Plasma Concentration of IGF-I Is Independently Associated With Insulin Sensitivity in Subjects With Different Degrees of Glucose Tolerance

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OBJECTIVE — We studied the relationships between plasma IGF-I concentrations and insulin sensitivity in subjects with various degrees of glucose tolerance.

RESEARCH DESIGN AND METHODS — A total of 357 nondiabetic subjects, 54 subjects with impaired glucose tolerance and 98 newly diagnosed type 2 diabetic subjects, were consecutively recruited, and anthropometric and biochemical characteristics were collected.

RESULTS — IGF-I concentrations were negatively correlated with age, BMI, waist-to-hip ratio, triglyceride levels, and systolic and diastolic blood pressure. IGF-I concentrations were positively correlated with HDL cholesterol and homeostasis model assessment of insulin sensitivity (HOMA-S). The correlations remained significant after adjusting for sex, age, and BMI. Correlations for HOMA-S with these metabolic and anthropometric variables were of a similar degree and direction to those for IGF-I concentrations. Stepwise linear regression analysis in a model, which included well-known modulators of insulin sensitivity such as sex, age, BMI, glucose tolerance status, family history of diabetes, waist-to-hip ratio, systolic and diastolic blood pressure, HDL cholesterol, and triglyceride levels, revealed that IGF-I concentrations were independently associated with insulin sensitivity accounting for 10.8% of its variation ($P < 0.0001$). IGF-I concentrations were significantly lower in subjects with World Health Organization (WHO)-defined metabolic syndrome compared with subjects without metabolic syndrome ($P < 0.0001$). Logistic regression analysis showed that each unit increase in log-transformed IGF-I concentrations was associated with a 90.5% reduction in the risk of WHO-defined metabolic syndrome.

CONCLUSIONS — These data indicate that IGF-I has the characteristics to be a marker for the insulin resistance syndrome. This suggests that low IGF-I levels may be a useful marker for identifying subjects at risk for cardiovascular disease.

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It is well known that the insulin resistance syndrome or metabolic syndrome, a clustering of abnormalities including altered glucose tolerance, visceral adiposity, hypertension, low HDL cholesterol, and high triglyceride levels, is linked with atherosclerotic cardiovascular diseases (1,2). In the last few years, increasing evidence has suggested that IGF-I may have a role in both glucose homeostasis and cardiovascular disease. Animals with liver-specific IGF-I gene deletion are characterized by hyperinsulinemia and skeletal muscle insulin resistance (3,4). Treatment of these animals with recombinant human IGF-I caused a reduction in insulin levels and an increase in insulin sensitivity (3). Clinical studies performed on normal subjects, patients with extreme insulin resistance, and patients with type 1 or type 2 diabetes have shown that recombinant IGF-I administration significantly lowered blood glucose and increased insulin sensitivity (5–8). Supporting the concept that IGF-I promotes insulin action, a recent study (9) concluded that low concentrations of IGF-I in the circulation increased the risk for developing type 2 diabetes considerably during a 4.5-year follow-up. Low circulating IGF-I levels have been associated with angiographically documented coronary artery disease in nondiabetic subjects as well as with atherosclerotic plaques in the carotid arteries and with coronary artery disease (10,11). Reduced IGF-I levels have been observed in individuals with effort angina pectoris and angiographically normal epicardial coronary arteries, also referred to as cardiac syndrome X (12). Individuals without ischemic heart disease but with low IGF-I levels have an increased risk of developing ischemic heart disease during a 15-year follow-up period (13). Nondiabetic patients who died after an acute myocardial infarction during 2 years of follow-up had, at admission, significantly lower IGF-I levels than survivors (14). Furthermore, nondiabetic patients with myocardial infarction had significantly lower IGF-I levels at admission than age- and sex-matched healthy control subjects (15). In view of the close link between the insulin resistance syndrome and atherosclerotic cardiovascular diseases, it is possible that low IGF-I levels may increase cardiovascular risk by affecting insulin sensitivity. Indeed, some studies

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Abbreviations: GH, growth hormone; HOMA-S, homeostasis model assessment of insulin sensitivity; IGFBP, IGF binding protein; IGT, impaired glucose tolerance; WHO, World Health Organization.

