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Triglyceride–high-density lipoprotein cholesterol is associated with microvascular complications in type 2 diabetes mellitus

Giacomo Zoppini[a,*], *Carlo Negri*[a], *Vincenzo Stoico*[a], *Stefano Casati*[b], *Isabella Pichiri*[a], *Enzo Bonora*[a]

[a] *Department of Medicine, Section of Endocrinology and Metabolic Diseases, University of Verona, Verona, Italy*
[b] *Department of Neurological and Visual Sciences, Section of Ophthalmology, University of Verona, Verona, Italy*

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ABSTRACT

The purpose of this study was to evaluate whether a high triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio is associated with an increased incidence of retinopathy and chronic kidney disease (CKD) in type 2 diabetes mellitus. Individuals with type 2 diabetes mellitus (n = 979) with an estimated glomerular filtration rate greater than 60 mL/min and without retinopathy and cardiovascular disease at baseline were followed up for the incidence of diabetic retinopathy (diagnosed by retinography) and CKD (diagnosed by estimated glomerular filtration rate ≤60 mL/min/1.73 m^2). On follow-up (mean, 4.9 years), 217 (22.2% of total) subjects experienced CKD and/or diabetic-specific retinal lesions (microvascular complication). Of these, 111 subjects developed isolated retinopathy, 85 developed CKD alone, and 21 developed both complications. The TG/HDL-C ratio was positively associated with an increased risk of incident retinopathy and/or CKD (composite microvascular end point) independently of age, sex, body mass index, diabetes duration, hemoglobin A_{1c}, hypertension, smoking history, low-density lipoprotein cholesterol, albuminuria, and current use of hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs (multivariable-adjusted odds ratio, 2.15; 95% confidence intervals, 1.10-4.25; P = .04). These findings suggested that the TG/HDL-C ratio was associated with an increased incidence of microvascular complications in individuals with type 2 diabetes mellitus without prior cardiovascular disease, independently of several potential confounders.

1. Introduction

Retinopathy and chronic kidney disease (CKD) are major microvascular complications of type 2 diabetes mellitus and represent a challenge for health care systems [1,2]. In industrial societies, diabetic retinopathy is the first cause of blindness, accounting for approximately 15% of new cases of blindness; and the risk of blindness is about 25 to 30 times higher in people

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* *Corresponding author*. Tel.: +39 045 8123748; fax: +39 045 8027314.
E-mail address: giacomo.zoppini@univr.it (G. Zoppini).

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with type 2 diabetes mellitus than in the general population [1]. Diabetic nephropathy is one of the most frequent causes of end-stage renal disease, accounting for 30% to 50% of all new patients initiating renal replacement therapy [2].

It is known that treatment of diabetic retinopathy and nephropathy in their earlier stages is effective in slowing the progression toward blindness and end-stage renal disease [1,2]. Thus, the early identification of risk factors for retinopathy and nephropathy in the diabetic population is of major clinical importance. The role of chronic hyperglycemia and hypertension in the development and progression of microvascular complications of diabetes is well established [1,2]. Evidence is also accumulating to support the concept that plasma lipid abnormalities may be also involved in the pathogenesis of diabetic retinopathy and nephropathy [3-6], suggesting a potential benefit of lipid-lowering drugs in their prevention [7-11]. Interestingly, the EURODIAB IDDM Complications Study reported that elevated fasting triglycerides (TGs) and lower high-density lipoprotein cholesterol (HDL-C) levels were associated with autonomic neuropathy in patients with type 1 diabetes mellitus [12]. Taken together, the evidence seems to suggest a possible role of TG/HDL-C ratio as a predictor of microvascular complications.

Therefore, because no large prospective studies to date have specifically examined the prognostic role of TG/HDL-C ratio in predicting the risk of developing microvascular complications in type 2 diabetes mellitus, we assessed whether a higher TG/HDL-C ratio is associated with an increased incidence of diabetic retinopathy and CKD in a large cohort of individuals with type 2 diabetes mellitus.

2. Methods

The research was performed within the frame of the Verona Diabetes Study, an observational longitudinal study on chronic complications in patients with type 2 diabetes mellitus attending our Diabetes Clinic at the University Hospital of Verona [13].

