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Abnormalities in the relationship of paraoxonase 1 with HDL and apolipoprotein A1 and their possible connection to HDL dysfunctionality in type 2 diabetes

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ABSTRACT

Aims: Lipid parameters, lipid risk indexes and lipid-related oxidative stress markers (paraoxonase 1 [PON1] and lipid peroxides [LPO]) reflect the actual status of lipid metabolism in type 2 diabetes (T2DM). We hypothesized that relationships of high-density lipoprotein cholesterol (HDL-c) with PON1 and apolipoprotein A1 (ApoA1) and/or PON1 with ApoA1 under conditions of hyperglycaemia and oxidative stress might reveal HDL functionality. We investigated relationships between PON1, LPO, and lipid risk markers in T2DM subjects and compared them with those in healthy subjects.

Methods: A total of 107 Caucasian subjects, 67 T2DM outpatients (mean age 52.2 ± 6.9 years) and 40 healthy subjects (mean age 48.1 ± 7.5 years) were included in the study.

Serum levels of total cholesterol (CHOL-T), HDL-c, low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), apolipoprotein B (ApoB), ApoA1, LPO, and PON1 activity were measured. Non-HDL-c, ApoB/ApoA1 and non-HDL/HDL (lipid risk indexes) were calculated.

Results: Higher levels of TG, LPO ($P < 0.0001$), nonHDL/HDL and ApoB/ApoA1 ($P < 0.001$, 0.05, respectively), and lower levels of HDL-c, ApoA1, and PON1 ($P < 0.0001$) were observed in T2DM subjects than in controls. There is a lack of relationship among PON1, HDL-c, and ApoA1 in T2DM patients. PON1 activity positively correlated with these parameters ($P < 0.0001$) in controls. Strong correlations between non-HDL-c and ApoB ($r = 0.956$ vs.

Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; aryPON1, arylesterase activity of PON1; BMI, body mass index; CVD, cardiovascular disease; CHOL-T, total cholesterol; DM-C, patients with diabetes and CVD complications; DM-N, patients with diabetes and without CVD complications; GGC, good glycaemic control; HbA1C, glycated haemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; LPO, lipid peroxides; MPO, myeloperoxidase; non-HDL-c, non-high density lipoprotein cholesterol; OAD, oral anti-hyperglycaemic drugs; PON1, paraoxonase 1; PGC, poor glycaemic control; RGC, reasonable glycaemic control; TG, triglycerides; T2DM, type 2 diabetes

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0.756; P < 0.0001), LPO and TG (r = 0.831 vs. 0.739; P < 0.0001) were recorded in both study groups (P < 0.0001).

Conclusions: Impaired anti-oxidant and anti-atherogenic HDL properties associated with weakened PON1 function and lipid peroxidation may contribute to the development of atherosclerosis-related diseases in T2DM.

1. Introduction

Atherosclerosis-related diseases are the major cause of mortality and morbidity in subjects with diabetes. Type 2 diabetes is usually characterized by atherogenic dyslipidaemia with lower HDL-c levels, higher TG levels, excessive accumulation of cholesterol in the non-HDL (apolipoprotein B-containing) lipoproteins and altered composition of LDL particles [1,2]. When TG levels exceed the 2.3 mmol/L (200 mg/dL) threshold, there is an increased accumulation of the small, dense LDL particles in venous walls [3]. This status is closely linked to an increased risk of cardiovascular disease (CVD).

HDL functionality is based on the optimal function of all structural HDL components, such as apolipoproteins, lipid transfer proteins, enzymes, and phospholipids [4,5]. Anti-oxidant, anti-atherogenic and cardioprotective effects of HDL are associated with PON1 activity that is responsible for inhibition of lipid peroxidation by hydrolysis of phospholipid and cholesteryl ester hydroperoxides in lipoproteins. PON1 binds to HDL by an interaction with ApoA1 and phospholipids. It can protect not only LDL but also HDL against oxidative modification and thereby may inhibit the progression of atherosclerosis [6]. ApoA1 is responsible for the stability of enzymes such as PON1 and lecithin cholesterol acyl transferase.