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

	Nondiabetic subjects	Subjects with IGT	Newly diagnosed type 2 diabetic subjects	*P*
Sex (men/women)	158/199	28/26	56/42	0.62
Family history of diabetes (yes/no)	124/233	16/38	18/80	0.008
Age (years)	47.8 ± 14	51.7 ± 10	60.1 ± 11	0.0001
BMI (kg/m^2)	29.4 ± 6.7	32.5 ± 6.6	30.1 ± 6.4	0.003
Waist-to-hip ratio	0.91 ± 0.1	0.96 ± 0.07	0.99 ± 0.08	0.0001
Systolic blood pressure (mmHg)	135 ± 19	140 ± 26	147 ± 20	0.0001
Diastolic blood pressure (mmHg)	83 ± 11	85 ± 12	83 ± 11	0.60
Total cholesterol (mg/dl)	199 ± 39	208 ± 37	199 ± 42	0.21
Triglycerides (mg/dl)	117 ± 63	140 ± 80	135 ± 82	0.007
HDL cholesterol (mg/dl)	52 ± 14	50 ± 12	48 ± 13	0.03
Fasting glucose (mgl/dl)	90 ± 11	99 ± 13	123 ± 35	0.0001
Fasting insulin (mU/ml)	12 ± 8	20 ± 13	15 ± 8	0.0001
IGF-I (ng/ml)	169 ± 80	127 ± 47	124 ± 59	0.0001
HOMA-S	0.50 ± 0.31	0.30 ± 0.21	0.30 ± 0.22	0.0001
Subjects with WHO-defined metabolic syndrome [*n* (%)]	20 (5.6)	32 (59.3)	51 (52)	0.0001

Data are means ± SD, unless otherwise indicated. Group differences of continuous variables were compared using ANOVA. Categorical variables were compared by χ^2 test.

(16) have shown an inverse correlation between IGF-I levels and baseline insulinemia, but it remains to be shown whether a low IGF-I concentration is independently associated with insulin sensitivity in subjects with different degrees of glucose tolerance. Therefore, we studied the relationships between plasma IGF-I concentrations and insulin sensitivity before and after adjusting for known components of the insulin resistance syndrome, including glucose tolerance status, anthropometric measures of obesity, arterial blood pressure, and triglyceride and HDL cholesterol concentrations.

RESEARCH DESIGN AND METHODS

The study included 357 nondiabetic subjects, 54 subjects with impaired glucose tolerance (IGT) and 98 newly diagnosed type 2 diabetic patients, who were consecutively recruited at the Department of Internal Medicine, University of Rome-Tor Vergata, and at the Department of Experimental and Clinical Medicine, University "Magna Graecia" of Catanzaro, from January 2002 to January 2004. All subjects were Caucasian and were participating in a metabolic disease prevention campaign for risk factors including age, blood pressure, lipids, glucose tolerance, BMI, waist-to-hip ratio, insulin resistance, and family history for diabetes. Recruitment mechanisms included word-of-mouth, fliers, and newspaper advertisements. A total of 2,350 subjects were evaluated. Subjects were excluded if they had 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 able to modify glucose metabolism. Type 2 diabetes was diagnosed according to the American Diabetes Association criteria. No newly diagnosed type 2 diabetic subject was treated with any hypoglycemic agents. The metabolic syndrome was defined according to the World Health Organization (WHO) as having at least either insulin resistance or impaired glucose regulation in addition to two or more of the other components, including insulin resistance, impaired glucose regulation, raised arterial pressure, raised triglycerides, low HDL cholesterol, and central obesity (17). Readings of clinic blood pressure were obtained in the left arm of the supine patients after 5 min of quiet rest with a mercury sphygmomanometer. A minimum of three blood pressure readings were taken on three separate occasions at least 2 weeks apart. The study was approved by institutional ethics committees, and informed consent was obtained from each subject in accordance with principles of the Declaration of Helsinki.

