CLINICAL STUDY

Positive association between plasma IGF1 and high-density lipoprotein cholesterol levels in adult nondiabetic subjects

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Abstract

Aims: Low IGF1 levels have been associated with an increased cardiovascular risk. It is unknown however whether IGF1 mediates the atherosclerotic process by modulating high-density lipoprotein cholesterol (HDL-C) independently from confounders. To address this issue, we evaluated the association between IGF1 levels and HDL-C in nondiabetic subjects.

Methods: A cross-sectional analysis was used in the context of the CATanzaro MEtabolic Risk factors Study. One thousand and four participants (aged 20–69 years), for whom HDL-C and IGF1 measurements were available, were eligible for the study.

Results: After adjusting for gender and age, IGF1 levels were positively correlated with HDL-C, and negatively correlated with body mass index (BMI), waist circumference, blood pressure (BP), triglyceride, fasting insulin, and homeostasis model assessment (HOMA). In a logistic regression model adjusted for age and gender, IGF1 in the lowest tertile (<125 ng/ml) was associated with an increased risk of having low HDL-C (odds ratio (OR) 2.14, 95% confidence interval (CI) 1.4–3.0; $P=4 \times 10^{-5}$) compared with the highest tertile (>186 ng/ml). When BMI, waist circumference, total cholesterol, triglyceride, and HOMA index were added to the model, IGF1 remained significantly associated with increased risk of low HDL-C (OR 1.52, 95% CI 1.01–2.31; $P=0.04$). A stepwise multivariate regression analysis in a model including age, gender, BMI, total cholesterol, triglycerides, IGF1, HOMA, and BP showed that the variables significantly associated with HDL-C were gender ($P<0.0001$), triglycerides ($P<0.0001$), total cholesterol ($P<0.0001$), BMI ($P<0.0001$), IGF1 levels ($P<0.0001$), and HOMA ($P=0.001$), accounting for 32.6% of its variation.

Conclusions: These data provide evidence that IGF1 may be an independent modulator for HDL-C in nondiabetic individuals.

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Introduction

It has been suggested by several studies that low circulating levels of insulin-like growth factor 1 (IGF1) within the normal range play an important role in the development of cardiovascular diseases (1–6). Cross-sectional studies have shown an inverse linear correlation between IGF1 levels and carotid intima-media thickness in healthy individuals (1), and low circulating IGF1 levels have been associated with angiographically documented coronary artery disease (2). In subjects with acute myocardial infarction, circulating IGF1 levels on hospital admission were decreased compared with those of healthy controls, and lower levels were associated with a worse prognosis (3). Moreover, population-based prospective studies have suggested that low circulating levels of IGF1 within the normal range may predict an increased risk of ischemic

heart disease (4, 5), and nonfatal myocardial infarction (6). In contrast with these findings, it has been reported that serum IGF1 levels are independently associated with coronary artery disease progression in young male survivors of myocardial infarction, and a reduction in serum IGF1 levels could account, at least in part, for the effect of benzafibrate on progression of focal coronary atherosclerosis (7). In addition, coronary heart disease has been reported to be independently associated with higher serum levels of IGF1 (8). Furthermore, in a cross-sectional study, carried out in 6773 primary care patients, high IGF1 levels were reported to be associated with an increased risk for coronary artery disease; interestingly, in the same cohort, women, but not men, with the lower IGF1 levels also showed an increased risk for coronary artery disease (9).

The mechanism by which low IGF1 levels exert their detrimental effects on the cardiovascular system has not

yet been completely elucidated. Low circulating IGF1 levels have been associated with several cardiovascular risk factors, including obesity (7), impaired glucose tolerance/diabetes (10, 11), insulin resistance (12, 13), endothelial dysfunction (14), left ventricular hypertrophy (15), and inflammatory factors (16), all of which are potential contributors to the observed increased risk.

Additionally, IGF1 could mediate the atherosclerotic process by affecting high-density lipoprotein cholesterol (HDL-C), a strong, independent risk factor for cardiovascular disease (17, 18). HDL-C is a significant predictor of cardiovascular events even in subjects who have achieved low-density lipoprotein (LDL) cholesterol targets with statin therapy (19). Although HDL-C is one of the component of the metabolic syndrome, and low circulating IGF1 has been associated with the risk of having the metabolic syndrome (12), there is only sparse evidence in the literature on the relationship between circulating IGF1 levels and HDL cholesterol (1, 20, 21). A positive association between serum IGF1 levels and HDL-C has been reported in 132 elderly subjects (age range, 69–91 years) (20), but not in 174 healthy individuals (age range, 18–80 years) (1), or in 81 men (<45 years old) who survived a first myocardial infarction (7), whereas a weak negative correlation between IGF1 levels and HDL-C has been observed in 6773 primary care patients (>18 years old) (9). A positive association between fetal IGF1 levels and HDL-C has been reported in 139 offspring of mothers with type 1 diabetes and 48 control subjects at birth (21). Therefore, data on the relationship between circulating IGF1 levels and HDL-C in middle-aged nondiabetic adults are limited. In particular, in a mechanistic perspective, it is poorly understood whether IGF1 has a role in modulating HDL-C independently from insulin resistance, a known modulator of HDL-C. The investigation of the putative role played by IGF1 and insulin resistance requires the use of multivariable statistical models in large-scale studies. We used this approach with the aim to evaluate whether circulating IGF1 levels are independently associated with HDL-C in a large cohort of nondiabetic adult subjects.

