CLINICAL STUDY

Relationships between serum IGF1 levels, blood pressure, and glucose tolerance: an observational, exploratory study in 404 subjects

Annamaria Colao, Carolina Di Somma, Teresa Cascella, Rosario Pivonello, Giovanni Vitale[1], Ludovica F S Grasso, Gaetano Lombardi and Silvia Savastano

Department of Molecular and Clinical Endocrinology and Oncology, University 'Federico II' of Naples, Via S. Pansini 5, 80131 Naples, Italy and [1]Chair of Endocrinology, Italian Auxologic Institute, University of Milan, Milan, Italy

(Correspondence should be addressed to A Colao; Email: colao@unina.it)

Abstract

Background: In the general population, low IGF1 has been associated with higher prevalence of cardiovascular disease and mortality.
Objective: To investigate the relationships between IGF1 levels, blood pressure (BP), and glucose tolerance (GT).
Subjects: Four-hundred and four subjects (200 men aged 18–80 years). Exclusion criteria: personal history of pituitary or cardiovascular diseases; previous or current treatments with drugs interfering with BP, GT, or lipids, corticosteroids (>2 weeks), estrogens, or testosterone (>12 weeks); smoking of >15 cigarettes/day and alcohol abuse (>3 glasses of wine/day).
Results: Two hundred and ninety-six had normal BP (73.3%), 86 had mild (21.3%), and 22 had severe (5.4%) hypertension; 322 had normal GT (NGT (79.7%)), 53 had impaired glucose tolerance (IGT (13.1%)), 29 had diabetes mellitus (7.2%). Normotensive subjects had significantly higher IGF1 levels (0.11 ± 0.94 SDS) than those with mild (-0.62 ± 1.16 SDS, $P<0.0001$) or severe (-1.01 ± 1.07 SDS, $P<0.0001$) hypertension. IGF1 SDS ($t=-3.41$, $P=0.001$) independently predicted systolic and diastolic BP ($t=-2.77$, $P=0.006$) values. NGT subjects had significantly higher IGF1 levels (0.13 ± 0.90 SDS) than those with IGT (-0.86 ± 1.14 SDS, $P<0.0001$) or diabetes mellitus (-1.31 ± 1.13 SDS, $P<0.0001$). IGF1 SDS independently predicted fasting glucose ($t=-3.49$, $P=0.0005$) and homeostatic model assessment (HOMA)-R ($t=-2.15$, $P=0.033$) but not insulin ($t=-1.92$, $P=0.055$) and HOMA-β ($t=-0.19$, $P=0.85$).
Conclusion: IGF1 levels in the low normal range are associated with hypertension and diabetes in subjects without pituitary and cardiovascular diseases.

European Journal of Endocrinology **159** 389–397

Introduction

Growth hormone (GH) is principally involved in the regulation of somatic growth, and exerts its effects either directly or indirectly, by stimulating the production of insulin-like growth factor-1 (IGF1) that mediates GH action on peripheral tissues (1, 2). IGF1 levels are strongly determined by changes in GH secretion; they are low in patients with GH deficiency (GHD) and high in those with acromegaly (1, 2). Age and sex also affect serum IGF1 concentrations; at the age of 65 years, daily spontaneous GH secretion is reduced by 50–70% and consequently IGF1 levels decline progressively (3), while male gender is associated with higher IGF1 levels than females (4).

Besides, GH and IGF1 are anabolic hormones, so that malnutrition and other catabolic states, such as severe trauma and sepsis, reduce serum IGF1 concentration. Patients with insulin-dependent diabetes have some hepatic resistance to GH, with elevated serum GH levels and reduced IGF1 levels (5). Moreover, subtle changes in IGF1 levels in the general population are associated with changes in blood pressure (BP) and insulin sensitivity: IGF1 levels in the upper normal range are associated with reduced BP (6) and vascular tone (7), increased insulin sensitivity (8, 9), and reduced prevalence of diabetes mellitus (10). Epidemiological studies have suggested that IGF1 levels in the lower normal range are associated with an increased risk of ischemic heart disease (11–13) and stroke (14–17). In this setting, a protective role in the development of atherosclerosis was suggested for free IGF1 levels (17). We also reported the existence of tight relationships between IGF1, IGF binding protein 3 (IGFBP3), and a

surrogate marker of atherosclerosis such as the measurement of intima-media thickness (IMT) of common carotid arteries in a group of 174 healthy individuals (18). We found that IGF1 levels were the best predictors of total cholesterol levels and total/high density lipoprotein (HDL) cholesterol ratio; additionally, mean IMT was best predicted by subjects' age (as expected), but IGF1 and IGFBP3 were its second best predictors (18).