Biochemical assays

Fasting blood glucose, total and HDL cholesterol, and triglycerides were measured by enzymatic methods (Roche Diagnostics, Mannheim, Germany). Plasma insulin concentrations were determined by radioimmunoassay (Adaltis, Casalecchio di Reno, Italy). Plasma IGF-I concentrations were determined by chemiluminescent immunoassay (Nichols Institute Diagnostic, San Juan Capistrano, CA). Insulin sensitivity was estimated by using the previously validated homeostasis model assessment for insulin sensitivity (HOMA-S) index, calculated from the fasting glucose and insulin concentrations according to the following formula: HOMA-S = 1/[(insulin × glucose)/22.5] (18).

Statistical analysis

Continuous variables are expressed as means ± SD. Nonnormally distributed parameters were logarithmically transformed to approximate a normal distribution. Group differences of continuous variables were compared using ANOVA or unpaired Student's *t* test. Categorical variables were compared by contingency χ^2 test. Relationships between variables were determined by Pearson's correlation coefficient. Relationships between variables were sought by stepwise multivariate linear regression analysis with forward selection in order to assess the magnitude of their individual effect on insulin sensitivity. For all analyses, a P value ≤ 0.05 was considered to be statistically significant. All analyses were performed using SPSS software program version 10.0 for Windows.

RESULTS

Anthropometric and biochemical characteristics of the study subjects are shown in Table 1. Subjects with IGT and new type 2 diabetes were older and had significantly higher BMI, waist-to-hip ratio, systolic blood pressure, and glucose and triglyceride levels than nondiabetic subjects. By contrast, HDL cholesterol was significantly lower in subjects with IGT and newly diagnosed type 2 diabetes compared with nondiabetic subjects. As expected, insulin sensitivity, estimated as HOMA-S, was significantly lower in subjects with IGT and newly diagnosed type 2 diabetes compared with

Table 2—*Univariate correlations with HOMA-S and plasma IGF-I concentrations*

	Nondiabetic subjects				Subjects with IGT				Subjects with newly diagnosed type 2 diabetes			
	HOMA-S		IGF-I		HOMA-S		IGF-I		HOMA-S		IGF-I	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Age (years)	−0.22	0.0001	−0.33	0.0001	0.12	0.36	−0.19	0.16	−0.10	0.29	−0.32	0.001
BMI (kg/m^2)	−0.42	0.0001	−0.26	0.0001	−0.44	0.001	−0.42	0.002	−0.53	0.0001	−0.15	0.13
Waist-to-hip ratio	−0.30	0.0001	−0.36	0.0001	−0.07	0.7	−0.13	0.40	−0.15	0.12	−0.20	0.05
Systolic blood pressure (mmHg)	−0.30	0.0001	−0.30	0.0001	−0.30	0.04	−0.15	0.29	−0.03	0.81	−0.28	0.005
Diastolic blood pressure (mmHg)	−0.18	0.001	−0.18	0.0001	0.17	0.23	0.17	0.24	0.04	0.62	−0.02	0.90
Total cholesterol (mg/dl)	−0.07	0.19	−0.03	0.60	−0.30	0.02	−0.23	0.09	−0.05	0.63	−0.32	0.001
Triglycerides (mg/dl)	−0.32	0.0001	−0.20	0.0001	−0.49	0.0001	−0.34	0.01	−0.15	0.14	−0.08	0.42
HDL cholesterol (mg/dl)	0.38	0.0001	0.26	0.0001	0.22	0.10	0.32	0.01	0.05	0.54	0.13	0.21
IGF-I (ng/ml)	0.38	0.0001	—	—	0.32	0.01	—	—	0.40	0.0001	—	—
HOMA-S	—	—	0.38	0.0001	—	—	0.32	0.01	—	—	0.40	0.0001

nondiabetic subjects ($P < 0.0001$). These differences remained significant ($P = 0.0001$) after adjusting for sex, age, and BMI. Plasma IGF-I concentrations were significantly lower in subjects with IGT and newly diagnosed type 2 diabetes compared with nondiabetic subjects ($P < 0.0001$). These differences remained significant ($P = 0.004$) after adjusting for sex, age, and BMI.

