0.185	0.003		Glu	0.194	0.002
	LDL-C	0.130	0.037		HbA1c	0.138	0.024
	HbA1c	0.510	<0.001		SystBP	0.201	0.014
	WC	0.241	0.004		HDL-C	-0.786	<0.001
BUN	CT	0.622	<0.001		TG	0.907	<0.001
	eGFR	-0.462	<0.001		TC	0.178	0.004
	SystBP	0.210	0.012	eGFR	TC	-0.498	<0.001
CT	eGFR	-0.643	<0.001		TG	-0.347	<0.001
	HDL-C	-0.136	0.027		HDL-C	-0.222	0.006
TC	TG	0.322	<0.001		SystBP	0.224	0.008
	HDL-C	0.127	0.038				
	LDL-C	0.901	<0.001				
	DiastBP	0.204	0.022				

Table 2: Bivariate correlation of the variables in these type 2 diabetes patients.

Variables	Elevated TG/HDL-C ratio in T2DM patients		
	OR	95% CI	*P-value*
CKD	4.21	2.13-8.33	<0.001
Elevated HbA1c	2.47	1.23-4.95	0.011
Glucose levels	1.01	0.98-1.01	0.182
WC	0.99	0.97-1.03	0.949
SystBP	0.99	0.97-1.02	0.514
DiastBP	0.99	0.97-1.03	0.957
Age	1.01	0.98-1.04	0.588
Sex	0.76	0.39-1.47	0.418

Table 3: Association of elevated TG/HDL-C ratio with CKD and HbA1c after adjusting for their covariates in these T2DM patients.

Discussion

Our present study demonstrated that elevated TG/HDL ratio group had lower HDL-C, eGFR levels and higher Glu, HbA1c, TC, TG and LDL-C. We also demonstrated the association between elevated TG/HDL-C ratio with CKD and elevated HbA1c after adjusting for their covariates. Dyslipidemia in T2DM patients is common, and is the major risk factor in cardiovascular disease (CVD). It also has a role in the pathogenisis and progression of diabetic nephropathy (DN). Many research studies demonstrated that the large amount of the excessive lipids and lipoproteins worsens diabetes-related microvascular diseases with complications including glomerular injury, tubulointerstitial fibrosis and accelerated progression of DN [22,23]. Patients with T2DM and CKD also have higher VLDL, LDL, IDL and TG but lower HDL levels than levels in patients without diabetes [3,23,24]. The LDL particles in T2DM patients tend to be smaller, denser and more atherogenic [19,25]. TG/HDL-C ratio was used as the estimation of insulin resistance and the indicator of LDL particle size in T2DM patients [17,19]. Insulin resistance and the disorder of insulin action in lipid and lipoprotein metabolism are the major mechanisms changed in lipid and lipoprotein profile in T2DM and DN patients. The enhancing of lipolysis results in increased free fatty acids and VLDL synthesis concomitant with the defection in LPL activity leading to prolong the life span of chylomicron, VLDL and TG elevation in circulation, increased TG transfer with cholesterol esters in lipoproteins resulting in triglyceride-rich LDL, HDL and reduction of LPL to hepatic lipase ratio to cause the acceleration of HDL breakdown in circulation [26]. Further, all the lipoprotein abnormalities and triglyceride-rich lipoproteins (TGRLs) are involved in the increasing albuminuria, declining renal function and development of CKD [26-28], concomitant with increased total cholesterol and LDL levels which are associated with the progression of nephropathy [27]. Nelson et al. demonstrated the possible mechanism of hyperlipidemia-induced renal injury by TGF-β stimulation, which promotes ROS production in kidneys to cause glomeruli and glomerular glycocalyx damage [28].

The most interesting results of elevated TG/HDL-C ratio in the present study come from the decreased HDL-C levels. Speer et al. demonstrated that HDL in CKD patients becomes dysfunction and loss the vasoprotective and anti-inflammatory properties frequency caused endothelial dysfunction [29]. The endothelial dysfunction has been associated with increased risk of CVD and is part of the pathophysiologies of atherosclerosis (inflammation), hypertension, and diabetes. Lower HDL-cholesterol levels in type 1 diabetes patients put them at risk of renal injury [28]. Thus, lower HDL-C levels are associated with the increased risk of diabetic CKD.

Fasting plasma glucose levels of these T2DM patients demonstrated slightly good glycemic control levels but they had higher HbA1c levels; these may result from postprandial hyperglycemia. Postprandial hyperglycemia and hyperlipdemia have been implicated to increase risk of CVD in T2DM patients [30,31]. In addition, T2DM patients may have the postprandial hyperglycaemia and hyperlipdemia, as implied by the results showing increased glucose, VLDL and chylomicron remnants levels 2 hours after a meal [26,31]. Postprandial hyperglycemia and hyperlipdemia can increase oxidative stress and consequently trigger the release of a variety of inflammatory cytokines that are associated with endothelial dysfunction and increased risk of diabetic CKD [31,32]. Recent study demonstrates that increased oxidative stress and inflammation was the major underling mechanism in the progression and decline of renal function and structural damage to kidneys in T2DM patients [33].

Management of hyperglycemia has been focused on the lowering of glycosylated hemoglobin (HbA1c) levels, as the recommendation of the International Diabetes Federation and the American College of Endocrinology the HbA1c values is <48 mmol/mol (<6.5%) in T2DM patients. Large outcome trials study suggested that the >48 mmol/mol (>6.5%) HbA1c was the predictor of the diabetes complications [34]. T2DM patients in the present study demonstrated the HbA1c levels >48 mmol/mol (>6.5%), perhaps indicating prevalence of postprandial hyperglycemia.

Many research studies demonstrated that diet management and exercise strategies can improve postprandial hyperglycemia and hyperlipidemia, inflammation, and endothelial function [35,36]. Pharmacologic management for postprandial dysmetabolism with statins (simvastatin is the HMG CoA reductase inhibitors drug) reduced LDL-C, TG and increased HDL-C and also exerts antioxidant activity [37,38]. This drug has demonstrated the inflammatory reduction. Ceriello, et al. demonstrated that atorvastatin can reduce the adverse effect of postprandial dysmetabolism in T2DM patients [38]. Conventional diabetic drugs such as sulfonylurea's and insulin can predominantly lower fasting glucose while metformin is effective in reducing both fasting and postprandial hyperglycemia. Acarbose, exenatide, incretin enhancers, and fast-acting insulin are the most effective drugs for lowering postprandial glucose [39]. Thus, all of these intervention regimens in these T2DM patients may need to revisit (or readjust or reconsider in treatment dose).

Conclusion

The evidence demonstrated that increased TG/HDL-C ratio associated with CKD, along with elevated HbA1c, may increase the progression of renal disease in these T2DM patients. The reduction of HDL-C levels may play the major role in the development of CKD and the progression of renal function and structural damage.

Acknowledgement

Conflict of Interest

The authors declare that they have no competing interests.

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