The present analysis is based upon a sample of 979 white type 2 diabetes mellitus outpatients, who had a baseline assessment during the period 2000-2002 and were followed-up until September 30, 2007. Type 2 diabetes mellitus was established when diagnosis was made after the age of 35 years, irrespective of treatment, or when the disease was treated with diet or oral hypoglycemic agents, irrespective of age at diagnosis.

The 979 subjects represented approximately 30% of the entire sample of patients with type 2 diabetes mellitus (n = 3924) who regularly attended our outpatient clinic during the years 2000-2002 after excluding (1) subjects who had a history of malignancy or *cardiovascular disease* (CVD) defined as angina pectoris, myocardial infarction, revascularization procedures, or stroke (n = 688; 18.5% of total); (2) subjects who had any diabetic retinopathy (diagnosed by retinography) and/or *CKD* (defined as estimated glomerular filtration rate [eGFR] ≤60 mL/[min 1.73 m^2]) (n = 1498; 40.2%); and (3) those who had missing data for kidney function measures or retinography at baseline (n = 562; 15%). The 979 participants of the study were essentially similar to those who had missing data for kidney function measures or retinography (n = 562) in terms of demographic variables, glycemic control, and diabetes duration (data not shown).

The outcome measures of the study were the occurrence of *incident retinopathy* (defined as appearance of any diabetic retinopathy on retinography) and *CKD* (defined as occurrence of eGFR ≤60 mL/[min 1.73 m^2]). The local ethics committee approved the study protocol.

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters; height and weight were measured using a calibrated stadiometer and balance-beam scale. Blood pressure was measured with a standard mercury manometer. *Hypertension* was defined as a systolic blood pressure of at least 140 mm Hg and/or a diastolic blood pressure of at least 90 mm Hg or current use of any treatment with antihypertensive medications. Information on comorbidities, medication use, and smoking history was obtained by interviews during medical examinations. Venous blood was withdrawn in the morning after an overnight fast for standard biochemical workup. Serum creatinine, lipids, and other biochemical blood measurements were determined by automatic colorimetric methods (DAX 96, Bayer Diagnostics, Milan, Italy). Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula, except when TGs exceeded 4.55 mmol/L (n = 9). Hemoglobin A_{1c} was measured by a high-performance liquid chromatography analyzer (Bio-Rad Diamat, Milan, Italy), and the upper limit of normality was 5.8%. The inter- and intraassay coefficient of variation for all the biochemical determinations ranged between 5% and 8%. The *atherogenic index of plasma* was defined as the base 10 logarithm of the ratio of the concentration of TG to HDL-C, where each concentration was expressed in millimoles per liter [14].

At baseline and follow-up, glomerular filtration rate was estimated from the abbreviated Modification of Diet in Renal Disease formula [15] as follows: eGFR = 186.3 × (serum creatinine$^{-1.154}$) × (age$^{-0.203}$) × 1.212 (if black) × 0.742 (if female). The albumin to creatinine ratio was measured on an early morning spot urine sample by an immunonephelometric method. *Microalbuminuria* and *macroalbuminuria* were defined as albumin to creatinine ratio greater than 2.5 and greater than 30 mg/mmol for men and greater than 3.5 and greater than 30 mg/mmol for women, respectively [15].

Retinal fields were examined with indirect ophthalmoscopy after pupillary dilation, and then two-field stereoscopic retinal photographs (50°) were taken according to a standard protocol [16,17]. At baseline and follow-up, retinal photographs were examined and reviewed by a single trained ophthalmologist. Diabetic retinopathy was categorized as absent, nonproliferative, preproliferative, and proliferative [17].