Univariate correlations between plasma IGF-I concentrations and established components of the insulin resistance syndrome were assessed for the study subjects. In the whole population, plasma IGF-I concentrations were negatively correlated with age, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, and triglyceride levels. Plasma IGF-I concentrations were positively correlated with HDL cholesterol, and insulin sensitivity was estimated as HOMA-S. The correlations remained significant after adjusting for sex, age, and BMI. Correlations for HOMA-S with these metabolic and anthropometric variables were of a similar degree and direction to those for plasma IGF-I concentrations. HOMA-S was negatively correlated with age, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, total cholesterol, and triglyceride levels. HOMA-S was positively correlated with HDL cholesterol. The correlations remained significant after adjusting for sex, age, and BMI. The association between plasma IGF-I concentrations and insulin sensitivity assessed by HOMA-S was consistent across the three groups of subjects with different glucose tolerance status (Table 2). However, the correlations between plasma IGF-I concentrations and established components of the insulin resistance syndrome including BMI, HDL cholesterol, and triglyceride levels were significant in the nondiabetic group and the IGT group but not in the newly diagnosed type 2 diabetes group (Table 2). The correlations between plasma IGF-I concentrations and waist-to-hip ratio or systolic blood pressure were significant in the nondiabetic group and the newly diagnosed type 2 diabetes group but not in the IGT group (Table 2).

To estimate the independent contribution of plasma IGF-I concentrations to insulin sensitivity assessed by HOMA-S, we carried out forward stepwise linear regression analysis in a model that also included well-known modulators of insulin sensitivity such as sex, age, BMI, waist-to-hip ratio, glucose tolerance status, family history of diabetes (first degree), systolic and diastolic blood pressure, total and HDL cholesterol, and triglyceride levels (Table 3). The results of the multivariate analysis revealed that BMI was the strongest independent variable associated with insulin sensitivity, accounting for 20.2% of its variation ($P < 0.0001$). Plasma IGF-I concentrations appeared to be independently associated with insulin sensitivity, accounting for 10.8% of the variation in insulin sensitivity ($P < 0.0001$). Also, glucose tolerance status, triglycerides, and HDL cholesterol were independently associated with insulin sensitivity, accounting for a smaller proportion of the variation in insulin sensitivity. By contrast, sex, age, waist-to-hip ratio, family history of diabetes, total cholesterol levels, and systolic and diastolic blood pressure were not independently associated with insulin sensitivity. The model accounted for 40.5% of the variation in insulin sensitivity. Notably, after removing plasma IGF-I concentrations from the regression model, this accounted for 36.2% of the variation in insulin sensitivity.

Table 3—*Independent predictors of insulin sensitivity after forward stepwise linear regression analysis*

	Partial r^2	Total r^2	*P*
BMI (kg/m^2)	20.2	20.2	0.0001
IGF-I (ng/ml)	10.8	31.1	0.0001
Glucose tolerance status	4.7	35.8	0.0001
Triglycerides (mg/dl))	2.9	38.7	0.0001
HDL cholesterol (mg/dl)	1.8	40.5	0.005

Data are percentages. The model includes sex, age, BMI, waist-to-hip ratio, glucose tolerance status, family history of diabetes (first degree), systolic and diastolic blood pressure, IGF-I concentrations, total and HDL cholesterol, and triglyceride levels.