This cross-sectional study was designed to give insights into the relationships between IGF1 levels, BP levels, glucose tolerance (GT), and dyslipidemia in a sample of the general population used as control group. In none of the previous studies investigating the relationship between IGF1 levels and diabetes or hypertension, these two diseases were evaluated in the same cohort, despite the fact that they often are present in the same subjects.

Patients and methods

Study design

This is a cross-sectional study in a cohort of subjects initially selected as controls of patients with pituitary tumors in several studies. It presents data included in a study protocol dedicated to the effects of GH replacement on the cardiovascular system in patients with GHD compared with controls that was approved by the Ethical Committee of the 'Federico II' University of Naples (no. 63/97). The current study show data related to the controls, thus prospectively collected but with a different aim.

Exclusion criteria

Exclusion criteria were: 1) personal history of cardiovascular diseases or pituitary diseases as reported in interviews with individual subjects; 2) previous or current treatments with drugs known to interfere with glucose or lipid metabolism or to influence BP; 3) previous treatment with corticosteroids for longer than 2 weeks; 4) previous or current treatment with estrogens or testosterone for longer than 12 weeks; and 5) smoking of more than 15 cigarettes/day and alcohol abuse (more than three glasses of wine/day). Subjects with type 1 diabetes mellitus have been also excluded. Smoking was stratified into the following: 1) non-smokers, 2) ex-smokers, and 3) mild smokers (up to 15 cigarettes/day). Subjects with chronic severe liver and renal dysfunction were also excluded.

Subjects

Four-hundred and four subjects (204 women, 200 men aged 18–80 years), among the clerks, medical, and paramedical personnel of the Department of Molecular and Clinical Endocrinology and Oncology of the University

'Federico II' of Naples, and their relatives, as well as patients' relatives, agreed to participate in this study. All subjects gave their informed consent to the study. The clinical profile of the subjects is shown in Table 1.

Measurements

After an overnight fasting and 3 days of low-fat food intake (<30%; 7% saturated fat), in all subjects we measured the following.

1. Serum IGF1 levels by IRMA after ethanol extraction using Diagnostic System Laboratories Inc. (Webster, TX, USA). The normal ranges in ≤20, 21–30, 31–40, 41–50, 51–60, 61–70 and >70 year old men were 180–625, 118–475, 102–400, 100–306,

Table 1 Profile of all women and men at study entry.

	Women	Men	*P*
N	204	200	
Age (years)	45.9±19.2	45.0±19.7	0.84
Serum IGF1 levels (μg/l)	224.9±72.4	240.9±84.5	<0.0001
Body mass index (kg/m²)	24.6±3.7	25.5±3.8	0.051
Prevalence (no.(%)) of:			
Normal weight	121 (59.3)	104 (52.0)	0.17
Overweight	62 (30.4)	83 (41.5)	0.026
Obesity	21 (10.3)	13 (6.5)	0.23
Systolic blood pressure (mmHg)	127.0±16.1	129.9±17.0	0.051
Diastolic blood pressure (mmHg)	80.1±6.8	80.1±7.3	0.051
Prevalence (no.(%)) of:			
Normal blood pressure	147 (72.0)	149 (74.5)	0.66
Mild hypertension	46 (22.5)	40 (20.0)	0.61
Severe hypertension	11 (5.4)	11 (6.5)	0.86
Total cholesterol levels (mmol/l)	4.73±0.66	4.87±0.79	<0.0001
HDL cholesterol levels (mmol/l)	1.54±0.19	1.51±0.19	<0.0001
LDL cholesterol levels (mmol/l)	2.97±0.73	3.12±0.88	<0.0001
Total/HDL cholesterol ratio	3.14±0.78	3.34±1.04	<0.0001
LDL/HDL cholesterol ratio	1.99±0.73	2.17±0.97	<0.0001
Triglycerides levels (mmol/l)	1.12±0.31	1.20±0.35	
Prevalence (no.(%)) of:			
Hypercholesterolemia	32 (15.7)	47 (23.5)	0.064
Hypertriglyceridemia	20 (9.8)	22 (11.0)	0.82
Fasting glucose levels (mmol/l)	4.90±0.82	5.00±1.05	0.051
Fasting insulin levels (mmol/l)	7.9±5.2	7.9±5.0	0.051
HOMA-R index (%)	1.86±1.72	1.94±2.16	0.68
HOMA-β index (%)	132.8±89.5	115.9±63.1	0.029
Prevalence (no.(%)) of:			
Normal glucose levels	161 (78.9)	161 (80.5)	0.79
Impaired fasting glucose	29 (14.2)	24 (12.0)	0.61
Diabetes	14 (6.9)	15 (7.5)	0.96

Data are shown as mean±s.d. Prevalence is reported as percent value of the total number of female and male subjects.