2.1. Statistical analysis

Before analysis, skewed variables (TG/HDL-C ratio and TGs) were logarithmically transformed to improve normality. The 1-way analysis of variance and the χ^2 test with Yates correction for continuity (for categorical variables) were used to compare the baseline characteristics of participants stratified by tertiles of log TG/HDL-C ratio. A multivariable logistic regression analysis was used to evaluate the independent association of log TG/HDL-C ratio with the risk of *CKD* (defined as occurrence of eGFR ≤60 mL/[min 1.73 m^2]), *retinopathy*

(defined as occurrence of any degree of retinopathy), or both complications combined after adjustment for several baseline potential confounders. In separate logistic regression analyses, log TG/HDL-C ratio was included as either a continuous or categorical variable (ie, tertiles). Further independent variables (covariates) included in the fully adjusted regression model were sex (male vs female), age (years), BMI (kilograms per square meter), diabetes duration (years), hemoglobin A_{1c} (percentage), hypertension (yes/no), smoking history (yes/no), LDL-C (millimoles per liter), albuminuria (normo-, micro-, or macroalbuminuria), and medication use (ie, hypoglycemic, antihypertensive, lipid-lowering, and antiplatelet drugs; yes/no). These covariates were chosen as potential confounders based on their biological plausibility or statistical association with microvascular complications in univariate analysis. All covariates were simultaneously included in the multivariable logistic regression models (forced-entry model). We also formally tested for an interaction between log TG/HDL-C ratio and sex for each of the study outcomes by including their cross-product in the multivariable logistic regression models. The TG/HDL-C ratio × sex interaction term was not statistically significant ($P > .6$). Results of logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs), and statistical significance was evaluated by the likelihood ratio test. The ORs for continuous variables were computed for 1 SD change. Statistical analyses were performed with statistical package SPSS (Chicago, IL) 14.0. P values < .05 were considered statistically significant.

3. Results

Because of the exclusion criteria, none of the participants had any diabetic retinopathy (diagnosed by retinography) or an eGFR less than or equal to 60 mL/(min 1.73 m^2) at baseline. Most subjects had an eGFR of 60 to 89 mL/(min 1.73 m^2) (n = 737, 75.3% of total), whereas the remaining 242 subjects (24.7%) had an eGFR equal to or greater than 90 mL/(min 1.73 m^2). Approximately 15% (n = 155) of subjects had microalbuminuria, whereas 3% had macroalbuminuria. At baseline, mean TG/HDL-C ratio was 1.29 ± 1.0 (range, 0.06-15.6); and mean log TG/HDL-C ratio was 0.015 ± 0.29 (range, –1.22 to +1.19).

Baseline clinical characteristics of subjects stratified by tertiles of log TG/HDL-C ratio are listed in Table 1. Body mass index, diastolic blood pressure, hemoglobin A_{1c}, LDL-C, and proportion of patients treated with antihypertensive or lipid-lowering drugs significantly increased across tertiles of log TG/HDL-C ratio, whereas age and duration of diabetes decreased. The 3 groups did not significantly differ for sex, smoking status, kidney function markers (ie, eGFR and albuminuria), diabetes treatment, or use of antiplatelet drugs. During the follow-up (mean ± SD, 4.9 ± 1.0; range, 1-6 years), 217 (22.2%) subjects developed incident CKD and/or retinopathy. Of these, 111 subjects developed isolated retinopathy (101 had nonproliferative retinopathy and 10 had advanced retinopathy), 85 developed CKD alone (mean eGFR at follow-up, 51 ± 8.4 mL/[min 1.73 m^2]), and 21 developed both

Table 1 – Baseline clinical and biochemical characteristics of individuals with type 2 diabetes mellitus grouped according to tertiles of log TG/HDL-C ratio