One hundred three out of 509 subjects (20.2%) were classified as having the metabolic syndrome according to the WHO definition (17). Plasma IGF-I concentrations were significantly lower in subjects with metabolic syndrome (106 ± 46 ng/ml) compared with subjects without metabolic syndrome (169 ± 77 ng/ml; $P < 0.0001$). Logistic regression analysis showed that each unit increase in log-transformed IGF-I concentrations (or 2.7 ng/dl increase in actual IGF-I concentrations) was associated with a 90.5% reduction in the risk of WHO-defined metabolic syndrome. After adjusting for sex and age, the odds ratio for the association of log-transformed IGF-I concentrations with metabolic syndrome was 0.095 (95% CI 0.05–0.18) ($P < 0.0001$).

CONCLUSIONS — The most important finding of the present analyses is the close association between plasma IGF-I concentrations and insulin sensitivity in subjects with different degrees of glucose tolerance and that this relation is independent of well-known modulators of insulin sensitivity. Plasma IGF-I concentration was positively correlated with insulin sensitivity and HDL cholesterol and negatively correlated with age, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, and triglyceride levels. These relations were similar in degree and direction to those observed for HOMA-S. In a stepwise linear regression analysis, a low plasma IGF-I concentration was significantly associated with insulin sensitivity independent of age, sex, measures of adiposity, such as BMI and waist-to-hip ratio, glucose tolerance status, family history of diabetes, arterial blood pressure, triglycerides, and HDL cholesterol levels. Notably, removing plasma IGF-I concentrations from the regression model reduced the proportion of the variation in insulin sensitivity explained, thus suggesting that IGF-I concentrations add more than their component parts. Furthermore, a low plasma IGF-I concentration was significantly associated with the metabolic syndrome according to the WHO definition. These results extend previous observations showing that low IGF-I levels are associated with risk for the metabolic syndrome, as defined by the WHO (17). Moreover, the findings are consistent with animal studies demonstrating reduced insulin sensitivity in mice with liver-specific deletion of the IGF-I gene that is reversed by treatment with recombinant human IGF-I (3,4). Liver-specific knockout mice exhibit increased systolic blood pressure associated with endothelial dysfunction, as revealed by impaired acetylcholine-induced vasorelaxation of resistance vessels and increased levels of endothelin-1 mRNA in aorta (19). Increased blood pressure and slightly enhanced plasma insulin concentrations have been reported in mice with a mutant IGF-I allele, causing a marked decrease in circulating IGF-I levels (20).

However, caution has to be taken when interpreting the results because these studies are cross-sectional, which makes it impossible to draw any conclusions on causality. Nevertheless, they may provide a plausible explanation for the increased risk of development of IGT and type 2 diabetes in individuals with normal glucose concentrations at baseline (9). The present study was also limited by the fact that the analyses were based on total IGF-I rather than the biologically active free IGF-I. Although the reproducibility of total IGF-I assays is high, it is possible that nutritional and genetic factors might influence the actual levels of circulating IGF-I. In this respect, a polymorphism in the promoter region of the *IGF-I* gene was associated with low total serum IGF-I levels and increased risk of type 2 diabetes (21). In addition, we did not measure IGF-binding proteins (IGFBPs), which play a key role in regulating the bioavailability of circulating IGF-I. IGFBP-1 has been proposed as an acute regulator of IGF-I bioactivity and might have both inhibitory and stimulatory effects on IGF-I action depending on experimental conditions (22). IGFBP-1 synthesis is suppressed by hepatic portal insulin, and low levels of this binding protein have been associated with insulin resistance, IGT, and the metabolic syndrome (8,16,23). It has been reported that IGFBP-1 modified the association between plasma IGF-I levels and 2-h glucose concentrations during an oral glucose tolerance test, with a strong inverse association observed only in subjects with low IGFBP-1 levels (8). Thus, it is possible that among individuals with insulin resistance and low IGF-I concentrations, those characterized by low IGFBP-1 levels due to compensatory hyperinsulinemia may be more susceptible to developing glucose intolerance.