Methods

The study group consisted of 1004 Caucasian subjects participating in the CATanzaro MEtabolic RIsk factors Study (CATAMERIS), a disease prevention campaign having, at least, one cardiometabolic risk factor including age, blood pressure (BP), lipids, glucose tolerance, body mass index (BMI), and family history for diabetes (12, 16). Recruitment mechanisms included word-of-mouth, flyers, and newspaper advertisements. Subjects, aged 20–69 years, were excluded if they had diabetes mellitus (fasting plasma glucose >126 mg/dl), serum triglycerides >400 mg/dl, chronic gastrointestinal diseases associated with

malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatments with lipid-lowering agents. After 12-h fasting, all subjects underwent anthropometrical evaluation, and a venous blood sample was drawn for laboratory determinations. Height and weight were measured to the nearest 0.5 cm and 0.1 kg respectively. BMI was calculated as body weight (kilograms) divided by the square of height (meters). Waist (at the midpoint between the lateral iliac crest and lowest rib) was measured to the nearest 0.5 cm. Readings of clinical BP were obtained in the left arm of the supine patients, after 5 min of quiet rest, with a mercury sphygmomanometer. Values were calculated as the average of the last two of three consecutive measurements obtained at 3-min intervals. Glucose, triglyceride, and total and HDL cholesterol concentrations were measured by an enzymatic method (Roche). Plasma insulin concentration was determined by a chemiluminescence-based assay (Immulite, Siemens, Italy). Plasma IGF1 concentrations were determined by chemiluminescent immunoassay (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA). The minimum detectable concentration was 0.03 mg/l, and the maximal intra- and inter-assay coefficients of variation were 6 and 7% respectively. All samples were assayed in triplicate, and in random order, blinded to HDL values. Insulin resistance was estimated by the homeostasis model assessment (HOMA) index.

Low HDL-C was defined as levels of 40 mg/dl for men or <50 mg/dl for women, according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III. The study was approved by Institutional Ethics Committees, and written consent was obtained from all participants.

Statistical analysis

Triglyceride and IGF1 were natural log transformed for statistical analysis due to their skewed distribution. Partial correlation coefficients adjusted for age and gender were computed between variables. Relationships between variables were sought by multivariable linear regression analysis in order to assess their independent contribution to HDL-C. A multivariable logistic regression analysis was used to determine the association between the tertiles of IGF1 and the low HDL-C. A two-tailed *P* value <0.05 was considered statistically significant. All analysis were performed using SPSS (Chicago, IL, USA) software programme Version 12.0 for Windows.

Apriori power calculation using the Russ Lenth's power analysis software, <http://www.stat.uiowa.edu/~rlenth/Power/index.html>, indicated that the sample used in this study would allow the detection of an association between HDL levels and up to ten variables with 98% power ($\alpha < 0.05$) in a regression analysis. Using the PS power analysis software, <http://biostat.mc.vanderbilt.edu/PowerSampleSize>, we estimated to have

Table 1 Anthropometric and biochemical characteristics of the study subjects, and correlation. Data are means $\pm$ s.d.

	Study subjects	Age- and gender-adjusted correlations between plasma IGF1 levels and cardiometabolic variables		Age- and gender-adjusted correlations between HDL levels and cardiometabolic variables	
		Pearson's correlation coefficient (<i>r</i>)	<i>P</i>	Pearson's correlation coefficient (<i>r</i>)	<i>P</i>
Gender (M/F)	455/549	—	—	—	—
Age (years)	46 $\pm$ 11	−0.41 ^a	<0.0001	−0.05 ^a	0.11
BMI (kg/m ²)	29.8 $\pm$ 6.1	−0.22	<0.0001	−0.29	<0.0001
Waist circumference (cm)	98 $\pm$ 14	−0.23	<0.0001	−0.29	<0.0001
SBP (mmHg)	133 $\pm$ 17	−0.14	<0.0001	−0.05	0.12
DBP (mmHg)	83 $\pm$ 10	−0.09	0.005	−0.06	0.08
Total cholesterol (mg/dl)	202 $\pm$ 39	0.03	0.22	0.14	<0.0001
HDL cholesterol (mg/dl)	52 $\pm$ 14	0.17	<0.0001	—	—
Triglycerides (mg/dl)	119 $\pm$ 61	−0.08	0.007	−0.33	<0.0001
Fasting glucose (mg/dl)	92 $\pm$ 11	−0.03	0.22	−0.10	0.001
Fasting insulin (μ U/ml)	12 $\pm$ 8	−0.11	<0.0001	−0.23	<0.0001
IGF1 (ng/ml)	168 $\pm$ 79	—	—	0.18	<0.0001
HOMA	3.0 $\pm$ 2.2	−0.14	<0.0001	−0.24	<0.0001

