Artery Research (2011) 5, 8–14

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

Cholesterol metabolism, endothelial dysfunction, and carotid artery stiffness in type 1 diabetes☆

Timo Koponen [a], Maarit Hallikainen [b], Jukka Lipponen [c], Tiina Lyyra-Laitinen [a], Pasi A. Karjalainen [c], Mika P. Tarvainen [c], Chaiyasit Sittiwet [d,e], Tatu A. Miettinen [d], Tomi Laitinen [a], Helena Gylling [b,f,*]

[a] *Department of Clinical Physiology and Nuclear Medicine, Kuopio University Hospital, Kuopio, Finland*
[b] *Institute of Public Health and Clinical Nutrition, Department of Clinical Nutrition, University of Eastern Finland, Kuopio, Finland*
[c] *Department of Physics and Mathematics, University of Eastern Finland, Kuopio, Finland*
[d] *Department of Medicine, Division of Internal Medicine, University of Helsinki, Helsinki, Finland*
[e] *Department of Chemistry, Faculty of Science, Mahasarakham University, Thailand*
[f] *Department of Medicine, Kuopio University Hospital, Kuopio, Finland*

Received 1 April 2010; received in revised form 26 August 2010; accepted 3 September 2010
Available online 25 September 2010

KEYWORDS
Cholesterol metabolism;
Endothelial function;
Carotid artery stiffness;
Desmosterol;
Sitosterol;
Type 1 diabetes

Abstract *Background:* Type 1 diabetes is associated with increased risk of cardiovascular diseases and altered metabolism of cholesterol. We studied whether the markers of arterial stiffness reflecting preclinical atherosclerosis are related to markers of cholesterol metabolism in type 1 diabetes.

Methods: In eighteen type 1 diabetes subjects aged from 20 to 56 years, serum squalene and non-cholesterol sterols were measured with gas–liquid chromatography, and carotid arterial stiffness (elastic and Young's modulus, beta index, distensibility, and compliance), intima-media thickness (IMT), and brachial artery endothelial function (flow-mediated dilatation, FMD) were measured with ultrasound imaging.

Results: Variables of arterial stiffness were not related to serum lipids or HbA_{1c} except Young's modulus and compliance to triglycerides ($r = 0.541$ and $r = -0.552$, $p < 0.05$ for both, respectively). Stiffness of carotid artery was related to mean blood pressure (elastic modulus $r = 0.590$, distensibility $r = -0.486$, $p < 0.05$ for both). Stiffness of carotid artery was associated with serum desmosterol concentration, marker of cholesterol synthesis (e.g. compliance $r = -0.600$, $p < 0.01$), and with markers of cholesterol absorption (e.g. distensibility and sitosterol to cholesterol ratio $r = 0.628$, $p < 0.01$), and the associations between

☆ Grant support: The study was supported by grants from KuopioUniversity Hospital (EVO 5031340 and 5031316), Finnish Cultural Foundation of Northern Savo, Academy of Finland (project numbers 126873 and 123579), and Yrjö Jahnsson Foundation.

* Corresponding author. University of Eastern Finland, Department of Clinical Nutrition, P.O. Box 1627, FI-70211 Kuopio, Finland. Tel.: +358 503302402; fax: +358 17162792.
E-mail address: Helena.Gylling@uef.fi (H. Gylling).

1872-9312/$ – see front matter
doi:10.1016/j.artres.2010.09.001

absorption markers and arterial stiffness remained significant after adjustment on age and mean blood pressure.
Conclusions: Carotid arterial stiffness was associated with markers of cholesterol metabolism, but not with serum lipid levels. Low absorption-high synthesis of cholesterol was related to increased arterial stiffness. Cholesterol metabolism seems to play a role in vascular health beyond serum lipids in type 1 diabetes.

Introduction

Atherosclerosis develops under several years, even for decades, and is frequently undetectable until the appearance of clinical signs. However, early vascular changes, such as increased arterial intima-media thickness (IMT), impaired endothelial function measured as flow-mediated dilatation (FMD), and stiffening of arterial wall can be detected years before the clinical manifestations of atherosclerosis.[1]

Previous studies have shown that the risk of vascular events, such as myocardial infarction, cerebral stroke, and peripheral arterial insufficiency, increases with IMT[2] and with decreasing endothelial function,[3] and there is a good correlation between IMT and atherosclerosis.[4] Arterial stiffening has been associated to myocardial infarction and atherosclerosis,[5] and also to hypertension.[6] IMT is a well-established method for assessment of preclinical atherosclerosis. However, FMD, despite its wide use in research, is not yet introduced in clinical practice because of the lack of a standardized method. On the contrary, arterial stiffness, as measured with pulse wave velocity, is incorporated in clinical practice as is also suggested by the ESC/ESH guidelines.[7]

Macrovascular complications, such as coronary artery disease, stroke, and peripheral obliterate arterial disease, are major causes of morbidity and mortality in type 1 diabetes.[8] Accordingly, type 1 diabetes can be considered as a risk factor for atherosclerosis, and it has been associated with increased IMT and decreased endothelial function even in childhood.[3] It has been proposed that increased serum blood glucose level affects vascular stiffness through glycosylation.[9] Although type 1 diabetes patients may frequently have normal levels of LDL cholesterol, diabetic patients have altered LDL cholesterol characteristics and enhanced foam cell formation.[3] These changes are known to be associated with thicker intima-media layer,[3] decreased endothelial function,[3] and increased arterial stiffening.[10] In addition, we have shown earlier that cholesterol metabolism is perturbed in type 1 diabetes, so that cholesterol absorption efficiency is enhanced and cholesterol synthesis is downregulated.[11] Furthermore,[12] in type 1 diabetes IMT was associated with LDL cholesterol, brachial artery diameter was inversely associated with HDL cholesterol, and endothelial function was associated with serum sitosterol to cholesterol ratio, a marker of cholesterol absorption.[13] Accordingly, the objective of this study was to evaluate in more detail the interrelation of different vascular markers of preclinical atherosclerosis, especially those of arterial stiffness, and cholesterol metabolism. As a high-risk population of atherosclerosis, we recruited type 1 diabetes subjects without earlier macrovascular atherosclerotic complications.

Research design and methods

Subjects

Twenty-two subjects with type 1 diabetes were recruited to the cross-sectional study from our earlier study populations and through announcements in the local newspaper. The inclusion criteria were normal liver, kidney and thyroid function. The exclusion criteria were the presence of cardiovascular diseases, active inflammatory gastrointestinal disease, or lipid-lowering medication. Four subjects dropped out because ultrasound images of their carotid arteries were not possible to analyze adequately. Accordingly, eighteen subjects were included in the following analyses (Table 1).

Five subjects were males and 13 were females. The age of the subjects ranged from 20 to 56 years, and $HbA1_{1c}$ from 5.9% to 12.2%. The duration of diabetes was 13.3 $\pm$ 2.1 years with a range of 2—31 years. Mean body mass index (BMI) was 25.1 kg/m^2. Two subjects had microalbuminuria. Two were smokers. Serum total and LDL cholesterol values varied from 3.6 to 6.0 and from 1.3 to 3.8 mmol/l, and HDL cholesterol from 1.3 to 2.4 mmol/l, respectively. Serum triglycerides varied from 0.5 to 2.0 mmol/l.

Of the medication of the subjects in addition to long- and short acting insulin, one subject had calcium channel blockers, and four had angiotensin converting enzyme- or angiotensin receptor blocking agents, and one subject had a diuretic for hypertension. One subject used hormone replacement therapy, and two subjects used hormonal contraceptives. All medications and doses had been unchanged at least for three previous months. All subjects gave their written informed consent. The investigation was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was accepted by the Ethics Committee of the University of Kuopio.

Methods

Blood samples were drawn after 12-h fasting. Serum total and HDL cholesterol and serum triglycerides were analyzed using routine enzymatic methods, and LDL cholesterol was calculated with the Friedewald equation.

Serum cholesterol, squalene and non-cholesterol sterols were analyzed with gas—liquid chromatography (GLC) with