(Log) TG/HDL-C ratio tertiles	I tertile (n = 332) <0.11	II tertile (n = 321) 0.11-0.14	III tertile (n = 326) >0.14	P values for trend
Sex (% male)	60.1	59.7	65.2	.26
Age (y)	68 ± 9	66 ± 10	64 ± 9	<.001
Diabetes duration (y)	15 ± 9	14 ± 9	12 ± 8	<.001
BMI (kg/m^2)	26.8 ± 4	28.3 ± 4	29.3 ± 5	<.001
Systolic blood pressure (mm Hg)	137 ± 18	138 ± 18	138 ± 19	.87
Diastolic blood pressure (mm Hg)	80 ± 8	81 ± 9	82 ± 9	.03
Hypertension (%)	81	84	86	.06
Current smokers (%)	22	25	25	.21
Fasting plasma glucose (mmol/L)	8.7 ± 2.6	8.9 ± 2.4	9.1 ± 2.6	.09
Hemoglobin A_{1c} (%)	7.2 ± 1.3	7.4 ± 1.4	7.5 ± 1.5	.04
Total cholesterol (mmol/L)	5.2 ± 0.9	5.4 ± 0.9	5.7 ± 1.0	<.001
LDL-C (mmol/L)	3.20 ± 0.8	3.45 ± 0.8	3.45 ± 0.9	<.001
HDL-C (mmol/L)	1.67 ± 0.4	1.35 ± 0.2	1.09 ± 0.2	<.001
TGs (mmol/L)	0.86 ± 0.3	1.41 ± 0.3	2.42 ± 0.8	<.001
eGFR (mL/[min 1.73 m^2])	81.4 ± 16	81.0 ± 14	80.7 ± 15	.62
Microalbuminuria (%)	14	20	16	.31
Macroalbuminuria (%)	3	3	4	.28
Treatments				
Diet only (%)	12	9	8	.17
Oral hypoglycemic drugs (%)	62	68	70	.13
Insulin treatment (%)	26	23	23	.21
Antihypertensive drugs (%)	67	74	75	<.05
Antiplatelet drugs (%)	43	40	43	.76
Lipid-lowering drugs (%)	39	50	58	<.001

Cohort size, n = 979. Data are expressed as means ± SD or percentages. *Hypertension* was defined as blood pressure ≥140/90 mm Hg or on antihypertensive treatment.

Table 2 – Baseline clinical and biochemical characteristics of individuals with type 2 diabetes mellitus grouped according to the development of microvascular complications

Microvascular complication	No (n = 762)	Yes (n = 217)	P values
Sex (% male)	60.9	63.1	.30
Age (y)	66 ± 10	68 ± 9	<.001
Diabetes duration (y)	13 ± 6	16 ± 9	.001
BMI (kg/m^2)	28.0 ± 4.5	28.7 ± 4.6	.06
Systolic blood pressure (mm Hg)	137.4 ± 18.0	140.7 ± 18.0	.03
Diastolic blood pressure (mm Hg)	80.7 ± 9.0	80.6 ± 9.0	.83
Hypertension (%)	82	89	.01
Current smokers (%)	23	26	.47
Fasting plasma glucose (mmol/L)	8.7 ± 2.5	9.4 ± 2.5	<.001
Hemoglobin A_{1c} (%)	7.2 ± 1.3	7.7 ± 1.4	<.001
Total cholesterol (mmol/L)	5.5 ± 1.0	5.3 ± 0.9	<.03
LDL-C (mmol/L)	3.4 ± 0.1	3.3 ± 0.8	.03
HDL-C (mmol/L)	1.4 ± 0.4	1.3 ± 0.3	.02
TGs (mmol/L)	1.5 ± 0.8	1.6 ± 0.8	.17
TG/HDL-C	1.2 ± 1.0	1.4 ± 1.0	.002
eGFR (mL/[min 1.73 m^2])	82.0 ± 14.4	77.4 ± 14.5	<.001
Microalbuminuria (%)	16	20	.23
Macroalbuminuria (%)	4	11	.003
Treatments			
Diet only (%)	11	5	.01
Oral hypoglycemic drugs (%)	85	89	.13
Insulin treatment (%)	19	39	<.001
Antihypertensive drugs (%)	71	77	.08
Antiplatelet drugs (%)	38	53	<.001
Lipid-lowering drugs (%)	48	49	.81

Continuous variables were age-adjusted. Cohort size, n = 979. Data are expressed as means ± SD or percentages. *Hypertension* was defined as blood pressure ≥140/90 mm Hg or on antihypertensive treatment.

microvascular complications (mean eGFR at follow-up, 50.6 ± 10 mL/[min 1.73 m^2]).

Table 2 lists the differences according to the presence of microvascular complications. Considering the large age difference between groups, the comparison of continuous variables was adjusted for age. Patients who developed microvascular complications had significantly longer duration of diabetes and higher systolic blood pressure, glycated hemoglobin, and fasting plasma glucose. The eGFR was significantly lower in patients with microvascular complications. The TG/HDL-C was significantly higher in subjects who developed complications. Patients with microvascular complications were more frequently hypertensive, more frequently treated with insulin or antiplatelet drugs, and more frequently macroalbuminuric.

