Serum triglycerides are a predictive factor for the development and the progression of renal and retinal complications in patients with type 1 diabetes

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Objectives: It is controversial that serum lipids affect the development and progression of microvascular complications in patients with type 1 diabetes.

Methods: We prospectively followed 297 patients with type 1 diabetes without end-stage renal disease for 7 years (range: 2-10). Serum lipids were measured at baseline (total and HDL-cholesterol, triglycerides and calculated LDL-cholesterol, Lipoprotein (a)). The primary end-point was the occurrence of a renal event and the secondary end-point was the occurrence of a retinal event, defined as the progression to a higher stage of diabetic nephropathy or retinopathy, respectively.

Results: Serum triglyceride (TG) levels were higher in patients who progressed in nephropathy than in those who did not [median 1.21 (range 0.41-2.96) vs 0.91 (0.31-11.07) mmol/l; p = 0.0037] and in those who developed retinal events than in those who did not [1.05 (0.46-8.27) vs 0.87 mmol/l (0.31-11.07); p = 0.0302], both in the whole cohort and in patients with normoalbuminuria at baseline. After adjustment for systolic blood pressure (SBP), diabetes duration, gender, stage of complications at baseline and glycohemoglobin (HbA1c), the relative risk for progression was 2.01 (95% CI: 1.07-3.77) for nephropathy and 2.30 (95% CI: 1.03-5.12) for retinopathy for patients having serum TG in the highest tertile, compared to the others. This result persisted when only patients with normoalbuminuria were considered.

Conclusion: High triglyceride levels are an independent predictive factor of both renal and retinal complications in patients with type 1 diabetes.
Diabetic nephropathy is the main reason for the increase in the number of patients with end-stage renal disease (ESRD) worldwide, including in France [1]. Type 1 diabetes patients with nephropathy have an altered lipid profile [2] and an increased risk of cardiovascular mortality [3]. Plasma lipids are a risk factor for the development [4] and progression of diabetic nephropathy [5]. The results of animal studies suggested that lipids may play a role in the development and progression of diabetic nephropathy [6]. A recent microarray analysis showed that the genes involved in lipid metabolism are overexpressed in the kidneys of rats with streptozotocin-induced diabetes [7]. It is difficult to demonstrate convincingly that serum lipids play a primary role in the development and/or progression of diabetic nephropathy and to exclude the possibility that lipid changes be secondary to nephropathy, as glomerular disease may cause changes in lipoproteins [8].

Lipids might also be involved in the pathogenesis of other microvascular complications like retinopathy. Lipemia retinalis is a well-known complication of extreme hypertriglyceridemia [9]. Cross sectional epidemiological studies have reported an association between dyslipidemia and retinopathy in type 1 diabetes [10-11]. Lipoprotein (a) [(Lp(a))] is a cholesterol-rich lipoprotein with a high homology with plasminogen [12]. Several studies have reported that high Lp(a) concentrations were associated with coronary artery disease [13], with diabetic renal disease [14, 15] and diabetic retinopathy [16]. However, very few studies examined this association in longitudinal study [17].

We carried out a large, prospective, follow-up, observational study to analyze the role of the lipid profile including Lp(a) on the development and progression of renal and retinal complications in patients with type 1 diabetes.

**Patients and methods**

**Patient selection**

The patient cohort has been already described [18]. All patients with type 1 diabetes (age at diabetes onset < 40 years and time to definitive insulin therapy less than 1 year) who attended the diabetes clinic of the Angers University Hospital (France) from 1989 to 1996 were invited to participate in a prospective observational study on the determinants of diabetic nephropathy, if they fulfilled the following criteria: type 1 diabetes for 3 or more years and any stage of retinopathy, intensified insulin treatment [19]. Nephropathy was classified as described by Mogensen et al. [21]: absent (normoalbuminuria), incipient (microalbuminuria), established (proteinuria), advanced (plasma creatinine > 150 micromol/l) or end-stage renal disease — ESRD — (dialysis or kidney transplant). Normoalbuminuria was defined as UAE < 20 mg/L on two or three times out of three consecutive visits, persistent microalbuminuria as UAE between 20 and 200 mg/L, and clinical proteinuria as UAE > 200 mg/L in the same conditions. Diabetic retinopathy was classified according to Kohner’s classification: absent, background, pre-proliferative or proliferative [22].

