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Incident type 2 diabetes is associated with HDL, but not with its anti-oxidant constituent - paraoxonase-1: The prospective cohort PREVEND study

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ABSTRACT

Objective. High-density lipoprotein cholesterol (HDL-C) is an established risk marker for cardiovascular disease and consistently associated with type 2 diabetes risk. Serum paraoxonase-1 (PON-1) - an anti-oxidant constituent of HDL - is inversely associated with cardiovascular disease risk, but its relationship with incident type 2 diabetes is uncertain. We aimed to investigate the prospective association between PON-1 and type 2 diabetes risk.

Methods. PON-1 was measured as its arylesterase activity at baseline in the Prevention of Renal and Vascular End-stage Disease (PREVEND) prospective study of 5947 predominantly Caucasian participants aged 28–75 years with no pre-existing diabetes, that recorded 500 type 2 diabetes cases during a median follow-up of 11.2 years.

Results. Serum PON-1 was positively correlated with HDL-C ($r = 0.17$; $P < 0.001$). In analyses adjusted for conventional diabetes risk factors, the hazard ratio (95% CI) for type 2 diabetes per 1 standard deviation increase in PON-1 was 1.07 (0.98 to 1.18; $P = 0.13$), which remained non-significant (1.02 (0.93 to 1.12) $P = 0.65$) after additional adjustment for potential confounders. The association was unchanged on further adjustment for HDL-C (1.05 (0.96 to 1.15; $P = 0.29$). However, in subsidiary analyses in the same set of participants, serum HDL-C concentration was inversely and independently associated with risk of type 2 diabetes.

Conclusions. Incident type 2 diabetes is associated with HDL cholesterol but not with its anti-oxidant constituent - PON-1 - in a large cohort of apparently healthy men and women. The current data question the importance of PON-1 activity for the development of diabetes.

Abbreviations: BMI, body mass index; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HR, hazard ratio; PON-1, paraoxonase-1; PREVEND, Prevention of Renal and Vascular End-stage Disease; SD, standard deviation; SBP, systolic blood pressure; UAE, urinary albumin excretion.

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1. Introduction

High-density lipoprotein cholesterol (HDL-C) is an established risk marker for atherosclerotic cardiovascular disease (CVD) [1]. HDL-C levels have also been shown to be consistently associated with risk of type 2 diabetes [2–4]. HDL is known to exert antioxidant and anti-inflammatory properties [5,6]. Paraoxonase-1 (PON-1), which is synthesized by the liver [7], is an HDL-bound esterase enzyme and has well-established antioxidant and anti-inflammatory properties [5,6,8,9]. HDL essentially provides a vector that facilitates the secretion of PON-1 by the liver [10] and also creates a hydrophobic environment which could be important for PON-1 function [11]. In our recent prospective cohort analysis and meta-analysis of six population-based prospective studies, we have shown that serum PON-1 activity is inversely associated with CVD risk, but this association is at least in part dependent on HDL-C levels [12]. Evidence suggests that the ability of the HDL fraction to inhibit oxidative modification of low-density lipoproteins and its anti-atherogenic and cardioprotective effects are to a considerable extent explained by PON-1 activity [6,13,14]. Oxidative stress is known to play a central role in the aetiopathogenesis of diabetes [15–17] and therefore HDL may contribute to the pathophysiology of type 2 diabetes via its antioxidant effects. Patients with type 2 diabetes have also been consistently shown to exhibit low circulating PON-activity, albeit in conjunction with low HDL-C [18–20]. Taking together all the evidence, we hypothesized that PON-1 activity may be linked to type 2 diabetes risk. Data showing the relationship between serum PON-1 and type 2 diabetes are sparse and have largely been based on animal models and cross-sectional or case–control study designs [19,21,22]. Though a consistent body of observational evidence shows HDL to be prospectively linked to the development of type 2 diabetes [2–4], our search of the literature showed that the prospective relationship between serum PON-1 activity and type 2 diabetes has not been previously investigated. It is therefore not clear whether increased PON-1 activity reduces the risk of type 2 diabetes among apparently healthy individuals. Our primary objective was, therefore, to evaluate in detail the nature and magnitude of the prospective association between serum PON-1 activity and risk of type 2 diabetes in a population-based sample of 5947 participants free from pre-existing diabetes at baseline. A secondary objective was to investigate if the expected inverse association of serum HDL-C concentration with risk of type 2 diabetes was independent of PON-1 activity in the same set of participants.

2. Material and Methods

This report was conducted according to STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (Appendix A) [23].

2.1. Participants and Study Settings

The study population is based on the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, an observational, general population-based prospective cohort study which began in 1997, with participants (age range 28–75 years) drawn from inhabitants living in the city of Groningen in The Netherlands. The PREVEND study was designed to investigate the natural course of urinary albumin excretion and its relationship to renal disease and cardiometabolic outcomes. The description of the study design and recruitment processes has been described in detail previously [24]. The actual baseline cohort consisting of 8592 participants had baseline measurements performed between 1997 and 1998. For the present analyses, we excluded participants with a prevalent history of diabetes [defined by either a self-report of physician diagnosis or screening at first visits (1996–1997)], leaving a final cohort of 5947 participants who were free of baseline diabetes with non-missing information on serum PON-1 activity, several diabetes risk markers, and incident type 2 diabetes. The local medical ethics committee of the University Medical Center Groningen approved the PREVEND study and which was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent which was documented in a consent form approved by the medical ethics committee.

2.2. Risk factor Assessment

During two outpatient visits by study participants, baseline data on demographics, physical measurements (including anthropometrics), and cardiovascular and metabolic risk factors were assessed during five rounds of screening from 1997 to 1998 until January 1st, 2011. Information on use of medications was collected via data from pharmacy registries of all community pharmacies in the city of Groningen. Hypertension was defined by self-reported physician diagnosis, use of antihypertensive medication, or blood pressure ≥ 140/90 mmHg. After an overnight fast and 15 min of rest, venous blood was obtained from participants. All blood samples were taken between 8.00 and 10.00 am. Plasma samples were prepared by centrifugation at 4 °C.

Sera were stored at −80 °C until analysis. Serum PON-1 enzymatic activity was measured as its arylesterase activity, i.e. as the rate of hydrolysis of phenyl acetate into phenol, as described previously [25]. The inter-assay CV was 8%. Arylesterase activity, measured with this assay, is positively correlated with PON-1 enzymatic activity toward paraoxon [26]. HDL-C was measured by a homogeneous method (direct HDL, Aeroset System; Abbott Laboratories, Abbott Park, Illinois). Glucose, total cholesterol, triglycerides, total bilirubin, fasting insulin, creatinine, and cystatin C were measured using standard methods described previously [27–29]. Urinary albumin excretion (UAE) was estimated as the mean of two 24-h urine collections. Estimated glomerular filtration rate (eGFR), was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined creatinine-cystatin C equation [30]. Insulin resistance was estimated according to the homeostasis model assessment of insulin resistance (HOMA-IR) (the product of fasting glucose [mmol/l] and insulin [units/ml] divided by the constant 22.5 [31]).

2.3. Endpoint Ascertainment

New onset type 2 diabetes was ascertained if one or more of the following criteria were met during follow-up beyond 3 months after baseline: (i) fasting plasma glucose ≥7.0 mmol/L (126 mg/dL); (ii) random sample plasma glucose ≥11.1 mmol/L (200 mg/dL); (iii)