Table 3 summarizes the results of multivariate logistic regression analyses. Higher log TG/HDL-C ratio was associated with a greater risk of incident CKD and/or retinopathy (combined end point), independently of age and sex (adjusted OR, 1.82; 95% CI, 1.04-3.16; $P \leq .001$). Additional adjustments for diabetes duration and hemoglobin A_{1c} did not modify the relation (adjusted OR, 1.90; 95% CI, 1.08-3.33; $P = .006$). Finally, further adjustments for BMI, hypertension, LDL-C, albuminuria, and medication use did not essentially change the results (adjusted, OR 2.15; 95% CI, 1.09-4.25; $P = .02$). Other independent predictors of incident CKD and/or retinopathy were older age, higher hemoglobin A_{1c}, and use of insulin therapy and antiplatelet drugs. Hypertension and macroalbuminuria also tended to be associated with a higher risk of microvascular complications.

When we repeated the above-mentioned multivariate regression analyses to assess separately the independent association of log TG/HDL-C ratio with the risk of developing isolated CKD or retinopathy alone, we found that higher TG/HDL-C ratio was significantly associated with an increased risk of both CKD and retinopathy after adjustment for age and sex. However, when we additionally adjusted for all other covariates, the association of log TG/HDL ratio with incident CKD remained statistically significant (adjusted OR, 4.65; 1.5-14.9; $P = .02$), whereas the association of log TG/HDL-C ratio with diabetic retinopathy did not (adjusted OR, 1.61; 0.9-3.6; $P = .20$; Table 4). Table 5 shows the contribution of the single parameter, TG or HDL-C, on the microvascular outcome. They showed an opposite effect, but only HDL-C significantly protected from the development of microvascular disease.

Results remained essentially unchanged even when log TG/HDL-C ratio was modeled as a categorical variable (ie, tertiles) in the fully adjusted regression model. In this analysis, the risk of incident CKD and/or retinopathy steadily increased across TG/HDL-C ratio tertiles (II tertile vs I tertile: adjusted OR, 1.71; 95% CI, 1.06-2.72; III tertile vs I tertile: adjusted OR, 1.89; 1.13-3.20; $P < .01$ for linear trend). We performed receiver operating characteristic analysis of the ratio of TG/HDL-C and the major microvascular risk factors: glycated hemoglobin, duration of diabetes, age, and systolic blood pressure. The ratio of TG/HDL-C did not add any further advantage in discriminating microvascular disease over the traditional risk factors.

No significant interaction was found in this analysis between TG/HDL-C ratio and LDL-C ($P = .51$ for the interaction term).

4. Discussion

A high TG/HDL-C ratio is associated with increased risk of death and major CVD events [18-20] and with insulin resistance and small dense LDL-C particles [14,21].

The main finding of the present study, which was carried out in a large outpatient cohort of individual with type 2 diabetes mellitus without prior CVD or other important comorbidities, is that a higher TG/HDL-C ratio confers an approximately 2-fold increased risk of developing microvascular complications (ie, incident nephropathy and/or retinopathy) during a mean follow-up of about 5 years. Notably, such increased risk is independent of several baseline confounding factors, such as age, sex, BMI, diabetes duration, hemoglobin A_{1c}, hypertension, smoking, LDL-C, kidney function markers, and medication use and is more pronounced in subjects with a plasma LDL-C concentration less than 100 mg/dL.