**Analytical methods**

Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured five times at 2-minute intervals in supine patients with an automatic device (BP-8800 tensiometer, CoElectronics Co, Ltd, Japan). Mean values were recorded.

Urinary albumin was measured by nephelometry (Dade Behring SA — Mahburg — Germany — sensitivity 2 mg/L; intra- and inter-assay coefficient of variation: 2% and 4%) on a random urine sample. Plasma creatinine was measured by a modified version of Jaffé’s method. Glycaemic control was assessed by hemoglobin A1c using high performance liquid chromatography (HPLC) (Diamat Biorad — Ivry sur Seine — France; normal values 4.1-6.0%).

Lipid levels and Lp(a) were determined in serum samples collected in the fasting state. Total cholesterol (TC) and triglycerides (TG) were determined by use of colorimetric enzymatic methods (“cholesterol CHOP PAP” — Boe-
The serum TG level increased similarly: 0.87 ± 0.46 mmol/l compared to those of the lowest two tertiles (p = 0.03). Adding HDL-Cholesterol in the model did not substantially modify the results: each increase of 1 mmol/l of HDL-C levels was lower in progressors than in non-progressors. Serum TC, Lp(a) and LDL-C levels were not statistically different. When we restricted the analysis to patients with normoalbuminuria at baseline, the results were unchanged (Tab II).

The rate of renal events in the whole cohort was 1.89 per 100 patient-years (95% CI: 1.60-2.20). Total cholesterol and LDL-C levels were not different from the Friedman equation. Lp(a) was determined using a nephelometric method (Behring Diagnostics — Marburg — Germany; sensitivity 0.07 g/l).

Statistical analysis

All data were stored and analyzed using the STATVIEW V program (SAS Institute Inc Cary, NC 27153 USA). Data are presented as means ± SD, or as medians (ranges) if the distributions were skewed. Means and 95% confidence intervals (95% CI) are given for relative risks and adjusted hazard ratios. The status of each patient with regard to change in nephropathy or retinopathy stage was determined every year and a survival analysis was performed. A renal or retinal event was defined as progression to a higher stage of diabetic nephropathy or retinopathy, respectively. Time to first event curves were generated by Kaplan-Meier estimation and compared by the log-rank test. Multivariate analysis, including Cox’s proportional hazards model, was used to investigate the relationship between several candidate prognostic variables and the outcome variable. Groups were compared using the chi-squared test for categorical variables, and parametric (if normally distributed, ANOVA or Student’s t-test) or non-parametric tests (if not normally distributed, Mann-Whitney U-Test or Kruskal–Wallis) for continuous variables. The non parametric Spearman’s rank test was used to analyze the relationship between continuous variables. The level of significance was set at 0.05.

Results

Baseline characteristics

At baseline, 251 (81%) patients had no nephropathy, 35 (11%) had incipient nephropathy, 18 (6%) had established nephropathy and 6 (2%) had advanced nephropathy. Retinopathy was absent in 187 patients (60%), background in 48 (16%), pre-proliferative in 41 (13%) and proliferative in 34 (11%). For technical reasons, the lipid profile could not be determined in 13 patients: 7 absent, 1 incipient, 3 established and 2 advanced nephropathy patients (not different from the others). Thus, a total of 297 patients were included in this study.

At baseline, the severity of nephropathy was related to the duration of diabetes, and to higher SBP and DBP, as previously reported [18]. Total cholesterol and LDL-cholesterol increased with renal stages: absent: 5.29 ± 1.32 and 3.30 ± 1.25, incipient: 5.39 ± 1.26 and 3.44 ± 1.16, established: 6.48 ± 1.34 and 4.43 ± 1.25 and advanced: 6.32 ± 1.26 and 4.59 ± 1.11 mmol/l (ANOVA p = 0.0011 and p = 0.0197, respectively). The serum TG level increased similarly: 0.87 (0.31-1.04), 1.00 (0.46-4.10), 1.58 (0.62-2.47) and 1.37 (0.73-2.41) mmol/l, respectively (ANOVA after log transformation p = 0.0027).

