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Postprandial modulation of serum paraoxonase activity and concentration in diabetic and non-diabetic subjects

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Abstract *Objectives:* To analyse the HDL associated anti-oxidant enzyme paraoxonase-1, during postprandial hyperlipaemia.
Methods and results: Type 2 diabetic patients ($n = 72$), glucose intolerant patients ($n = 10$) and controls ($n = 38$) consumed a high fat:high carbohydrate meal. Blood samples were collected up to 4 h and analysed for lipids and paraoxonase-1. In vitro studies examined HDL function with respect to the enzyme. There were significant postprandial increases in serum triglycerides. Paraoxonase-1 activity decreased significantly throughout the postprandial phase. Concentrations of the enzyme initially decreased significantly, but returned to fasting concentrations at 4 h. Specific activities were significantly lower at 4 h, compared to fasting. The decrease in specific activity was linked to the dynamic phase of postprandial lipoprotein metabolism. Apo AI limited loss of paraoxonase-1. HDL isolated after being subjected to postprandial conditions in vitro had reduced capacity to associate with and stabilise PON1.
Conclusions: Postprandial hyperlipaemia was associated with changes to serum paraoxonase-1, consistent with a reduced anti-oxidant potential of HDL. No differences were observed between diabetic and non-diabetic patients, suggesting that the effect was linked to postprandial hyperlipaemia. Modifications to paraoxonase-1 could contribute to increased risk of vascular disease associated with postprandial lipaemia, particularly in diabetic patients, who are already deficient in serum paraoxonase-1.

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Introduction

Postprandial dyslipidaemia is a risk factor for cardiovascular disease [1]. It is of particular relevance to diabetic patients, as underlying metabolic anomalies linked to diabetes can exaggerate postprandial dyslipidaemia [2]. A number of pathological consequences arises from postprandial dyslipidaemia in type 2 diabetes, including an increase in oxidative stress and endothelial dysfunction [3,4].

The serum enzyme paraoxonase-1 (PON1) is considered to be one of the principal determinants of the anti-oxidant capacity of high density lipoproteins (HDL) [5]. This activity has led to the hypothesis that PON1 offers protection against atherosclerosis. In this context, absence of the enzyme has been unambiguously linked to lesion development in animal models [6,7], whilst data from human studies are consistent with reduced serum PON1 being associated with increased risk of coronary disease [8–10]. Moreover, certain patient subgroups at high risk of cardiovascular disease have reduced serum PON1, notably diabetic patients [11–14]. The ability to protect LDL from oxidation may be of particular relevance to diabetic patients as oxidized LDL has been implicated in endothelial dysfunction [3,15,16].

There is growing interest in factors that can modulate serum activity of PON1 [17]. Our recent studies have shown the importance of HDL, which greatly facilitates PON1 secretion [18]. Both the lipid and peptide components of HDL play a role, as phospholipids promote secretion of the enzyme whilst apolipoprotein (apo) AI stabilises PON1 after its association with HDL. In addition to a strong genetic influence [19], environmental factors also affect the enzyme. Amongst these, studies have shown that diet has an impact [20–24]. These reflect principally the longer-term impact of modulating diet composition. One group has reported on the enzyme in the postprandial phase, although this involved a fat meal with high content of oxidized lipids [25,26]. Oxidation products are known to inhibit PON1 activity [27]. Most studies have relied on activity alone to follow the enzyme, which may mask more fundamental changes in PON1 metabolism, given the susceptibility of enzyme activity to inactivation.

The present study was designed to examine serum PON1 in the postprandial phase after ingestion of a high fat meal. The aims were to examine the hypothesis that postprandial lipaemia would influence serum PON1 and to compare the responses in type 2 diabetic patients and non-diabetic subjects.

Methods

Study population

Type 2 diabetic and impaired fasting glucose (IFG) patients were recruited from the outpatient clinic, University Hospital, Lausanne. The diagnoses of type 2 diabetes and IFG were based on the 1998 WHO criteria. Healthy control subjects were matched for age and gender. The latter had fasting glycaemia <6.1 mmol/l, a BMI <30 and blood pressure $<140/90$. They had no history of heart, lung, kidney, endocrine or liver disease and were not taking any medication. The IFG subjects had the same characteristics as the healthy controls except for fasting glycaemia >6.1 mmol/l <7 mmol/l. The protocol was approved by the hospital Ethics Committee (Lausanne) and carried out in accordance with the principles of the declaration of Helsinki, as revisited in 2000. Written informed consent was obtained from all subjects.

Diabetic patients were treated with insulin alone ($n = 26$), oral anti-diabetics alone ($n = 30$; 8 with metformin alone, 1 with thiazolidinedione alone, 4 with sulfonylurea alone, 29 with more than one oral anti-diabetic) or with both insulin and oral anti-diabetic drugs ($n = 16$). Other medication included angiotensin converting enzyme inhibitor ($n = 46$), statin ($n = 35$), fibrate ($n = 5$), and aspirin ($n = 40$). The diabetic patients were routinely screened according to local guidelines for macroangiopathy and microangiopathy. In the presence of one or more cardiovascular risk factors, coronary artery disease was screened with either myocardial scintigraphy or stress test echocardiography, and if positive, a coronarography was performed. Peripheral vascular disease and cerebrovascular disease were screened for (history of claudication, stroke or with arterial Doppler of the legs and the carotid arteries if clinically relevant). Diabetic nephropathy was screened with the albumin:creatinine ratio calculated in a morning urinary spot [28] (considered positive if >2 mg/mmol) [18]. Diabetic retinopathy was screened by routine eye examination. Seven patients had macroangiopathy alone, 13 patients had microangiopathy alone, 17 had both macro- and microangiopathy and 35 were free of vascular complications.

Meal

All participants reported fasting at 8 a.m. The diabetic patients were asked not to take their usual medication, including insulin, the last dose