The prognostic role of atherogenic dyslipidemia in the development of microvascular complications in type 2 diabetes mellitus is still poorly defined because data are

Table 3 – Multivariable logistic regression analyses

	Age and sex adjusted	P	Age, sex, diabetes duration, and HbA_{1c} adjusted	P	Fully adjusted	P
(log) TG/HDL-C ratio	1.82 (1.04-3.16)	<.001	1.90 (1.08-3.33)	.006	2.15 (1.10-4.25)	.02
Age (y)	1.46 (1.23-1.74)	<.001	1.41 (1.17-1.70)	<.001	1.49 (1.18-1.87)	.001
Sex (men vs women)	1.09 (0.78-1.48)	.65	1.15 (0.83-1.58)	.41	1.04 (0.70-1.54)	.85
Diabetes duration (y)			1.20 (1.02-1.43)	.03	1.17 (0.95-1.44)	.15
Hemoglobin A_{1c} (%)			1.36 (1.17-1.61)	.001	1.23 (1.01-1.53)	.04
BMI (kg/m^2)					1.03 (0.99-1.08)	.13
Smoking history (yes/no)					1.11 (0.78-1.92)	.41
Hemoglobin A_{1c} (%)					1.23 (1.01-1.53)	.04
LDL-C (mmol/L)					0.90 (0.73-1.10)	.26
Hypertension (yes/no)					1.52 (0.97-2.70)	.08
Lipid-lowering drugs (yes/no)					0.88 (0.59-1.30)	.53
Antiplatelet drugs (yes/no)					1.48 (1.01-2.17)	.04
Oral hypoglycemic drugs (vs diet)					1.82 (0.69-4.78)	.23
Insulin treatment (vs diet)					4.31 (1.55-11.9)	.01
Microalbuminuria (yes/no)					1.03 (0.64-1.67)	.42
Macroalbuminuria (yes/no)					2.13 (0.98-4.60)	.05

Odds ratios (95% CIs) for the incidence of retinopathy and/or CKD (combined dependent variable) in individuals with type 2 diabetes mellitus. All covariates were simultaneously included in the multivariate regression models (forced-entry model). Cohort size, n = 979. The ORs for continuous variables were computed for 1 SD change. *Hypertension* was defined as blood pressure ≥140/90 mm Hg or on antihypertensive treatment. HbA_{1c} indicates hemoglobin A_{1c}.

quantitatively limited and inconclusive. Low levels of HDL-C were found to be independently associated with the development of microalbuminuria in 574 patients with type 2 diabetes mellitus followed up for approximately 8 years [22]. Low HDL-C levels have also been associated with a greater incidence of *CKD* (defined as occurrence of eGFR ≤60 mL/[min 1.73 m^2]), independently of classic risk factors, presence of diabetic retinopathy, and other potential confounders, in approximately 2000 patients with type 2 diabetes mellitus with normal or near-normal kidney function at baseline [23]. Other small observational studies in diabetic subjects confirmed a significant association between HDL-C or TGs and the risk of renal disease progression [7]. A significant association of elevated total cholesterol or other plasma lipid abnormalities with the appearance and progression of diabetic retinopathy was found in participants of some prospective studies [4-7]. In the Early Treatment Diabetic Retinopathy Study [6], neither HDL-C nor TGs were independently associated with a higher risk of diabetic retinopathy.

Two recent meta-analyses suggested that statin treatment has an uncertain renoprotective effect and that this effect appears to be more pronounced in participants with preexisting CVD but is not significant in participants with diabetic nephropathy [9,10]. Some small intervention

Table 4 – Multivariable logistic regression analyses

Dependent variable	Retinopathy	P	Nephropathy	P
(log) TG/HDL-C ratio	1.61 (0.90-3.60)	.20	4.65 (1.50-14.90)	.02
Age (y)	0.94 (0.71-1.25)	.68	4.22 (2.65-6.72)	<.001
Sex (men vs women)	1.38 (0.81-2.33)	.24	0.78 (0.40-1.49)	.45
Diabetes duration (y)	1.17 (0.89-1.54)	.25	1.14 (0.84-1.57)	.40
BMI (kg/m^2)	0.97 (0.76-1.25)	.81	1.26 (0.94-1.69)	.13
Smoking history (yes/no)	0.80 (0.41-1.59)	.53	1.02 (0.43-2.41)	.96
Hemoglobin A_{1c} (%)	1.22 (0.94-1.59)	.13	1.19 (0.84-1.68)	.33
LDL-C (mmol/L)	0.76 (0.60-1.00)	.51	1.02 (0.74-1.41)	.90
Hypertension (yes/no)	1.26 (0.62-2.56)	.52	1.91 (0.55-6.67)	.31
Lipid-lowering drugs (yes/no)	0.91 (0.55-1.51)	.72	1.22 (0.65-2.31)	.54
Antiplatelet drugs (yes/no)	1.40 (0.85-2.30)	.19	1.96 (1.06-3.64)	.03
Oral hypoglycemic drugs (vs diet)	2.33 (0.54-10.01)	.26	0.99 (0.27-3.61)	.99
Insulin treatment (vs diet)	6.7 (1.49-30.17)	.01	1.91 (0.41-7.81)	.34
Microalbuminuria (yes/no)	0.48 (0.23-1.01)	.06	2.19 (1.12-4.29)	.02
Macroalbuminuria (yes/no)	1.35 (0.46-3.96)	.58	2.72 (0.88-8.39)	.07