95–270, 88–250, 78–200 µg/l respectively, whereas in women they were 151–530, 118–450, 100–390, 96–288, 90–250, 82–200, 68–188 µg/l respectively. The sensitivity of the assay was 0.8 µg/l. The intra-assay coefficient of variations (CVs) were 3.4, 3.0, and 1.5% for low, medium, and high points of the standard curve respectively. The inter-assay CVs were 8.2, 1.5, and 3.7% for low, medium, and high points of the standard curve. Since IGF1 levels are related to age, to analyze the relationships between IGF1 levels and the other variables we calculated the SDS of IGF1 levels according to age (zSDS). To this aim, we calculated the mean and S.D. of IGF1 levels in young (<20 years), adults (21–40 years), middle-aged (41–65 years), and elderly (>65 years) women and men. Subjects found to be obese and/or with diabetes mellitus were excluded from SDS calculation. Data are summarized in Table 2. In 16 subjects found to have IGF1 levels below 2 S.D. from the mean, IGF1 levels were assayed again within 1 month from first assay and a diagnosis of pituitary diseases was searched by sellar magnetic resonance imaging. Six subjects were diagnosed with pituitary diseases and their IGF1 results were excluded from the calculation of normal IGF1 distribution.

2. Arterial BP was measured at the right arm, with the subjects in relaxed sitting position. The average of six measurements (three taken by each of two examiners in the same day between 0800 and 0900 h) with a mercury sphygmomanometer was used for analysis. The fourth Korotkoff phase was considered as diastolic BP (DBP). The arterial pulse pressure was calculated as the difference between the systolic BP (SBP) and DBP. According to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (19), severity of hypertension was classified as mild (stage 1) when SBP and DBP were between 140 and 159 mmHg and between 90 and 99 mmHg respectively; severe (stage 2) when SBP and DBP were ≥160 and ≥100 mmHg respectively; target BP levels to define adequate control were SBP <140 and DBP <90 mmHg.

3. Measurement of glucose and insulin levels at fasting. Diabetes mellitus was diagnosed when fasting glucose was above 7 mmol/l (125 mg/dl) at two consecutive measurements (20). Impaired fasting

glucose (IFG) was diagnosed when glucose level was between 5.6 and 6.9 mmol/l at fasting (20). Normal glucose level was considered to be below 5.6 mmol/l at fasting. To predict insulin resistance (homeostatic model assessment (HOMA)-R (%)) and β-cell function (HOMA-β (%)) the HOMA was used according to Matthews et al. (21). By assuming that normal weight healthy subjects aged <35 years have a HOMA-β of 100% and a HOMA-R of 1, the values for individual subjects can be assessed from the insulin and glucose concentrations by the formulae: HOMA-R=(insulin (mU/l)×fasting glucose (mmol/l))/22.5; HOMA-β (%)=(20×insulin (mU/l))/(glucose (mmol/l)−3.5). The conversion factors (mg/dl to mmol/l) for glucose was 0.05551.

4. Cholesterol and triglyceride levels were measured by standard methods. Hypertriglyceridemia was diagnosed when triglyceride levels were >150 mg/dl (1.7 mmol/l) (22) while hypercholesterolemia was diagnosed when total cholesterol levels were >200 mg/dl (5.2 mmol/l) (23). The conversion factors (mg/dl to mmol/l) for lipids were respectively, cholesterol 0.02586 and triglycerides 0.01129.

Statistical analysis

The statistical analysis was performed by StatDirect Statistical Software (version 2.6.2 of April 23, 2007, Cheshire, UK, http://www.statsdirect.com/update.htm). Results were expressed as median or mean±S.D. unless otherwise specified. Categorical variables were compared using Pearson's χ^2-test. A preliminary analysis by the Shapiro and Wilk test was used to indicate variables normally or non-normally distributed. According to data distribution, the comparison among different groups was made by the ANOVA or the Kruskal–Wallis, while that between two groups was made by Student's t-test or the Mann–Whitney test respectively. The post hoc analysis was performed by the Newman–Keuls or the Dunns test for each pair of columns respectively. A two-tailed P value less than 0.05 was considered as statistically significant. When more than three groups were compared, Bonferroni's correction was applied. In this case, a two-tailed P value less than 0.01 was considered as statistically significant. To evaluate whether IGF1 SDS was correlated with SBP and DBP values, fasting total cholesterol, triglycerides,

Table 2 Mean insulin-like growth factor-1 (IGF1) levels in women and men grouped according to age[a].

