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High-density lipoproteins and adrenal steroidogenesis: A population-based study

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BACKGROUND: Cholesterol trafficked within plasma lipoproteins, in particular high-density lipoproteins (HDL), may represent an important source of cholesterol that is required for adrenal steroidogenesis. Based on a urinary gas chromatography method, compromised adrenal function has been suggested in men but not in women with (genetically determined) low plasma HDL-cholesterol (HDL-C).

OBJECTIVE: The objective of the article was to examine the extent to which glucocorticoid production relates to HDL-C in a population-based cohort.

METHODS: A total of 240 subjects (120 men and 120 women, aged 20–79 years) without relevant comorbidities were recruited from the general population. Glucocorticoid metabolites were measured by gas chromatography with tandem mass spectrometric detection in 24-hour urine collections to estimate total glucocorticoid production (TGP). Fasting plasma (apo)lipoproteins were assayed by routine methods.

RESULTS: TGP was not decreased but tended to be increased in subjects with low HDL-C (NCEP-ATPIII criteria; $P = .094$). In univariate analysis, TPG was correlated inversely with HDL-C ($r = -0.353$, $P < .001$) and apoA-I ($r = -0.263$, $P = .01$). Multivariable linear regression analysis demonstrated that TGP was still inversely related to HDL-C ($\beta = -0.145$, $P = .019$) or alternatively to low HDL-C ($\beta = -0.129$, $P = .013$) taking age, sex, current smoking, and other metabolic syndrome components into account.

CONCLUSION: In this population-based study, urinary glucocorticoid metabolite excretion was inversely associated with HDL-C. We found no evidence for an attenuated adrenal function in men and women with low HDL-C.
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Introduction

Steroid hormones synthesized by adrenal glands play a key role in multiple physiologic processes including glucose metabolism, (inflammatory) stress responses, and the maintenance of fluid and electrolyte balance.[1] Cholesterol is the

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precursor of adrenal steroid hormones including glucocorticoids.[2] Cholesterol required for adrenal steroidogenesis can be derived from *de novo* intracellular synthesis, from intracellular catabolism of stored cholesteryl esters, as well as via uptake of cholesterol transported by circulating lipoproteins.[3,4] Cholesterol trafficked within plasma lipoproteins is considered to represent an important source of cholesterol that is used for steroidogenesis by the adrenal glands.[5–7] Accordingly, studies in rodents have delineated that impaired adrenal steroidogenesis is a feature of scavenger receptor class B, type 1 deficiency, the receptor that plays a pivotal role in cellular uptake of high-density lipoprotein (HDL)-cholesteryl esters.[8–10] Likewise, attenuated adrenal function has been documented in a few human subjects with heterozygous scavenger receptor class B, type 1 deficiency.[11] Interestingly, decreased urinary 17-ketogenic steroid excretion, suggestive of compromised adrenal function, has been suggested in men with low HDL-cholesterol (HDL-C) both with and without heterozygous lecithin:cholesterol acyltransferase (LCAT) or ATP-binding cassette transporter 1 (ABCA1) deficiency.[7] Remarkably, no relationship of partial HDL-C deficiency with diminished urinary glucocorticoid metabolite excretion has been observed in women.[12] Moreover, even mild glucocorticoid excess is likely to be associated with a greater waist circumference and higher triglycerides,[13,14] which are well known to be associated with low HDL-C.[15,16]

In view of the uncertainties with respect to the relationships between low HDL-C and glucocorticoid metabolism, it is relevant to better delineate the relationship of HDL-C with cortisol production in men and women subjects without rare genetic deficiencies affecting HDL metabolism. The aim of the present cross-sectional study was to delineate the relationship of urinary steroid metabolite excretion, measured using a novel gas chromatography-tandem mass spectrometry (GC-MS/MS)-based method, with HDL-C levels among healthy subjects recruited from the general population.

Subjects and methods

Two-hundred forty subjects were selected from the LifeLines Cohort Study, a large population-based cohort study in the northern part of The Netherlands.[13] The study had been approved by the Medical Ethics Committee of the University of Groningen, The Netherlands, and all participants provided written informed consent. From 6 age decades (20–79 years), 20 men and 20 women were selected, resulting in a cohort of 120 men and 120 women. The 60 women aged >50 years were considered to be postmenopausal. None of the subjects had reported comorbidities, and none used medications. Women using oral contraceptives were excluded. Biometric data were collected by a trained technician. Blood pressure was recorded every minute for 10 minutes using automated Dinamap Monitor (GE Healthcare, Freiburg, Germany) and the average of the last 3 readings was determined. Blood was drawn after overnight fasting between 8.00 and 10.00 AM. A 24-hour urine collection was obtained from all participants.

Laboratory methods

Total cholesterol and HDL-C levels were determined using an enzymatic colorimetric method, low-density lipoprotein-cholesterol (LDL-C) using a homogenous enzymatic colorimetric assay and triglycerides using an enzymatic colorimetric method, all on a Roche Modular P chemistry analyzer (Roche, Basel, Switzerland). For cholesterol, 1 mmol/L corresponds to 38.67 mg/dL; for triglycerides, 1 mmol/L corresponds to 88.5 mg/dL. Apolipoprotein (apo) A-I and B were determined using a nephelometric immunoassay (BN II, Siemens Healthcare Diagnostics, Germany). Glucose was measured by the hexokinase method; 1 mmol/L corresponds to 18 mg/dL.

Urinary steroid profiling using gas chromatography with tandem mass spectrometric detection (GC-MS/MS) was performed at the Laboratory, University Medical Centre Groningen of 24-hour urine collections of all subjects. Based on our elaborate experience with GC-MS,[17] we further improved this assay by developing a GC-MS/MS method, which measures 33 selected steroid metabolites to evaluate adrenal steroidogenesis.[18] Cortisol is interconverted to cortisone by the 11β-hydroxysteroid dehydrogenase system, followed by reduction to tetrahydrocortisol (THF), allo-tetrahydrocortisol (allo-THF), and tetrahydrocortisone (THE), respectively. THF and allo-THF can then be further reduced to α- and β-cortols, whereas THE is reduced to cortolones.[19] Total glucocorticoid production (TGP) was estimated as the sum of THF, allo-THF, cortols, and cortolones.[20] Total androgen production (TAP) was estimated as the sum of A, E, DHEA, 11keto-E, 11OH-A, 11OH-E, 16OH-DHEA, 16keto-A2, 16keto-A3, and di-OH-DHEA.

Statistical analysis

Statistical analysis was done using SPSS (version 22; IBM Corporation, Armonk, NY, USA). Data are expressed as mean ± standard deviation or median with interquartile range as appropriate. To compare subjects with and without low HDL-C, cut-off values according to NCEP-ATP III criteria were applied (<1.03 mmol/L for men <1.30 mmol/L for women).[21] Differences between groups were determined by unpaired *t*-test, Mann–Whitney U test, or Chi-square test where appropriate. Because of skewed distribution, logarithmically transformed values were used of TGP, TAP, and triglycerides for correlation analysis. Univariate relationships were determined using Pearson's correlation coefficients. Multivariable linear regression analyses were carried out to disclose the relationship of TGP with HDL-C or apoA-I taking account of age, sex, and smoking status, as well as systolic blood pressure, waist, glucose, and triglycerides, representing metabolic syndrome components. Two-sided *P* values <.05 were considered significant.

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