Conversely HDL-cholesterol did not differ significantly according to nephropathy stage: absent: 1.50 ± 0.49, incipient: 1.46 ± 0.48, established: 1.57 ± 0.48 and advanced: 1.54 ± 0.46 mmol/l (ANOVA p = 0.9014), while Lp(a) was of borderline statistical significance: absent: 0.13 (0.07-2.00), incipient: 0.10 (0.07-1.11), established: 0.28 (0.09-2.88) and advanced: 0.15 (0.10-0.60) g/l (ANOVA after log transformation p = 0.085).

The clinical and biological data at baseline examination according to the diabetic retinopathy stages are summarized in Table I. Age, diabetes duration, SBP and DBP and body mass index (BMI) increased with retinopathy stage. The serum TC, TG and Lp(a) and the proportion of participants on lipid-lowering therapy also differed according to the severity of the retinopathy.

Serum TG and HDL-C were correlated with baseline HbA1c (Rho = 0.206, p = 0.0005 and Rho = – 0.253, p < 0.0001, respectively). Lp(a) was not correlated with baseline HbA1c (Rho = 0.044, p = 0.4750). Mean HbA1c differed significantly according to the tertiles of serum TG: 8.8 ± 2.2 in the lowest vs 9.4 ± 2.2 in the second and 9.9 ± 2.5% in the highest tertile (p = 0.0055).

Changes in nephropathy stages and serum lipids

A total of 50 patients progressed to a more severe stage of diabetic nephropathy during follow-up; of them, 36 had normoalbuminuria at baseline. The rate of renal events in the whole cohort was 2.61 per 100 patient-years (95% CI: 1.90-3.33). The clinical and biological characteristics of progressors and of non-progressors including lipid data are summarized in Table II. Triglyceride levels were higher and HDL-C levels were lower in progressors than in non-progressors, whereas TC, Lp(a) and LDL-C levels were not statistically different. When we restricted the analysis to patients with normoalbuminuria at baseline, the results were unchanged (Tab II).

The rate of renal events in the whole cohort was 1.89 per 100 patient-years (95% CI: 0.87-2.90) for patients in the lowest tertile of TG (range: 0.31-0.75 mmol/l), 1.53 (95% CI: 0.59-2.47) for patients in the second tertile (range: 0.76-1.14 mmol/l) and 4.73 (95% CI: 2.99-6.47) for patients in the highest tertile of TG (range: 1.15-11.10 mmol/l) (log-rank = 5.821, p = 0.0158). Using Cox’s proportional hazard model, the patients from the highest TG tertile had an adjusted hazard ratio of renal progression of 2.01 (95% CI: 1.07-3.77) compared to those of the lowest two tertiles (p = 0.03) (Tab III). Adding HDL-Cholesterol in the model did not substantially modify the results: each increase of 1 mmol/l of HDL-C induced a protection against renal events with an
adjusted hazard ratio of renal progression of 0.41 (95% CI: 0.20-0.84) while the effect of TG remained significant (p = 0.0443).

Similar data were obtained when we restricted the analysis to patients with normoalbuminuria at baseline (log-rank = 6.64, p = 0.01); patients in the highest tertile (range: 1.10-11.10 mmol/l) had a higher risk of progression than those in the lowest (range: 0.31-0.69 mmol/l) and second tertiles (range: 0.70-1.09 mmol/l). In patients with normoalbuminuria at baseline, patients from the highest TG tertile had an adjusted hazard ratio of progression to microalbuminuria of 2.06 (95% CI: 1.05-4.05) (p = 0.04) (Tab IV). HDL-C was introduced into this model; it was not associated with the risk of progression to microalbuminuria (p = 0.09), while the effect of TG was then of borderline signification (p = 0.0921).