	Subjects aged ≤20 years		Subjects aged 21–40 years		Subjects aged 41–60 years		Subjects aged >60 years	
	No.	Mean±S.D.	No.	Mean±S.D.	No.	Mean±S.D.	No.	Mean±S.D.
Women	25	293.3±40.1	53	284.5±46.5	60	219.2±35.6	38	143.8±27.4
Men	28	343.0±48.0	53	287.8±58.4	52	224.6±42.6	44	159.0±34.2

[a]In this analysis all obese and diabetic subjects were excluded.

glucose and insulin levels, HOMA-R, and HOMA-β, we calculated Pearson's coefficient after correction for gender and body mass index (BMI). To evaluate whether IGF1 SDS was independently correlated with the variable above, the stepwise multiple regression analysis was performed: in this analysis were entered those variable with a two-tailed P value lower than 0.01 in the univariate analysis (variables considered were SBP, DBP, total cholesterol, HDL cholesterol, fasting glucose, and insulin). The diagnostic accuracy of zSDS of IGF1 in predicting the presence of severe hypertension and diabetes was analyzed by receiving-operator characteristics (ROC) curves calculated using MedCalc Software for Windows (MedCalc, Mariakerke, Belgium). Accuracy was reported as sensitivity, specificity, and positive and negative predictive values with their 95% confidence intervals.

Results

Serum IGF1 levels and BP levels

Of the 404 subjects, 296 had normal BP (73.3%), 86 had mild hypertension (21.3%), while 22 had severe hypertension (5.4%). The prevalence of hypertension was similar in women and men (Table 1). The subjects with normal BP had significantly higher IGF1 levels (0.11 ± 0.94 SDS) than those with mild (-0.62 ± 1.16 SDS, $P < 0.0001$) or severe (-1.01 ± 1.07 SDS, $P < 0.0001$) hypertension. Individual results are shown in Fig. 1. IGF1 SDS was significantly correlated with SBP ($r = -0.38$, $P < 0.0001$) and DBP values

($r = -0.28$, $P < 0.001$). IGF1 SDS ($t = -3.41$, $P = 0.001$) independently predicted SBP and DBP ($t = -2.77$, $P = 0.006$) values.

Serum IGF1 levels and GT

Of the 404 subjects, 322 had normal GT (NGT) (79.7%), 53 had IFG (13.1%), while 29 had diabetes mellitus (7.2%). The prevalence of glucose abnormalities was similar in women and men (Table 1). The subjects with NGT had significantly higher IGF1 levels (0.13 ± 0.90 SDS) than those with IFG (-0.86 ± 1.14 SDS, $P < 0.0001$) or diabetes mellitus (-1.31 ± 1.13 SDS, $P < 0.0001$); these latter were similar to each other. Individual results are shown in Fig. 2. IGF1 SDS was significantly correlated with fasting glucose ($r = -0.41$, $P < 0.0001$) and insulin ($r = -0.53$, $P < 0.0001$) levels, HOMA-R ($r = -0.31$, $P < 0.0001$), and HOMA-β ($r = 0.11$; $P = 0.023$). IGF1 SDS independently predicted fasting glucose ($t = -3.49$, $P = 0.0005$) and HOMA-R ($t = -2.15$, $P = 0.033$) but not insulin ($t = -1.92$, $P = 0.055$) levels. In Fig. 3 are shown the individual data of HOMA-R according to IGF1 SDS in the subset of subjects with NGT.

