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.
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 (>4.64 pg/ml) was associated with an increased risk of having MetS (3.21 [1.8–11.9]) 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-1 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-

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

| 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 |
|----------------|-------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Sex (M/F)      | 80/106                                                                        | 80/106                                                                            |
| Age (years)    | 41 ± 14                                                                       | 41 ± 14                                                                          |
| BMI (kg/m²)    | 30.1 ± 8.4                                                                   | 30.1 ± 8.4                                                                      |
| Waist circumferene (cm) | 97 ± 16                                      | 97 ± 16                                                                         |
| SBP (mmHg)     | 127 ± 19                                                                      | 127 ± 19                                                                        |
| DBP (mmHg)     | 80 ± 11                                                                       | 80 ± 11                                                                          |
| Total Cholesterol (mg/dl) | 198 ± 41                         | 198 ± 41                                                                        |
| HDL Cholesterol (mg/dl) | 54 ± 14                                    | 54 ± 14                                                                         |
| Triglyceride (mg/dl) | 121 ± 69                                      | 121 ± 69                                                                        |
| Fasting Glucose (mg/dl) | 90 ± 14                                    | 90 ± 14                                                                         |
| 2-h glucose (mg/dl) | 117 ± 39                                      | 117 ± 39                                                                        |
| Fasting Insulin (µU/ml) | 12 ± 7                                     | 12 ± 7                                                                          |
| IGF-1 (ng/ml)  | 191 ± 90                                                                      | 191 ± 90                                                                        |
| IL-6 (pg/ml)   | 2.5 ± 2.2                                                                     | 2.5 ± 2.2                                                                       |
| HOMA           | 7.6 ± 3.7                                                                     | 7.6 ± 3.7                                                                       |
| AHA-NHLB-defined metabolic syndrome (yes/no) | 60/126 (32.3)                   | 60/126 (32.3)                                                                  |
| High waist circumference (≥102 cm for men and ≥88 cm for women) (yes/no) | 91/95 (48.9)                     | 91/95 (48.9)                                                                   |
| High fasting glucose (≥100 mg/dl) (yes/no) | 47/139 (25.3)                   | 47/139 (25.3)                                                                  |
| High triglyceride (≥150 mg/dl) (yes/no) | 50/136 (26.8)                   | 50/136 (26.8)                                                                  |
| Low HDL (<40 mg/dl in men or <50 mg/dl in women) (yes/no) | 54/132 (29.0)                   | 54/132 (29.0)                                                                  |
| High blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg) (yes/no) | 101/85 (54.6)                   | 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.
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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