Changes in retinopathy stages and serum lipids

At baseline, 32 patients had proliferative retinopathy. As patients with proliferative retinopathy could not further deteriorate according to our definition, only the 265 patients with absent, background or pre-proliferative retinopathy at baseline were taken into account for this analysis. A total of 66 patients were classified as progressors. Forty-two of the progressors had no retinopathy at baseline.

During the follow-up period, 42 of the 180 patients without retinopathy developed background, pre-proliferative or proliferative retinopathy, 14 of the 47 patients with background retinopathy at baseline developed pre-proliferative (n = 9) or proliferative (n = 5) retinopathy, and 10 of the 38 patients with pre-proliferative progressed to proliferative retinopathy. The rate of retinal complications in patients with-
out retinopathy at baseline was 3.51 events per 100 patient-years (95% CI: 2.63–4.27).

The clinical and biological characteristics of retinal progressors vs non-progressors including lipid data are summarized in Table V. Triglycerides, diabetes duration and blood pressure were higher in progressors than in non-progressors but not Lp(a). When we restricted the analysis to patients with normoalbuminuria at baseline, triglyceride levels remained significantly higher in progressors than in non-progressors [1.03 (0.46–2.96) vs 0.86 (0.31–1.10), *p = 0.0114§].

Patients from the highest tertile of serum TG at baseline (range: 1.11–11.10 mmol/l) were more likely to be retinal progressors than were patients from the lowest (range: 0.31–0.69 mmol/l) and second tertiles (range: 0.70–1.10 mmol/l); relative risk = 1.98 (95% CI: 1.07–3.64). In the normoalbuminuric patients, the relative risk for retinal progression was 2.17 (95% CI: 1.10–4.28) for patients in the highest tertile compared to those in the lowest two tertiles. No differences were found with regard to TG or LDL-C.

In multivariate analysis, patients from the highest tertile of TG had a higher adjusted risk of retinal progression than those from the lowest two tertiles [adjusted hazard ratio 2.30 (95% CI: 1.03–5.12)] (*p = 0.0188). When HDL-C was added to the model, this did not substantially modify the results; the relative risk for retinal progression was 2.49 (95% CI: 1.04–5.07) for patients in the highest tertile of TG. When we analyzed only patients with normoalbuminuria at baseline, high TG levels were associated with a significantly higher risk of retinal progression (adjusted hazard ratio 2.04 [95% CI: 1.01–4.13] together with baseline retinopathy stage (compared to stage 1, *p = 0.20 for stage 2 and *p = 0.03 for stage 3), glycemic control [adjusted hazard ratio for each increase of 1% of mean HbA1c during follow-up: 1.37 (95% CI: 1.04–1.79), *p = 0.0163] and diabetes duration [adjusted hazard ratio for