Fasting triglyceride, insulin, and IGF1 levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale. M, male; F, female; SBP, systolic blood pressure; DBP, diastolic blood pressure.

^aAdjusted for gender.

a 97% power ($\alpha < 0.05$) to detect an association with an OR as small as 1.50 between low HDL levels and IGF1 concentrations.

Results

Anthropometric and biochemical characteristics of the study subjects are shown in Table 1. After adjusting for gender and age, IGF1 levels were positively correlated with HDL-C, and negatively correlated with BMI, waist circumference, systolic and diastolic BP, triglyceride, fasting insulin, and HOMA index (Table 1). After adjusting for gender and age, HDL-C was negatively correlated with BMI, waist circumference, triglyceride, fasting glucose, fasting insulin, and HOMA index, and positively correlated with total cholesterol (Table 1).

The prevalence of low HDL-C was 32.6% (179 out of 549) in women, and 28.6% (130 out of 455) in men. In a logistic regression model adjusted for age and gender, IGF1 in the lowest tertile (< 125 ng/ml) was associated with an increased risk of having low HDL-C (odds ratio (OR) 2.14, 95% confidence interval (CI) 1.4–3.0; $P = 4 \times 10^{-5}$) compared with the highest tertile (> 186 ng/ml). When BMI, waist circumference, total

cholesterol, triglyceride, fasting glucose, and insulin levels were added to the model, IGF1 remained significantly associated with an increased risk of low HDL-C (OR 1.54, 95% CI 1.02–2.33; $P = 0.04$). When fasting glucose and insulin levels were replaced by HOMA index into the logistic regression model, IGF1 remained significantly associated with an increased risk of low HDL-C (OR 1.52, 95% CI 1.01–2.31; $P = 0.04$).

To estimate the independent contribution of the different variables to HDL-C, we carried out a stepwise forward multivariable regression analysis in a model including age, gender, BMI, total cholesterol, triglycerides, IGF1, and HOMA index. As shown in Table 2, the variables that remained significantly associated with HDL were gender ($P < 0.0001$), triglycerides ($P < 0.0001$), total cholesterol ($P < 0.0001$), BMI ($P < 0.0001$), IGF1 levels ($P < 0.0001$), and HOMA ($P = 0.001$), accounting for 32.6% of its variation. Each unit increase in log transformed IGF1 concentrations (or 2.71 ng/dl increase in actual IGF1 concentrations) was associated with a 2.96 mg/dl increase in HDL levels. The same results were obtained when HOMA was replaced by fasting insulin and glucose levels (data not shown).

Table 2 Stepwise forward multivariate regression analysis.

	Partial r^2 (%)	Total r^2 (%)	β	<i>t</i>	<i>P</i>
Gender	13.0	13.0	−0.299	−10.864	<0.0001
Triglycerides	8.5	21.5	−0.309	−10.150	<0.0001
Total cholesterol	5.4	26.9	0.241	8.389	<0.0001
BMI	3.7	30.6	−0.146	−4.956	<0.0001
IGF1 levels	1.2	31.8	0.104	3.770	<0.0001
HOMA	0.8	32.6	−0.100	−3.415	0.001

Independent predictors of HDL after stepwise forward multivariate regression analysis in a model including gender, age, BMI, total cholesterol, triglycerides, HOMA, and IGF1 levels.

Discussion

In this study, we report a positive association between HDL-C and plasma IGF1 levels in a relatively large cohort of adult nondiabetic subjects. This observation is consistent with two previous studies carried out in elderly subjects and offspring of mothers with type 1 diabetes at birth (20, 21), but not with three other studies carried out in healthy individuals (1), in men who survived a first myocardial infarction (7), and in primary care patients bearing various cardiometabolic risk factors (9). It is possible that differences in clinical characteristics and concomitant treatments for cardiometabolic risk factors may explain these divergent results. Furthermore, the findings that adult patients with GH deficiency have lower HDL-C levels than age-matched controls, and that their HDL-C levels are increased by a GH replacement therapy (22) support the notion that IGF1 has a relevant role in modulating serum HDL concentration.