The mechanisms by which low IGF-I concentrations may induce insulin insensitivity are not clear. IGF-I has hypoglycemic effects and enhances insulin sensitivity in both experimental animals and human subjects. The biological action of IGF-I is thought to be mediated via its type 1 receptors and/or hybrid insulin/IGF-1 receptors (24). Hybrid insulin/IGF-I receptors are widely distributed in human tissues, including skeletal muscle and adipose tissue (25,26). They behave as IGF-I homoreceptor rather than insulin homoreceptor or some intermediate version of the two receptors with respect to various receptor functions (27). It has been proposed that an increased proportion of hybrid insulin/IGF-1 receptors would reduce insulin sensitivity in target tissues of insulin action, contributing to cellular insulin resistance. According to this view, we have previously demonstrated that expression of hybrid insulin/IGF-I receptors was significantly higher in skeletal muscle from patients with type 2 diabetes or obese subjects compared with normal subjects and was negatively correlated with in vivo insulin sensitivity (28,29). Because plasma concentrations of both insulin and IGF-I regulate the expression of their own receptors, it is conceivable that changes in insulin and/or IGF-I receptor content induced by their respective hormones would result in modifications in hybrid insulin/IGF-1 receptor formation in proportions determined by the molar ratio of the two receptors. Consistent with this idea, in patients with insulinoma, a condition characterized by marked hyperinsulinemia, downregulation of insulin receptors induced by elevated plasma insulin was associated with increased abundance of hybrid insulin/IGF-I receptors (30). Furthermore, in obese individuals, who were characterized by increased fasting insulin levels and decreased plasma IGF-I concentrations, we have demonstrated that the proportion of hybrid insulin/IGF-I receptors was correlated with a decrease in insulin receptor content and an increase in IGF-I receptor content (29). Although a consensus is yet to emerge, these observations are supportive of the notion that low circulating IGF-I levels can lead to upregulation of IGF-I receptors, resulting in increased formation of hybrid insulin/IGF-I receptors, which might contribute to impair insulin action by sequestering insulin receptors in a less responsive form. This phenomenon may also help to explain the results of clinical studies

showing the effectiveness of recombinant human IGF-I treatment in improving insulin sensitivity and metabolic control in patients with type 1 or type 2 diabetes and in patients with extreme insulin resistance (5–8).

Alternatively, low plasma IGF-I concentrations may provide inadequate negative feedback at the level of the hypothalamus and/or pituitary, thus resulting in growth hormone (GH) hypersecretion and a decrease in insulin sensitivity, particularly in the skeletal muscle. In support of this possibility, it has been shown that mice with liver-specific deletion of the IGF-I gene exhibited elevated GH levels, which were associated with insulin resistance and impaired activation of early signaling events in response to insulin (3). Notably, treatment of these mice with GH-releasing hormone antagonist MZ4-71, which reduces GH levels, resulted in increased insulin sensitivity (3). Accordingly, it has been demonstrated that blocking of GH action in mice with liver-specific deletion of the IGF-I gene by crossing them with mice overexpressing a mutant form of GH, which prevents GH activation of its receptor, resulted in improved insulin sensitivity (31). When these results are considered together, they suggest that GH hypersecretion may be a major determinant of insulin resistance in subjects with low plasma IGF-I concentrations. Although a role for GH in inducing insulin resistance at skeletal muscle levels cannot be excluded, it is possible that in that tissue the role of IGF-1 may be predominant. In support of this view, a recent study has shown that recombinant IGF-I has a direct effect on glucose and protein metabolism in type 1 diabetic patients in whom GH secretion was suppressed with octreotide (32).

In conclusion, the present data indicate that plasma IGF-I concentrations are independently related to impaired insulin sensitivity and other components of the metabolic syndrome. We suggest that low IGF-I levels may be a useful marker for identifying subjects at risk for cardiovascular disease. Further prospective and clinical intervention studies are required to definitively prove this hypothesis.

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