Tableau II

<table>
<thead>
<tr>
<th></th>
<th>DN Progression</th>
<th>No DN progression</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort: clinical and biological data</td>
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<td>n = 247</td>
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<tr>
<td>Age at inclusion in the study (years)</td>
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<td>33.9 ± 13.6</td>
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<td>Sex (Male/Female)</td>
<td>34/16</td>
<td>140/107</td>
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<td>Diabetes duration (year)</td>
<td>17 ± 11</td>
<td>15 ± 10</td>
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<td>BMI (Kg/m²)</td>
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<td>22.7 ± 3.6</td>
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<td>Retinopathy Stage (1/2/3/4): n (%)</td>
<td>22(44)/10(20)/6(12)/12(24)</td>
<td>158(64)/37(15)/32(13)/20(8)</td>
<td>0.0042*</td>
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<tr>
<td>Nephropathy Stage (1/2/3/4): n (%)</td>
<td>36(72)/4(8)/7(14)/3(6)</td>
<td>205(83)/30(12)/9(4)/3(1)</td>
<td>0.0026*</td>
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<tr>
<td>Baseline HbA1c (%)</td>
<td>9.8 ± 2.7</td>
<td>9.3 ± 2.3</td>
<td>0.2270**</td>
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<td>Mean HbA1c during follow-up (%)</td>
<td>8.7 ± 1.5</td>
<td>8.6 ± 1.2</td>
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<td>SBP (mm Hg)</td>
<td>134 ± 19</td>
<td>126 ± 15</td>
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<td>DBP (mm Hg)</td>
<td>77 ± 13</td>
<td>73 ± 10</td>
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<td>Total cholesterol (mmol/l)</td>
<td>5.39 ± 1.19</td>
<td>5.39 ± 1.37</td>
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<td>Triglycerides (mmol/l)</td>
<td>1.21 (0.41-2.96)</td>
<td>0.91 (0.31-11.07)</td>
<td>0.0375**#</td>
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<td>HDL-Cholesterol (mmol/l)</td>
<td>1.37 ± 0.39</td>
<td>1.55 ± 0.49</td>
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<td>Molar ratio TG/HDL-C</td>
<td>0.83 (0.27-5.23)</td>
<td>0.62 (0.15-7.68)</td>
<td>0.0082§</td>
</tr>
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</table>
| LDL-Cholesterol (mmol/l) | 3.41 ± 1.08 | 3.38 ± 1.32 | 0.7867%
| Lp(a) (g/l) | 0.13 (0.08-2.88) | 0.13 (0.07-2.00) | 0.7800**# |
| Baseline normoalbuminuria: lipid data | n = 36 | n = 205 |         |
| Total cholesterol (mmol/l) | 6.17 ± 1.32 | 5.70 ± 1.37 | 0.3022# |
| Triglycerides (mmol/l) | 1.09 (0.41-2.96) | 0.86 (0.31-11.07) | 0.0114§ |
| HDL-Cholesterol (mmol/l) | 1.42 ± 0.39 | 1.52 ± 0.49 | 0.0527# |
| Molar ratio TG/HDL-C | 0.60 (0.15-7.68) | 0.75 (0.27-5.23) | 0.1737§ |
| LDL-Cholesterol (mmol/l) | 3.15 ± 0.80 | 3.33 ± 1.34 | 0.5175§ |
| Lp(a) (g/l) | 0.10 (0.08-1.00) | 0.13 (0.07-2.00) | 0.1178**# |

DN Progression was defined as the shift to a higher stage of diabetic nephropathy.
Data are means ± SD or median (range) * Chi-squared test, # Analysis of variance, § Mann-Whitney test, ** log-transformed data for calculations
Nephropathy stage was: 1 (absent), 2 (incipient), 3 (established), 4 (advanced); Retinopathy stage: 1 (absent)/2 (background)/3 (pre-proliferative)/4 (proliferative); UAE: Urinary Albumin Excretion; BMI: Body Mass Index; SBP/DBP: systolic blood pressure/diastolic blood pressure; TG/HDL, serum triglyceride divided by serum HDL-Cholesterol concentrations.

Tableau II
Changes in nephropathy and/or retinopathy stage and serum triglycerides

We analyzed patients who progressed in retinopathy only (DR progressors), in nephropathy only (DN progressors), in both complications (DN/DR progressors) and who did not progress (non-progressors). The baseline serum TG concentration was lowest in non-progressors [0.86 mmol/l (0.51-1.10)], intermediate in DR progressors [1.03 mmol/l (0.86-1.28)] and DN progressors [1.10 mmol/l (0.91-1.31)] and highest in DN/DR progressors 1.15 mmol/l (0.95-1.36) (p = 0.0419). Using two-way ANOVA we found no interaction between DN and DR progressions for serum TG (p value = 0.276).

DISCUSSION

In this prospective, observational study on a cohort of type 1 diabetes patients with various stages of diabetic retinopathy and nephropathy at baseline, we showed that serum TG levels are predictive for the development and progression of both diabetic nephropathy and retinopathy, the two main microvascular complications seen in type 1 diabetes. The absence of interaction between DN and DR progressions in relation to serum TG strongly suggests an ubiquitous effect of TG on diabetic microvascular disease. Conversely, we found that Lp(a) was not predictive of the risk of development or progression of microvascular complications.

The frequency of renal or retinal involvement at baseline and the rate of renal progression were similar to those observed in other large-scale studies [23, 24]. The finding that blood pressure, glycaemic control and UAE are progression promoters for diabetic nephropathy is consistent with the results of several longitudinal studies [4, 24]. The incidence of diabetic retinopathy in the patients without nephropathy at baseline was 3.51 events per 100 patient-years, which is similar to what was reported in the primary prevention cohort of type 1 diabetes patients in the DCCT trial [24], but...
lower than what was reported in the EURODIAB prospective complications study [25]. Consistently with other intervention [24] or epidemiological studies [25], retinal progression was strongly dependent on diabetes duration and metabolic control.

The relationship between serum lipids and diabetic nephropathy has been a matter of investigations for many years [5]. We found that baseline total cholesterol and LDL-cholesterol were not predictive for renal events, but that baseline TG levels had a significant and independent effect on renal events. As in other cross-sectional and longitudinal studies [4, 26] we found a predictive role of TG for renal events, even when the analysis was restricted to patients with normoalbuminuria at baseline. The present study confirms the results from longitudinal studies in normoalbuminuric patients [4, 26] and extends the predictive role of TG on the progression of microvascular disease to type 1 diabetes patients with any nephropathy stage.

As widely reported, we found that serum TG levels were partly dependent on metabolic control. However, the role of TG still persisted after adjustment for HbA1c. Our results therefore support an effect of serum TG, additional to the effect of metabolic control.

The association between baseline lipid levels and diabetic retinopathy has already been reported in cross-sectional [10-11] and prospective studies [26, 27]. However, our data are not biased by the effect of nephropathy on lipid profile, because the results were unchanged when retinal progression was analyzed in the sub-group of patients with normoalbuminuria at baseline, even after adjustment on UAE.

TG could be deleterious for microvessels in diabetic patients due to several mechanisms. TG may be directly deleterious due to the capture of TG-rich lipoparticles, mostly VLDL, by mesangial cells, which may induce renal injury [28]. However, this possibility cannot be applied to the retinal vasculature.

Alternatively, TG levels may be linked to microvascular disease by inducing the production of small dense LDL, which are strongly determined by TG [29]. Small dense LDLs are more susceptible to oxidation. Lipid peroxidation is significantly associated with diabetic retinal [30] and renal diseases and may be related to endothelial dysfunction. Oxidized LDLs have been reported to stimulate TGF-beta expression in glomerular epithelial cells [31]. The direct measurement of the small dense LDL profile should be assessed prospectively to ensure that this effect does exist.

Tableau V

<table>
<thead>
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<th></th>
<th>No DR progression</th>
<th>DR Progression</th>
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<tr>
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<td>n = 199</td>
<td>n = 66</td>
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<td>Sex (Male/Female)</td>
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<td>14/25</td>
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<td>Age at inclusion in the study (years)</td>
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<td>32.2 ± 12.7</td>
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<td>Baseline Diabetes duration (year)</td>
<td>13 ± 11</td>
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<td>Daily insulin dose (UI/kg body weight/day)</td>
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<td>0.73 ± 0.27</td>
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<td>BMI (Kg/m²)</td>
<td>22.4 ± 3.1</td>
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<td>Mean HbA1c during follow-up (%)</td>
<td>8.5 ± 1.3</td>
<td>9.0 ± 1.3</td>
<td>0.001**</td>
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<td>SBP (mm Hg)</td>
<td>124 ± 14</td>
<td>128 ± 16</td>
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<td>DBP (mm Hg)</td>
<td>71 ± 9</td>
<td>74 ± 12</td>
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<td>Baseline Retinopathy Stage (1/2/3): n (%)</td>
<td>138(69)/33(17)/28(14)</td>
<td>42(64)/14(21)/10(15)</td>
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<td>Baseline Nephropathy Stage (1/2/3/4): n (%)</td>
<td>175(88)/18(9)/5(2)/1(1)</td>
<td>53(80)/9(14)/3(5)/1(1)</td>
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<td>Progression in nephropathy (yes/no)</td>
<td>22/177</td>
<td>16/50</td>
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<td>Total cholesterol (mmol/l)</td>
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<td>Triglycerides (mmol/l)</td>
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<td>1.05 (0.46-8.27)</td>
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<td>HDL-Cholesterol (mmol/l)</td>
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<td>Molar ratio TG/HDL-C</td>
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<td>0.78 (0.28-5.32)</td>
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<td>LDL-Cholesterol (mmol/l)</td>
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<td>3.61 ± 1.55</td>
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<td>Lp(a) (g/l)</td>
<td>0.12 (0.07-2.88)</td>
<td>0.13 (0.07-1.50)</td>
<td>0.5942**#</td>
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</table>

