Reciprocal Association of Plasma IGF-1 and Interleukin-6 Levels With Cardiometabolic Risk Factors in Nondiabetic Subjects

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OBJECTIVE — To examine the relationship between plasma IGF-1 and interleukin-6 (IL-6) levels in Caucasian nondiabetic subjects and evaluate the association of IGF-1 and IL-6 with the cardiometabolic risk factors characterizing metabolic syndrome (MetS).

RESEARCH DESIGN AND METHODS — The study group consisted of 186 Caucasian nondiabetic subjects who underwent an oral glucose tolerance test and an euglycemic-hyperinsulinemic clamp. A logistic regression analysis, adjusted for age and sex, was used to determine the association between tertiles of IGF-1 and IL-6 and the MetS and its components.

RESULTS — After adjusting for age and sex, both IGF-1 and IL-6 were correlated with insulin resistance and individual components of MetS, but in opposite directions. In the logistic regression model adjusted for age and sex, higher IL-6 and lower IGF-1 levels confer increased risk of having MetS and its two underlying pathophysiological abnormalities, i.e., visceral obesity and insulin resistance.

CONCLUSIONS — The present results raise the possibility that lowered protection against inflammation, i.e., lower IGF-1 levels, may have a role in the development of MetS and its features, resulting in an imbalance between proinflammatory and anti-inflammatory proteins.

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Metabolic syndrome (MetS) is a condition characterized by a clustering of interrelated cardiometabolic risk factors and is associated with increased risk for both type 2 diabetes and atherosclerotic cardiovascular disease (1,2). Visceral obesity and insulin resistance are considered central to the pathophysiology of MetS. Growing evidence suggests a link between a low-grade inflammatory state and MetS (1,2). With increased visceral adiposity, proinflammatory cytokine production is enhanced, causing insulin resistance. MetS is associated with abnormalities in the growth hormone/IGF-1 axis, resulting in low plasma IGF-1 levels (3). IGF-1 has anti-inflammatory effects and decreases expression of proinflammatory cytokines such as interleukin-6 (IL-6) (4). There is also evidence in animal models that IL-6 decreases circulating IGF-1 levels (5), suggesting that an unpaired balance between proinflammatory and anti-inflammatory cytokines may have a role in the development of MetS. The aim of this study was to examine the relationship between plasma IGF-1 and IL-6 levels in a cohort of nondiabetic subjects and to evaluate the association of IGF-1 and IL-6 with the cardiometabolic risk factors characterizing MetS.

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RESEARCH DESIGN AND METHODS

— The study group consisted of 186 Caucasian nondiabetic subjects participating in the CAtanzaro MEtabolic RIsk factors Study (CATAMERIS), a metabolic disease prevention campaign for cardiometabolic risk factors (6). After 12-h fasting, subjects underwent an oral glucose tolerance test and a euglycemic-hyperinsulinemic clamp, as previously described (6). Whole-body glucose disposal (WBGD) was calculated as reported (6). Insulin resistance was also estimated by homeostasis model assessment (HOMA). MetS was defined according to American Heart Association and National Heart, Lung, and Blood Institute criteria. The study was approved by the institutional ethics committees, and written consent was obtained from all participants. Variables with skewed distribution were log transformed for analyses. Pearson's correlation coefficients were used to compute correlations between variables. A logistic regression analysis was used to determine the association between the tertiles of IGF-1 or IL-6 and the MetS and its individual components. Relationships between variables were sought by multivariate linear regression analysis to assess the magnitude of their effect on WBGD.

RESULTS

—Anthropometric and biochemical characteristics of the study subjects are shown in Table 1. After adjusting for sex and age, IGF-1 levels were negatively correlated with BMI, waist circumference, systolic blood pressure, triglycerides, fasting insulin, and HOMA and positively correlated with WBGD. After adjusting for age and sex, IL-6 levels were positively correlated with BMI, waist circumference, systolic blood pressure, fasting insulin, and HOMA and negatively correlated with WBGD and IGF-1 levels. In a logistic regression model adjusted for age and sex, IGF-1 in the lowest tertile (<135 ng/ml) was associated with an increased risk of having MetS (odds ratio [OR] 3.07 [95% CI 1.2–7.9]), low HDL choldesterol (3.15, [1.2–8.1]), and larger

Table 1—*Anthropometric and biochemical characteristics of study subjects*

		Age- and sex-adjusted correlations between plasma IGF-1 levels and cardiometabolic variables		Age- and sex-adjusted correlations between plasma IL-6 levels and cardiometabolic variables	
	Study subjects	Pearson's correlation coefficient (*r*)	*P*	Pearson's correlation coefficient (*r*)	*P*
Sex (M/F)	80/106	—	—	—	—
Age (years)	41 ± 14	−0.53*	0.0001	0.30*	0.0001
BMI (kg/m^2)	30.1 ± 8.4	−0.28	0.0001	0.33	0.0001
Waist circumference (cm)	97 ± 16	−0.29	0.0001	0.35	0.0001
SBP (mmHg)	127 ± 19	−0.15	0.04	0.15	0.04
DBP (mmHg)	80 ± 11	−0.10	0.18	0.13	0.08
Total Cholesterol (mg/dl)	198 ± 41	0.03	0.66	−0.006	0.95
HDL Cholesterol (mg/dl)	54 ± 14	0.11	0.11	−0.07	0.33
Triglyceride (mg/dl)	121 ± 69	−0.19	0.01	0.10	0.15
Fasting Glucose (mgl/dl)	90 ± 14	0.03	0.63	−0.007	0.93
2-h glucose (mg/dl)	117 ± 39	−0.07	0.42	0.13	0.11
Fasting Insulin (μU/ml)	12 ± 7	−0.16	0.03	0.28	0.0001
IGF-1 (ng/ml)	191 ± 90	—	—	−0.15	0.04
IL-6 (pg/ml)	2.5 ± 2.2	−0.15	0.04	—	—
HOMA	2.7 ± 1.8	−0.21	0.004	0.22	0.002
WBGD (mg · kg^{-1} · min^{-1})	7.6 ± 3.2	0.29	0.002	−0.35	0.0001
AHA-NHLB–defined metabolic syndrome (yes/no)	60/126 (32.3)	—	—	—	—
High waist circumference (≥102 cm for men and ≥88 cm for women) (yes/no)	91/95 (48.9)	—	—	—	—
High fasting glucose (≥100 mg/dl) (yes/no)	47/139 (25.3)	—	—	—	—
High triglyceride (≥150 mg/dl l) (yes/no)	50/136 (26.8)	—	—	—	—
Low HDL (<40 mg/dl in men or <50 mg/dl in women) (yes/no)	54/132 (29.0)	—	—	—	—
High blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg) (yes/no)	101/85 (54.6)	—	—	—	—

Data are means ± SD and *n* (%). Fasting plasma insulin, triglycerides, and IL-6 levels were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale. DBP, diastolic blood pressure; SBP, systolic blood pressure. *Adjusted for sex.

waist circumference (4.67, [1.8–11.9]) compared with the highest tertile (>221 ng/ml). After adjusting for age, sex, and lipid levels, IGF-1 in the lowest tertile was associated with increased risk of insulin resistance, i.e., the highest HOMA tertile (3.08, [1.2–7.6]) or lowest WBGD tertile (3.31, [1.01–10.9]). Conversely, in a logistic regression model adjusted for age and sex, IL-6 in the highest tertile (>2.5 pg/ml) was associated with an increased risk of having MetS (3.21 [1.2–8.1]), high blood pressure (2.63 [1.1–6.4]), and larger waist circumference (4.42 [1.8–11.0]) compared with the lowest tertile (<1.3 pg/ml). After adjusting for age, sex, and lipid levels, IL-6 in the highest tertile was associated with increased risk of insulin resistance, i.e., the highest HOMA tertile (2.14, [1.01–5.31]) or lowest WBGD tertile (4.64, [1.5–14.1]). To estimate the independent contribution of variables to WBGD, we carried out a multivariate regression analysis in a model including age, sex, BMI, waist circumference, triglycerides, HDL cholesterol, IL-6, IGF-1, and fasting and 2-h postchallenge glucose levels. The four variables that remained significantly associated with WBGD were age ($P = 0.01$), waist circumference ($P = 0.01$), 2-h postchallenge glucose ($P = 0.001$), and IL-6 ($P = 0.04$), accounting for 61.2% of its variation.

CONCLUSIONS — In this study, we report an inverse relationship between plasma IGF-1 and IL-6 levels consistent with clinical (7) and experimental data showing that IGF-1 acts as an anti-inflammatory molecule inhibiting IL-6 expression (4) and that IL-6 decreases IGF-I levels by increasing its clearance (5). Both IGF-1 and IL-6 are associated with MetS and its individual components, but in opposite directions. Higher IL-6 and lower IGF-1 levels confer increased risk of having MetS and its two underlying pathophysiological abnormalities, i.e., visceral obesity and insulin resistance. Interestingly, multivariate regression analysis showed that IL-6 but not IGF-1 levels were independently associated with WBGD. These results raise the possibility that proinflammatory molecules may have a more important role than anti-inflammatory proteins in the development of insulin resistance and MetS. This study has some limitations: first, its cross-sectional nature makes it impossible to draw any conclusions on causality. Furthermore, while increasing evidence supports the concept that a low-grade proinflammatory state associated with increased visceral adiposity may induce insulin resistance and hence MetS (1), it has been recently demonstrated (8) that acute IL-6 exposure directly increases glucose metabolism in intact human skel-

etal muscle; our data do not allow exclusion of the possibility that increased IL-6 levels in our population may represent an attempt to counteract insulin resistance by increasing glucose transport. However, it has also been observed (9) that reduced IGF-1 levels are protective and associated with prolonged lifespan in centenarians, and we cannot exclude that in the study population decreased IGF-1 levels represent a reactive rather than a causative state. This study should thus be considered hypothesis generating and requires further prospective investigations.

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