Odds ratios (95% CIs) for the incidence of retinopathy and CKD in individuals with type 2 diabetes mellitus. All covariates were simultaneously included in multivariate regression models (forced-entry). Cohort size, n = 979. The ORs for continuous variables were computed for 1 SD change. *Hypertension* was defined as blood pressure ≥140/90 mm Hg or on antihypertensive treatment.

Table 5 – Multivariable logistic regression analyses

	TGs alone Ln TG	P	HDL-C alone HDL-C	P
Refers to the heading of the column	1.47 (0.99-2.16)	.053	0.98 (0.97-0.99)	.03
Age (y)	1.46 (1.16-1.84)	.001	1.47 (1.16-1.84)	.001
Sex (men vs women)	1.09 (0.73-1.61)	.69	0.98 (0.66-1.47)	.93
Diabetes duration (y)	1.16 (0.94-1.43)	.17	1.17 (0.95-1.45)	.14
BMI (kg/m^2)	1.08 (0.89-1.30)	.44	1.09 (0.90-1.32)	.37
Smoking history (yes/no)	0.84 (0.49-1.44)	.53	0.82 (0.48-1.41)	.48
Hemoglobin A_{1c} (%)	1.21 (0.98-1.50)	.07	1.22 (0.99-1.50)	.07
LDL-C (mmol/L)	0.89 (0.72-1.08)	.21	0.92 (0.75-1.12)	.39
Hypertension (yes/no)	1.50 (0.82-2.71)	.19	1.49 (0.82-2.70)	.19
Lipid-lowering drugs (yes/no)	0.88 (0.60-1.31)	.56	0.91 (0.62-1.34)	.63
Antiplatelet drugs (yes/no)	1.50 (1.02-2.19)	.04	1.46 (1.00-2.15)	.05
Oral hypoglycemic drugs (vs diet)	1.80 (0.69-4.74)	.23	1.86 (0.71-4.90)	.21
Insulin treatment (vs diet)	4.26 (1.53-11.82)	.05	4.38 (1.58-12.16)	.005
Microalbuminuria (yes/no)	1.03 (0.64-1.67)	.90	1.05 (0.65-1.71)	.83
Macroalbuminuria (yes/no)	2.09 (0.97-4.52)	.06	2.32 (1.07-5.02)	.03

Odds ratios (95% CIs) for the incidence of retinopathy and/or CKD (combined dependent variable) in individuals with type 2 diabetes mellitus. All covariates were simultaneously included in the multivariate regression models (forced-entry model). Cohort size, n = 979. The ORs for continuous variables were computed for 1 SD change. *Hypertension* was defined as blood pressure ≥140/90 mm Hg or on antihypertensive treatment.

studies also suggested that statin treatment might exert beneficial effects on the progression of diabetic advanced retinopathy [7,8].

