

Reciprocal association of plasma insulin-like growth factor-1 and interleukin-6 levels with cardio-metabolic risk factors in nondiabetic subjects

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Objective: To examine the relationship between plasma IGF-1 versus IL-6 levels in Caucasian nondiabetic subjects, and evaluated their association with cardio-metabolic risk factors characterizing MetS.

Research Design and Methods: The study group consisted of 186 Caucasians non diabetic subjects, that underwent an oral glucose tolerance test (OGTT), and an euglycemic-hyperinsulinemic clamp,

Results: After adjusting for gender and age, both IGF-1 and IL-6 were correlated with insulin resistance and individual components of MetS, but in opposite direction. In a logistic regression model adjusted for age and gender, 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 unbalance between pro-inflammatory versus anti-inflammatory proteins.

Metabolic syndrome (MetS) is a condition characterized by a clustering of interrelated cardio-metabolic risk factors, and is associated with increased risk for both type 2 diabetes and atherosclerotic cardiovascular disease (CVD) (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, pro-inflammatory cytokines production is enhanced causing insulin resistance. MetS is associated with abnormalities in the GH/insulin-like growth factor I (IGF-I) axis resulting in low plasma IGF-I levels (3). IGF-I has anti-inflammatory effects, and decreases expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) (4). There is also evidence in animal models that IL-6 decreases circulating IGF-I levels (5), suggesting that an unpaired balance between proinflammatory versus 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 versus IL-6 levels in a cohort of nondiabetic subjects, and to evaluate their association with cardio-metabolic risk factors characterizing the MetS.

RESEARCH DESIGN AND METHODS

The study group consisted of 186 Caucasians participating to the CATanzaro METabolic RiSk factors Study (CATAMERIS), a metabolic disease prevention campaign for cardio-metabolic risk factors (6). After 12-hours fasting, subjects underwent an oral glucose tolerance test (OGTT), and an euglycemic-hyperinsulinemic clamp, as previously described (6). Whole-body glucose disposal (WBGD) was calculated as reported (6). Insulin resistance was also estimated by HOMA. The MetS was defined according to the American Heart Association and National

Heart, Lung, and Blood Institute (AHA-NHLBI) criteria. The study was approved by 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 employed 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 gender and age, IGF-1 levels were negatively correlated with BMI, waist circumference, systolic blood pressure (SBP), triglyceride, fasting insulin, and HOMA, and positively correlated with WBGD. After adjusting for gender and age, IL-6 levels were positively correlated with BMI, waist circumference, SBP, fasting insulin, and, HOMA, whereas negatively correlated with WBGD and IGF-1 levels. In a logistic regression model adjusted for age and gender, IGF-1 in the lowest tertile (<135 ng/ml) was associated with an increased risk of having MetS (OR 3.07, 95%CI 1.2–7.9), low HDL (OR 3.15, 95%CI 1.2–8.1), and larger waist circumference (OR 4.67, 95%CI 1.8–11.9) as compared with the highest tertile (>221 ng/ml). After adjusting for age, gender and lipid levels, IGF-1 in the lowest tertile was associated with increased risk of insulin resistance, i.e. highest HOMA tertile (OR 3.08, 95%CI 1.2–7.6) or lower WBGD tertile (OR 3.31, 95%CI 1.01–10.9). Conversely, in a logistic regression model adjusted for age and gender, IL-6 in the highest tertile (>2.5

pg/ml) was associated with an increased risk of having MetS (OR 3.21, 95%CI 1.2–8.1), high blood pressure (OR 2.63, 95%CI 1.1–6.4), and larger waist circumference (OR 4.42, 95%CI 1.8–11.0) as compared with the lowest tertile (<1.3 pg/ml). After adjusting for age, gender and lipid levels, IL-6 in the highest tertile was associated with increased risk of insulin resistance, i.e. highest HOMA tertile (OR 2.14, 95%CI 1.01–5.31) or lowest WBGD tertile (OR 4.64, 95%CI 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, gender, BMI, waist circumference, triglycerides, HDL, IL-6, IGF-1, fasting and 2-h post-challenge glucose. The four variables that remained significantly associated with WBGD were age ($P=0.01$), waist circumference ($P=0.01$), 2-h post-challenge glucose ($P=0.001$), and IL-6 levels ($P=0.04$) accounting for 61.2% of its variation.

CONCLUSION

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-1 levels by increasing its clearance (5). Both IGF-1 and IL-6 are associated with MetS and its individual components, but in opposite direction. 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 the concept that a low-grade proinflammatory state associated with increased visceral adiposity may induce insulin resistance, and hence MetS, has gained increasing evidence (1), it has by contrast been recently demonstrated (8) that acute IL-6 exposure directly increases glucose metabolism in intact human skeletal muscle; our data do not allow to exclude the possibility that increased IL-6 levels in our population may represent an attempt to counteract insulin resistance by increasing glucose transport. On the other hand, 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 as hypothesis generating requiring further prospective investigations.

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Table 1 – Anthropometric and biochemical characteristics of the study subjects

	Study subjects	Age and gender adjusted correlations between plasma IGF-1 levels and cardio-metabolic variables		Age and gender adjusted correlations between plasma IL-6 levels and cardio-metabolic variables	
		Pearson's correlation coefficient (<i>r</i>)	<i>P</i>	Pearson's correlation coefficient (<i>r</i>)	<i>P</i>
Gender (M/F)	80/106	---	---	---	---
Age (<i>yrs</i>)	41±14	-0.53*	0.0001	0.30*	0.0001
BMI (<i>kg/m²</i>)	30.1±8.4	-0.28	0.0001	0.33	0.0001
Waist circumference (<i>cm</i>)	97±16	-0.29	0.0001	0.35	0.0001
SBP (<i>mmHg</i>)	127±19	-0.15	0.04	0.15	0.04
DBP (<i>mmHg</i>)	80±11	-0.10	0.18	0.13	0.08
Total Cholesterol (<i>mg/dl</i>)	198±41	0.03	0.66	-0.006	0.95
HDL Cholesterol (<i>mg/dl</i>)	54±14	0.11	0.11	-0.07	0.33
Triglyceride (<i>mg/dl</i>)	121±69	-0.19	0.01	0.10	0.15
Fasting Glucose (<i>mg/dL</i>)	90±14	0.03	0.63	-0.007	0.93
2-h glucose (<i>mg/dl</i>)	117±39	-0.07	0.42	0.13	0.11
Fasting Insulin (<i>μU/ml</i>)	12±7	-0.16	0.03	0.28	0.0001
IGF-1 (<i>ng/ml</i>)	191±90	---	---	-0.15	0.04
IL-6 (<i>pg/ml</i>)	2.5±2.2	-0.15	0.04	---	---
HOMA	2.7±1.8	-0.21	0.004	0.22	0.002
Whole body glucose disposal (<i>mg x Kg⁻¹ x min⁻¹</i>)	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 reported in first column, lines 2 to 16 are means \pm SD. Fasting plasma insulin, triglyceride, and IL-6 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.

* Adjusted for gender.