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Low circulating insulin-like growth factor-1 levels are associated with high serum uric acid in nondiabetic adult subjects

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Abstract *Background and aims:* Low insulin-like growth factor-1 (IGF-1) levels and high uric acid concentrations are associated with cardio-metabolic disorders. Acute IGF-1 infusion decreases uric acid concentration in healthy individuals. In this study, we aimed to examine the relationship between IGF-1 and uric acid levels.
Methods and results: 1430 adult non diabetic subjects were stratified into quartiles according to their circulating IGF-1 values. Significant differences in uric acid concentration, measured by the URICASE/POD method were observed between low (quartile 1), intermediate (quartile 2 and 3), and high (quartile 4) IGF-1 levels groups after adjusting for age, gender, and body mass index ($P = 0.02$). These differences remained significant after adjustment for blood pressure, total cholesterol, high density lipoprotein, triglycerides, fasting and 2 h post-load glucose levels, HOMA-IR index ($P = 0.005$), liver enzymes ($P = 0.03$), glucose tolerance status ($P = 0.02$), growth hormone levels (GH) ($P = 0.05$), anti-hypertensive treatments ($P = 0.04$) or diuretics use ($P = 0.04$)). To clarify the molecular links between IGF-1 and uric acid, we performed an in vitro study, incubating human hepatoma cells with uric acid for 24 or 48 h in the presence of GH and observed a 21% and 26% decrease, respectively, in GH-stimulated IGF-1 mRNA expression ($P = 0.02$ and $P = 0.012$, respectively). This effect appears to be mediated by uric acid ability to down regulate GH intracellular signaling; in fact we observed a significant decrease of GH activated JAK2 and Stat5 phosphorylation.
Conclusions: These data demonstrate an inverse relationship between IGF-1 and uric acid levels in adults and suggest that uric acid might affect hepatic IGF-1 synthesis.

Acronyms: ALT, alanine aminotransferase; ADA, American Diabetes Association; AST, aspartate aminotransferase; BMI, body mass index; DMEM, Dulbecco's Modified Eagle's Medium; eGFR, estimated GFR; FPG, fasting plasma glucose; GGT, gamma-glutamyltransferase; GFR, glomerular filtration rate; GH, growth hormone; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL-C, high density lipoprotein-cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; IFG, impaired fasting glucose; IGF-1, insulin-like growth factor 1; IGFBP, IGF binding proteins; IGT, isolated impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; NGT, normal glucose tolerant; NO, nitric oxide; OGTT, oral glucose tolerance test; rhIGF-1, recombinant human IGF-I.

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Introduction

Increasing evidence suggests that low plasma insulin-like growth factor-1 (IGF-1) levels are associated with reduced insulin-sensitivity [1], obesity [2], metabolic syndrome [3], impaired glucose tolerance [4], and nonalcoholic fatty liver disease (NAFLD) [5], and predict development of both type 2 diabetes [6] and cardiovascular diseases [7]. Similarly, hyperuricemia has been linked to the same cluster of cardio-metabolic disorders including insulin resistance [8], obesity [9], metabolic syndrome [10], impaired glucose tolerance [11], and has been suggested to predict development of both type 2 diabetes [12,13] and cardiovascular diseases [14].

Several evidences suggest that IGF-1 enhances both renal plasma flow and glomerular filtration rate (GFR) by stimulating IGF-1 receptors. Thus, acute intravenous infusions of recombinant human IGF-I (rhIGF-1) in normal rats increases renal plasma flow and GFR and decreases renal vascular resistance [15,16]. Compelling evidence suggests that nitric oxide (NO) mediates some of the effects of IGF-1 on glomerular hemodynamics. IGF-1 induces NO production in human umbilical vein endothelial cells, an effect that is abolished by a neutralizing IGF-1 receptor antibody [17], and renal vasodilation induced by IGF-1 was completely inhibited by an inhibitor of NO biosynthesis [18]. Studies in humans have shown that plasma IGF-1 levels are associated with GFR [19], and acute (3-h) intravenous infusion of rhIGF-1 increases renal plasma flow and GFR in healthy subjects [20]. Additionally, in a pilot study carried out in two healthy adult subjects, IGF-1 infusion during 6 days increases GFR and decreases serum acid uric concentration [21]. Whether lower circulating levels of IGF-1 are independently associated with higher serum uric acid levels in adult individuals is still unsettled.