DR Progression was defined as the shift to a higher stage of diabetic retinopathy

Data are means ± SD or median (range) * Chi-squared test, # Analysis of variance, § Mann Whitney test, ** log-transformed data for calculations

Nephropathy stage was: 1 (absent), 2 (incipient), 3 (established), 4 (advanced)
Retinopathy stage: 1(absent)/2(background/3(pre-proliferative)

SBP/DBP: systolic blood pressure/diastolic blood pressure
BMI: Body Mass Index; TG/HDL, serum triglycerides divided by serum HDL-Cholesterol concentrations.
this issue, we calculated the molar ratio of TG/HDL-C, as it was found to be highly correlated with the presence of small dense LDL particles [32]. In our cohort, a few patients had Apolipoprotein B determined at baseline. The LDL-C/ApoB ratio was correlated with the molar ratio of TG/HDL-C (unshown data). We found that the molar ratio of TG/HDL-C was higher in renal or retinal progressors than in non-progressors, consistent with the hypothesis of a deleterious role of small dense LDL particles. However, this must be interpreted cautiously because the molar ratio of TG/HDL-C is by definition directly influenced by TG concentrations per se.

TG levels may also reflect insulin resistance, which was shown to be associated with microvascular complications in type 1 diabetes patients in cross-sectional [33], longitudinal [25, 34] and family-based studies [35]. In our study, other simple raw indicators of insulin resistance (i.e., daily insulin dose/body weight or BMI) were not statistically different between renal and retinal progressors and non-progressors, but insulin resistance was not measured directly. Thus, we cannot speculate further on the deleterious effects of insulin resistance on the microvasculature.

The lack of effect of Lp(a) on the development and progression of microvascular is at variance with other reports using a cross-sectional design where Lp(a) was higher in patients with diabetic nephropathy [14-15, 36] or retinopathy [16]. Our baseline data also showed that Lp(a) was higher when diabetic complications were more severe. However, no deleterious effect of high Lp(a) concentrations was evidenced in our prospective analysis, in accordance with Maser et al. [17]. This supports that Lp(a) plays no major role if any in the development and/or progression of diabetic microvascular complications and that high Lp(a) levels are probably due to deranged renal metabolism [37].

Some limitations must be acknowledged in the present study; firstly, this is a monocenter study but almost all people with type 1 diabetes in the Angers region are referred to our center. Secondly, the assessment of retinal disease must be discussed. Indeed, we did not use fundus photographs, however, all patients were examined by one trained ophthalmologist throughout the study. This method was therefore highly specific to detect retinal change. Retinal disease due to extremely high TG levels (Lipemia retinalis) was reported years ago [9]. However, this ophthalmological presentation cannot be confused with diabetic retinal disease. Furthermore, only 2 out of 291 patients had serum TG above 5 mmol/l at baseline. We verified that our data remained unchanged after post-hoc exclusion of these patients (data not shown).

In conclusion, our results support that serum triglycerides play a role in the development and progression of renal and retinal microvascular disease, while the role of Lp(a), suspected from cross-sectional data, was not confirmed using a longitudinal study design. The question of whether triglycerides play a causal role in the development and progression of diabetic microvascular disease merits further investigations including the use of hypotriglyceridemic agents.

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