Importantly, we found that the positive association between HDL-C and plasma IGF1 levels was independent from known modulators of plasma HDL-C including gender, adiposity, total cholesterol, triglyceride, and glucose levels.

Mechanistically, IGF1 may influence HDL-C by modulating insulin sensitivity. In fact, clinical studies carried out in patients with type 2 diabetes or with extreme insulin resistance have shown that recombinant IGF1 administration significantly increases insulin sensitivity (23). Moreover, low IGF1 levels may contribute to insulin resistance by up-regulating hybrid insulin/IGF1 receptors whose expression is increased in insulin-resistant individuals and is negatively correlated with insulin sensitivity (24). There is compelling evidence that insulin resistance plays a pathogenic role in several steps of the HDL-C metabolism (25, 26). Insulin resistance leads to an increased flux of free fatty acids from adipose tissue to the liver, and an enhanced synthesis of triglyceride-rich lipoproteins. This favors the exchange of core lipids, mediated by cholesterol ester transfer protein, between triglyceride-rich lipoproteins and HDL leading to triglyceride enrichment of HDL particles. These particles are good substrates for hepatic lipase, and hydrolysis of triglycerides produces smaller particles that are cleared by the kidneys (25). In addition, insulin resistance may lead to the down-regulation of the ATP-binding cassette, subfamily A, member 1, a key molecule in lipidating newly secreted apolipoprotein A-I (ApoA-I) to produce nascent HDL particles that undergo maturation in plasma, resulting in a reduction in HDL-C levels (27). In the present study, the finding that the strength of the association between IGF1 levels and low HDL-C is attenuated, but not abolished, in the multivariable analysis when HOMA index is added to the model indicates that the effects of IGF1 on HDL-C are only partly explained by the effect of IGF1 on insulin sensitivity. An alternative mechanism

by which IGF1 may modulate HDL-C levels involves IGF1-dependent regulation of hepatic scavenger receptor of class BI (SR-BI). SR-BI mediates the high affinity binding of HDL and the selective uptake of HDL-derived lipids into cells (28). It has been shown in *in vitro* studies with the human hepatoma cell line HepG2 that IGF1 downregulates the expression of SR-BI (29). Thus, it is possible to speculate that a reduction in circulating IGF1 levels may result in the upregulation of SR-BI leading to an increased HDL-C uptake by the liver and a decrease in circulating HDL-C concentration.

The relatively large sample size, the inclusion of both sexes, and the centralization of laboratory analysis are major strengths of this study. However, our study has some limitations that require consideration. Serum HDL-C and IGF1 were measured once. Small changes in these variables would therefore be expected if the same measurements were repeated on a separate day. However, a single nonfasting IGF1 assay has been shown to effectively characterize individual levels over at least 1 year (30). Unfortunately, measurements of ApoA1 and ApoB levels were available only for 222 subjects. In this subgroup, HDL-C was positively correlated with ApoA1 ($r=0.14$; $P=0.03$), but not with ApoB or ApoB/ApoA1 ratio, after adjusting for gender and age. Further studies with adequate power are needed to determine whether IGF1 modulates HDL-C by increasing ApoA1 levels. In addition, IGF-binding proteins (IGFBPs), such as IGFBP1 and IGFBP3, and free IGF1 levels were not measured, and this should be considered another limitation of the study. Moreover, it should be noted that to estimate insulin sensitivity, we used the HOMA index which may not be as solid and reliable as a direct measurement of insulin sensitivity by a 'gold standard' test such as the euglycemic hyperinsulinemic clamp technique. However, this is not feasible in large-scale studies, and HOMA index primarily reflects insulin sensitivity at the liver level, the main organ involved in HDL-C and IGF1 synthesis. Thus, we believe that HOMA index is a proxy measure of insulin sensitivity that is reliable with large datasets such as the one in this study. The present study is an observational study based on outpatients seen at a referral university hospital, representing subjects at increased risk for cardiometabolic disease, and, therefore, may not be extendible to the general population. Finally, the present findings are only based on Caucasian individuals, and different results might be observed in other ethnic groups.

In conclusion, we showed a positive association between HDL-C and plasma IGF1 levels in a cohort of nondiabetic adult subjects. The positive association between HDL-C and plasma IGF1 levels was independent from known modulators of plasma HDL-C including gender, adiposity, total cholesterol, triglyceride, and glucose levels. Low IGF1 levels (<125 ng/ml) were associated with an increased risk of having low HDL-C even after adjusting for several confounding variables.

An increase of 2.71 ng/dl in IGFI concentrations was associated with a 2.96 mg/dl increase in HDL levels, thus suggesting that variations in IGF1 concentrations may have a clinically meaningful impact on HDL levels.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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