Although uric acid has antioxidant properties in the extracellular environment, several studies have shown that uric acid entering cells via specific transporters can affect cellular function by inducing oxidative stress in a variety of cells [22–24]. Thus, it is conceivable that an elevation in serum uric acid as that observed in cardio-metabolic disorders may affect hepatic IGF-1 expression resulting in lower circulating levels of IGF-1. The aim of this study was to examine the relationship between plasma IGF-1 versus serum uric acid levels in a cohort of nondiabetic adult individuals and to test whether uric acid directly affects hepatic IGF-1 expression.

Methods

Study subjects

The study group consisted of 1430 adult individuals of European ancestry consecutively recruited at the Internal Medicine Units of the University of Rome-Tor Vergata and of the University "Magna Graecia" of Catanzaro [1–5]. Recruited subjects participated to a campaign for assessment of cardio-metabolic risk factors. The inclusion criteria were: age >21 years, and presence of one or more cardio-metabolic risk factors including elevated fasting glucose levels, hypertension, dyslipidemia, overweight/obesity, and family history for diabetes. Subjects were excluded if they had diabetes mellitus, defined as fasting plasma glucose >126 mg/dl or 2 h post-load plasma glucose >200 mg/dl, current treatment with anti-diabetic drugs or self-reported history of a previous diagnosis, end stage renal disease, gout, chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of use of toxins or drugs known to induce liver damage, self-reporting alcohol consumption of <20 g/day, and positivity for antibodies to hepatitis C virus (HCV) or hepatitis B surface antigen (HBsAg). Clinical cardiovascular disease was excluded on the basis of medical history and resting electrocardiogram.

All anthropometric and biochemical measurements were made in the morning after a 12 h fast using standardized methods. Brachial blood pressure was measured in the left arm of the supine subjects, after 5 min of quiet rest, with a digital electronic tensiometer (regular or large adult cuffs were used according to arm circumference). A minimum of three blood pressure readings were taken on three separate occasions at least 2 weeks apart, and the medians of these three values were used. A 75 g oral glucose tolerance test (OGTT) was performed with sampling for plasma glucose.

The protocol was approved by the Institutional Ethics Committees and written informed consent was obtained from participants. All the investigations were performed in accordance with the principles of the Declaration of Helsinki.

Analytical determinations

Serum uric acid was measured by the URICASE/POD method implemented in an autoanalyzer (Boehringer Mannheim, Mannheim, Germany). Plasma insulin concentration was measured with a chemiluminescence-based assay (Immulite®, Siemens, Italy), and total serum IGF-1 was assayed by one-step sandwich chemiluminescence immunoassay (CLIA) after prior separation of IGF-I from binding proteins on the Liaison® autoanalyzer (DiaSorin, Saluggia, Italy).

Definitions of metabolic status

Subjects were classified into glucose tolerance status according to the American Diabetes Association (ADA) criteria [25]: normal glucose tolerant (NGT) with fasting plasma glucose (FPG) < 100 mg/dl and 2 h post-load <140 mg/dl, isolated impaired fasting glucose (IFG) with FPG ranging from 100 mg/dl to 125 mg/dl and 2 h post-load <140 mg/dl, isolated impaired glucose tolerance (IGT) with FPG <100 mg/dl and 2 h post-load >140 mg/dl and <200 mg/dl, and combined IFG/IGT with FPG ranging from 100 mg/dl to 125 mg/dl and 2 h post-load >140 mg/dl and <200 mg/dl.

The so-called metabolic syndrome was defined according to the criteria released in 2009 by a joint statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung,