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Smoking and postprandial triglycerides are associated with vascular disease in patients with type 2 diabetes

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Abstract

Aims: To determine whether postprandial lipid levels are markers of clinical and subclinical macrovascular disease in a select group of patients with type 2 diabetes.
Methods: We recruited 119 local patients with type 2 diabetes and moderate metabolic control (HbA1c <8%). The patients were being treated with dietary measures and/or oral antihyperglycemic therapy. No patient was receiving lipid-lowering therapy. A history of cardiovascular events was recorded and the ankle–arm index was measured to assess subclinical peripheral artery disease. The patients underwent a lipid analysis after a 12-h fast and 4 h after a mixed breakfast (50 g of fat, 40 g of carbohydrates).
Results: The patients with clinical and subclinical macrovascular disease had a greater history of smoking, a longer disease duration, and higher serum creatinine levels. The groups with macroangiopathy had lower postprandial concentrations of HDL cholesterol ($p < 0.05$) and a trend towards lower fasting levels of HDL cholesterol ($p = 0.08$) and higher fasting and postprandial levels of triglycerides ($p = 0.07$). Multivariate analysis showed the presence of vascular (both clinical and subclinical) disease to be significantly associated with smoking (OR 3.06; 95% CI, 1.15–8.4), disease duration (for each year, OR 1.12; 95% CI, 1.03–1.22) and postprandial levels of triglycerides (for each 50 mg, OR 1.73; 95% CI, 1.13–2.65).
Conclusions: In our diabetic patients, the postprandial level of triglycerides 4 h after a fatty breakfast, though not fasting lipids, plus smoking and disease duration were independently associated to clinical and subclinical macrovascular disease.

Keywords: Type 2 diabetes; Postprandial lipemia; Arteriosclerosis; Ankle–arm index; Subclinical peripheral arterial disease

1. Introduction

Early arteriosclerosis and dyslipidemia are two particularly prevalent conditions in patients with type 2 diabetes mellitus (DM2). One of the most characteristic forms of arteriosclerosis in these patients is peripheral artery disease (PAD), a poorly recognized entity as it is asymptomatic in most patients [1]. Factors that increase the incidence of PAD in DM2 include smoking, a previous coronary event, and high fasting concentrations of triglycerides (>2.5 mmol/L) [2].

Postprandial lipidemia is a physiological phenomenon that is increased in patients with DM2 as compared with non-diabetic subjects [3]. Several clinical studies have shown that the magnitude and duration of postprandial lipidemia is positively related with the pathogenesis and progression of atherosclerosis [4]. The magnitude of postprandial lipidemia is generally expressed as the area under the curve after the intake of a fatty breakfast. This is a complex and laborious process, and some studies have suggested that measurement

Abbreviations: PAD, peripheral arterial disease

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4 h after a high fat, low carbohydrate, breakfast correlates well with an area under the curve after 8 h [5].

We examined the association between postprandial lipidemia and the presence of clinical or subclinical arteriosclerosis in patients with DM2, following a simple protocol of measuring the triglycerides 4 h after a standard mixed breakfast.

2. Subjects, materials and methods

We included 119 patients with DM2 who fulfilled the following criteria:

- Inclusion criteria:
  - type 2 diabetes with onset >40 years of age;
  - either sex;
  - treatment with diet and/or oral antihyperglycemic drugs;
  - glycated Hb < 8%.
- Exclusion criteria:
  - age >70 years;
  - treatment with insulin;
  - oral lipid-lowering drugs during the previous 6 weeks;
  - underlying disease that was severe (cancer) or recent (ischemic heart disease);
  - history of lipidemic pancreatitis;
  - fasting triglycerides >500 mg/dl at the most recent analysis or a history of fasting triglycerides >1000 mg/dl in any analysis.

All the patients gave written, informed consent and the study was approved by the Ethics and Research Committee of the Virgen de la Victoria Hospital, Málaga.

2.1. Medical record

All the patients were questioned about their smoking habits, the presence of other vascular risk factors, the duration of their diabetes, other medications, a family history of ischemic heart disease or dyslipidemia, and other possible kidney, retina, or neurologic disorders. In case of doubt, data obtained from questionnaire was contrasted with medical records. The patients were then examined and measurements taken of the weight, height, and waist and hip circumferences. The blood pressure was taken three times after a 5-min rest. The body mass index and the waist-to-hip ratio were calculated. Finally, the ankle–arm index was calculated by dividing the higher systolic pressure from each leg by the higher brachial systolic pressure. Asymptomatic PAD was diagnosed when ankle–arm pressure index was lower than 0.90 [6]. No patient in this series had an ankle–arm index >1.30. The systolic pressures were measured by a trained nurse using Flowsoft 15-Spectro-flow ANGIOLAB 2 (Spead-Doppler-Systeme, Kehl, Germany).

2.2. Definitions

Those patients with a previous vascular event were categorized as clinical arteriosclerosis group. Among patients with no previous event, those with an ankle–arm index below 0.90 were categorized as subclinical arteriosclerosis group. The remaining patients formed the group without arteriosclerosis. Microvascular disease was considered present when patient had diabetic retinopathy, polyneuropathy or microalbuminuria. Hypertension was present when patient was treated for hypertension or if they have blood pressure higher than 130/80 mmHg (average of three measurement). Body mass index was used to define obesity (BMI $\geq$30 kg/mt^2) and overweight (25–29.9 kg/mt^2).

2.3. Laboratory test

After a 12-h overnight fast, a sample of blood was drawn to measure levels of glycemia, glycated hemoglobin, lipids and lipid fractions. Serum glucose was measured with a Cobas Integra (Roche) autoanalyzer, using a hexokinase-based enzymatic method. The glycated hemoglobin was measured by HPLC (ADAMS-A1c HA 8160). The plasma lipids, cholesterol and triglycerides were measured with enzymatic techniques (HORIBA-ABX, Montpellier, France) in a Cobas Mira autoanalyzer. The HDL cholesterol was measured after precipitation with phosphotungstate magnesium (Sigma–Aldrich, St. Louis, MO). The LDL cholesterol was calculated from the Friedewald equation [7].

2.4. Breakfast

After providing the fasting sample, all the patients consumed, in 20 min or less, a mixed breakfast of milk, bacon, cheese, butter and bread, which contained 775 kcal, 50 g of fat (53% SAT, 41% MUFA, 6% PUFA) and 40 g of carbohydrates. The patients remained at rest, and were allowed to drink water ad libitum, but no other food or drink was permitted nor were they allowed to smoke. Four hours after the breakfast another blood sample was drawn for lipid analysis. Previous study in our lab demonstrated that measuring triglycerides fasting and 2, 4, 6 and 8 h after mixed breakfast, postprandial triglycerides peaked at 4 h and the single measurement of triglycerides at this point showed a good correlation coefficient with the area under the curve over 8 h (Spearman's ρ 0.954, $p < 0.01$) [8].

Statistical analysis: the differences in the variables in the patients with and without arteriosclerosis were analyzed with the Student's *t*-test, or the Mann–Whitney *U*-test if the variables did not adjust to a normal distribution. The analysis between the groups was done with ANOVA, or Kruskall–Wallis in the absence of normality. The association between qualitative variables was done with the χ^2 test. Analysis of which variables were independent predictors for the presence or absence of arteriosclerosis (both clinical and subclinical) was done with a forward, stepwise, multiple logistic