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Archives of Medical Research ■ (2017) ■

Archives of Medical Research

ORIGINAL ARTICLE

Total Serum Cholesterol Increases Risk for Development and Progression of Nonproliferative Retinopathy in Patients with Type 1 Diabetes Without Therapeutic Intervention: Prospective, Observational Study

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Received for publication April 26, 2017; accepted October 17, 2017 (ARCMED-D-17-00259).

Introduction. Results from studies investigating relationship between serum lipids and risk of development and progression of diabetic retinopathy (DR) in patients with type 1 diabetes (T1DM) are not consistent. The objective of this study was to explore the relationship between serum lipids and risk of development and progression of nonproliferative diabetic retinopathy (NPDR) in T1DM with normal renal function and with no therapeutic intervention that might influence on retinopathy and serum lipids status.

Methods. A total of 103 T1DM with normal renal function (urinary albumin excretion rate <30 mg/24 h, estimated glomerular filtration rate (eGFR) >60 mL $min^{-1}1.73m^{-2}$), and before any interventions with lipid-lowering therapy, ACE inhibitors or angiotensin II receptor blockers were included in this study and followed for 41 months. Photodocumented retinopathy status was made according to the EURODIAB protocol.

Results. Patients who developed NPDR or progressed to proliferative retinopathy were older (44 vs. 33 years, $p < 0.001$), had longer duration of diabetes (21.1 vs. 13.3 years, $p < 0.001$), and higher serum total cholesterol level (5.1 vs. 4.5 mmol/L, $p = 0.02$) compared to patients without retinopathy. In a backward stepwise Cox's multiple regression analysis serum total cholesterol was significantly associated with risk of development or progression of NPDR in our subjects ($p = 0.04$), with odds ratios of 1.27−1.91.

Conclusion. These data suggest that serum total cholesterol levels are associated with risk of development and progression of NPDR in T1DM and normal renal function. The study was conducted in patients with no therapeutic interventions. © 2017 Published by Elsevier Inc. on behalf of IMSS.

Key Words: Retinopathy, Type 1 diabetes, Total cholesterol.

Introduction

Since diabetic retinopathy (DR) is one of the leading causes of visual impairment and blindness in patients with type 1 diabetes (T1DM), identification of the determinants of the onset of DR is essential for reducing the invalidity and mortality associated with diabetes (1). With appropriate medical and ophthalmologic care visual impairment and blindness can be prevented in majority of cases (2).

Well known risk factors for development and progression of DR include duration of diabetes, age, hyperglycemia and hypertension, while relationship between serum lipids and DR are not consistent (3−5). Previous cross-sectional studies have shown positive associations between conventional lipid parameters, specifically total, LDL-cholesterol, and triglycerides with severity and progression of DR (6,7). Results from large Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort also found associations between serum lipoproteins and severity of DR in

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https://doi.org/10.1016/j.arcmed.2017.10.003

T1DM (2). Increased levels of total and LDL-cholesterol are not only associated with risk of DR but also with macular edema in T1DM (8,9). However, therapy with statins and fenofibrate protect against development and progression of DR and in some studies the associations between serum lipids and DR in T1DM was no longer observed after adjustment for covariates including statin use (10−13).

It is assumed that retinopathy and nephropathy, as most important microvascular complications in patients with diabetes, occur at the same time and that the severity of retinopathy parallels the presence and severity on nephropathy in diabetes (14,15). Moreover, it is suggested that relationship between DR and lipid variables are influenced by concurrent renal disease and that associations between renal disease and serum lipids are strongly influenced by retinopathy status in T1DM (16).

The objective of this study was to explore the relationship between serum lipids and risk of development and progression of nonproliferative diabetic retinopathy (NPDR) in T1DM with normal renal function and with no therapeutic intervention that might influence on retinopathy and serum lipids status.

Subjects, Materials and Methods

The study population was based on all 264 patients with T1DM who were referred to tertiary care specialist diabetes clinic between January 2010 and December 2010. T1DM was defined as an onset of diabetes before the age of 35 years, positive autoantibodies and permanent insulin treatment initiated within one year of diagnosis. The study included patients following characteristics: age of 18−65 years, minimum duration of type 1 diabetes of one year and absence of heart, liver and renal disease. 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.

Retinopathy was diagnosed by binocular indirect slit lamp fundoscopy and fundus photography after mydriasis with eye drops containing 0.5% tropicamide and 5% phenylephrine by a single grader. Final diagnosis of DR was made by fundus photographs. Color fundus photographs of two fields (macular field, disc/nasal field) of both eyes were taken with a 45° fundus camera (VISUCAM, Zeiss) according to the EURODIAB retinal photography methodology (17). In this study retinopathy was classified as NPDR or proliferative diabetic retinopathy (PDR). NPDR was defined as the presence of one or more microaneurysms, hemorrhages, and/or hard exudates. PDR was defined as any new vessels, fibrous proliferations, preretinal hemorrhage, vitreous hemorrhage, or photocoagulation scars (17). In each patient the ''worse'' eye was graded for retinopathy using fundus photographs. Patients with ungradable photographs for DR were excluded from the study.

Urinary albumin excretion rate (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. 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, which has been shown to be accurate in determining renal function in diabetic patients with normal renal function (18,19). Those with eGFR less than 60 mL min^{-1} 1.73 m^{-2} were excluded from the study. All subjects were confirmed to be free of urinary tract infections.

Numeric variables are given as means (SD) or medians (ranges) depending on the normality distribution tested using Kolmogorov-Smirnov test, or percentages and absolute numbers for nominal variables. We used the unpaired Students *t* test and Mann-Whithney to compare cross classified continuous variables and the χ^2 test to evaluate proportions when we compared baseline data in the group of patients who developed or have progression of NPDR with the group of patients who did not develop or have progression of NPDR. All tests were two sided. Cox's proportional hazards multiple regression analyses were used to examine the baseline variables predictive of development or progression of NPDR. Results are described as relative risk (hazard ratio). A p value of less than 0.05 was regarded as significant.

Results

From 264 patients at baseline we excluded 161 patients: four had developed PDR, 80 used statins and fenofibrate and 77 ACE-inhibitors or angiotensin II receptor blockers who showed to have protective role in NPDR development. This left 103 patients who fulfilled the inclusion criteria of being free of lipid-lowering therapy and ACE-inhibitors or angiotensin II receptor blockers use and without DR or with NPDR were included in the study (Figure 1).

The majority of patients (52.4%) had no retinopathy while 49 (47.6%) had NPDR at baseline. Baseline clinical and metabolic characteristics of patients without DR compared to those that developed NPDR or progressed to PDR are presented in Table 1. Patients who developed NPDR or progressed to PDR were older (44 vs. 33 years, $p < 0.001$), had longer duration of diabetes (21 vs. 13 years, $p < 0.001$) and higher serum total cholesterol (5.1 vs. 4.5 mmol/L, $p = 0.02$) compared to patients without retinopathy during the study. 21 patients without retinopathy developed NPDR during 41 months of following with cumulative incidence of 38.8% and incidence ratio of 24.1%. Ten patients who had NPDR at baseline progressed to PDR with the cumulative incidence of 20.4% and incidence ratio 16.9% for the same period of time (Figure 1).