PON1 is important for the anti-oxidant HDL function (*e.g.*, the redox inactivation of lipid hydroperoxides and their transfer to HDL) [7]. It is known that the oxidative hypothesis of atherosclerosis includes several mutually connected processes, such as oxidative stress; oxidative modification of lipids, lipoproteins and proteins; excessive production of reactive oxygen and nitrogen species in the vascular wall [8,9]. The formation and accumulation of oxidized LDL particles primarily within the vascular wall where they are taken up by macrophages by scavenger receptor pathways (formation of foam cells) leads to the production of pro-inflammatory cytokines [10]. PON1 activity can inhibit LDL oxidation and thereby atherogenesis.

Prolonged hyperglycaemia, dyslipidaemia and excessive oxidative stress are associated with oxidative and glycation damage to lipids and proteins, leading to the conversion of functional HDL into dysfunctional HDL. This status involves alterations in the reverse cholesterol transport, pro-oxidant, pro-inflammatory, pro-thrombotic and pro-apoptotic conditions, which are responsible for atherogenesis [11]. There is a strong interaction between glucose and lipid metabolism, mainly elevated TG and low HDL-c levels; therefore, glycated haemoglobin (HbA_{1C}) may play an important role in modulating this interaction. The altered metabolism of TG and HDL may not only be the consequence of disturbed glucose metabolism but also its cause [12]. Some studies have examined an impact of glycation on the HDL composition (ApoA1 structure) and HDL-associated PON1 activity [13–15]. The authors observed that the susceptibility to lipid peroxidation was higher in the HDL isolated from subjects with low PON1 activity than in subjects with higher PON1 activity. Moreover, HDL glycation was associated with the conformational changes of ApoA1 at the tryptophan position. It appears that glycated HDL and altered PON1 activity can potentiate the atherogenesis. Another study has shown that oxidative modification of tyrosine residues in the ApoA1 chain may worsen the anti-oxidant and anti-atherogenic functions of HDL (even at physiological HDL levels) and thus contribute to its dysfunction [9,16]. Specifically, structural modification of crucial HDL components by glycation or oxidation can impair the binding ability of apolipoproteins or enzyme activity [17]. Impaired binding ability of ApoA1 to the HDL particles and reduced PON1 activity may significantly affect anti-oxidant, anti-atherogenic and other HDL functions [18,19]. In summary, HDL dysfunctionality may be linked to an increased incidence of atherosclerosis-related diseases in T2DM subjects due to the loss of essential functions of some components bound to this lipoprotein.

We hypothesized that possible relationships of HDL with PON1 and ApoA1 and/or PON1 with ApoA1 under conditions of prolonged hyperglycaemia and oxidative stress could reflect HDL functionality in T2DM subjects. Therefore, the main objective of this study was to examine possible changes in the PON1 activity and LPO levels and to compare relationships between them and lipid risk markers in T2DM subjects with those in healthy subjects.

2. Materials and methods

2.1. *Study participants and design*

A total of 107 Caucasian subjects, 67 outpatients with previously diagnosed T2DM (43 men and 24 women; mean age 52.2 ± 6.9 years) and 40 healthy volunteers (22 men and 18 women; mean age 48.1 ± 7.5 years) were included in this study. T2DM patients were enrolled from the Department of Internal Medicine, Faculty of Medicine, Comenius University and Department of Diabetology and Metabolic Diseases, Metabol Clinik, Bratislava. Inclusion criteria were set as follows: age < 65 years, alanine aminotransferase and aspartate aminotransferase levels in the range of physiological values or less than 2.5 times the upper limit of this range. Because the incidence of non-alcoholic fatty liver disease is often associated with diabetes [20] and PON1 production is localized in the liver, patients with laboratory or clinical evidence