However, because statins are poorly effective at modifying circulating levels of HDL-C and TGs, an important contribution to better understand the possible role of a raised TG/HDL-C ratio in the development of microvascular complications of diabetes could come from randomized controlled trials with fibrates, which have a stronger effect on plasma HDL-C and TG levels [11]. In the Diabetes Atherosclerosis Intervention Study, long-term fenofibrate treatment was associated with a reduced progression from normoalbuminuria to microalbuminuria in patients with type 2 diabetes mellitus [24]. The Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) study recently showed a significant (ie, 31%) reduction in laser interventions required in patients with type 2 diabetes mellitus with advanced retinopathy receiving fenofibrate compared with the placebo group [25]. Moreover, in the FIELD study, fenofibrate treatment was also significantly associated with less albuminuria progression, although no data were reported on changes in renal function markers [26]. In this regard, Forsblom et al [27] recently observed that, in the FIELD Helsinki substudy, long-term fenofibrate treatment reduced measures of renal function (ie, resulting in a significant increase in plasma cystatin C levels and in a significant decrease in calculated creatinine clearance and eGFR) to a greater extent than placebo. Moreover, they failed to show any beneficial effect on albuminuria. This untoward effect, however, could be related to factors other than the amelioration of plasma lipid profile. Nevertheless, a recently published study showed that the pharmacological reduction of TG/HDL-C was the only independent parameter associated with slower progression of coronary atherosclerosis [28].

A high TG/HDL-C ratio might adversely act through endothelial dysfunction, chronic low-grade inflammation, increased oxidative stress, and abnormalities in fibrinolysis and coagulation [1,2,7]. Yet, a high TG/HDL-C ratio could be just a marker of other underlying pathophysiological abnormalities, contributing to the development and progression of microvascular complications such as insulin resistance, elevated small dense LDL-C particles, and increased visceral adiposity. Our findings may have potential clinical implications. First of all, the detection of a high TG/HDL-C ratio in patients with type 2 diabetes mellitus should alert clinicians to the possibility of an increased risk of developing microvascular complications. Moreover, treatments specifically aimed to improve the TG/HDL-C ratio could be implemented to reduce the incidence of these microvascular complications. In this respect, however, it must be noted that no data are available from large randomized clinical trials specifically designed to evaluate the potential benefits of fibrates or other drugs improving TG/HDL-C ratio on the development of diabetic microvascular complications (as a primary end point). Nonetheless, a program of lifestyle changes (eg, moderate weight reduction, increased physical activity, and smoking cessation when appropriate), which have been also demonstrated to have positive effects on TG/HDL-C ratio, could be reasonably implemented in people with type 2 diabetes mellitus with the aim of reducing the risk of incident microvascular complications.

Our study has some important limitations that should be mentioned: (1) CKD was assessed by an estimate rather than a direct measure of GFR, but direct measurements are rarely used in clinical practice; (2) the statistical analyses were based on a single measurement at baseline, and no information on the distribution of risk factors over the period of follow-up was available; and (3) whether these observations can also be extended to nonwhite ethnic groups remains to be determined. Finally, a substantial proportion of subjects had albuminuria at baseline even though the eGFR was greater than 60 mL/min.

With respect to the use of a single parameter, the TG/HDL-C ratio (which is a simple mathematical relation between TGs and HDL-C) may highlight the opposite contribution of the single parameters on microvascular outcome. Therefore, the ratio can make more evident the role of TGs in microvascular

risk. Moreover, some author claims that the TG/HDL-C ratio can reflect the TGs' participation in the production of large very low-density lipoprotein and small dense LDLs; and it has also been proposed to be the major determinant of cholesterol esterification/transfer and HDL remodeling in particles that regulate the esterification rate [29].

Despite these limitations, the present study, which is the first one assessing prospectively the prognostic utility of the TG/HDL-C ratio in the risk prediction of incident of microvascular complications in type 2 diabetes mellitus, has important strengths, including the large cohort size, the ability to adjust for multiple risk factors and potential confounders, and about 200 microvascular events, a sufficiently large number of events to detect significant phenomena. Finally, our patients were free of diagnosed CVD and malignancy; the evaluation of patients with such complications would almost certainly have confounded interpretation of the data.

In conclusion, our findings suggest that higher TG/HDL-C ratio independently predicts an increased incidence of retinopathy and CKD in individuals with type 2 diabetes mellitus without prior CVD. Further prospective and intervention studies are obviously needed to confirm our results and to establish whether the TG/HDL-C ratio may be another potential target for the treatment of type 2 diabetes mellitus to reduce the risk of developing these microvascular complications.

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Conflict of Interest

None to declare.

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