Serum IGF1 levels and hypercholesterolemia or hypertriglyceridemia

Of the 404 subjects, 79 had hypercholesterolemia (19.6%) and 42 had hypertriglyceridemia (10.4%). The prevalence of lipid abnormalities was similar in women and men (Table 1). The subjects with normal total
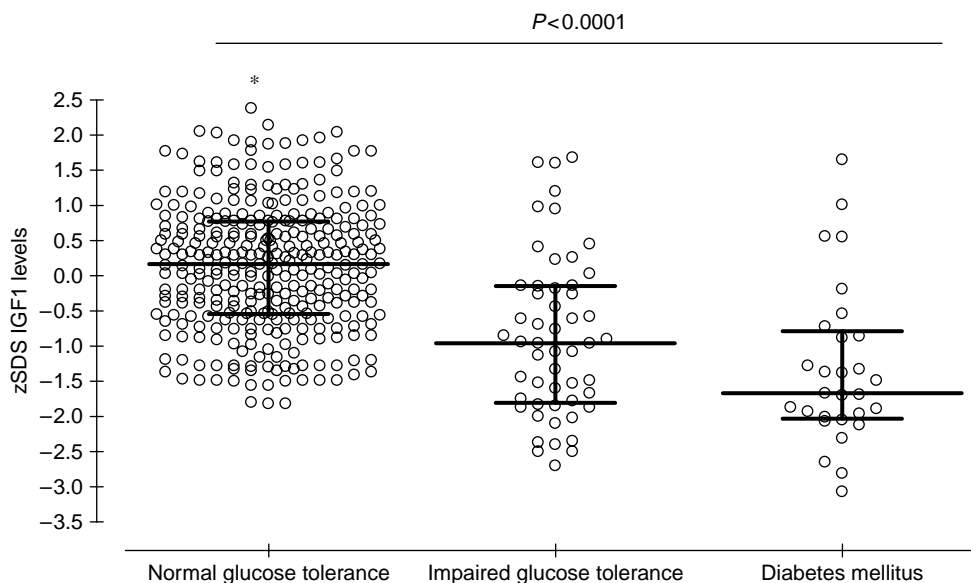

Figure 1 Individual values of IGF1 levels expressed as SDS as related to blood pressure categories. According to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (19), severity of hypertension was classified as mild (stage 1) when SBP or DBP were between 140 and 159 mmHg and between 90 and 99 mmHg respectively; severe (stage 2) when SBP or DBP were ≥160 and ≥100 mmHg respectively; target blood pressure levels to define adequate control were SBP <140 and DBP <90 mmHg. *$P < 0.001$ versus subjects with mild hypertension and severe hypertension.
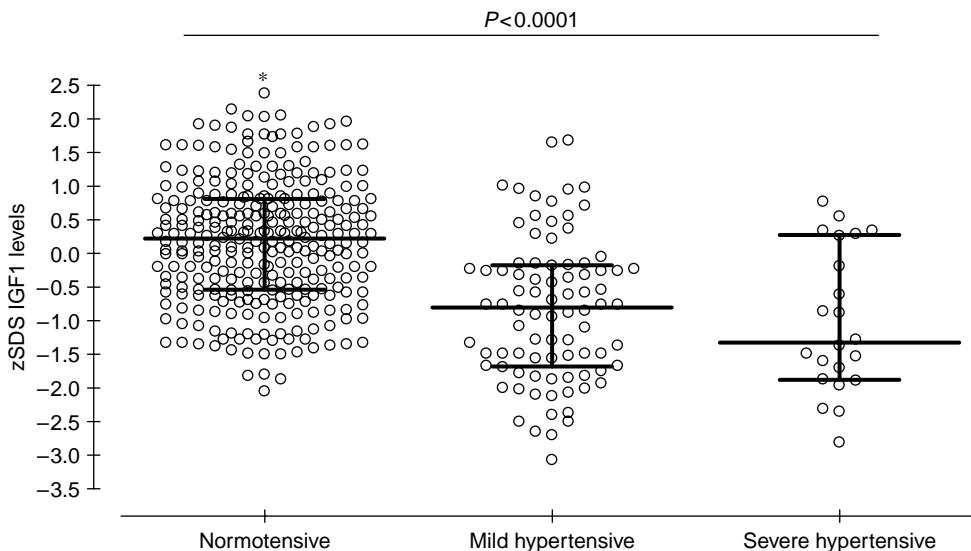
Figure 2 Individual values of IGF1 levels expressed as SDS as related to glucose tolerance categories. Diabetes mellitus was diagnosed when fasting glucose was above 7 mmol/l (125 mg/dl) at two consecutive measurements; impaired fasting glucose (IFG) was diagnosed when glucose levels were between 5.6 and 6.9 mmol/l at fasting; normal glucose level was considered when below 5.6 mmol/l at fasting (20). *P<0.001 versus subjects with impaired glucose tolerance and diabetes mellitus.

cholesterol (0.09 ± 0.94 SDS) or triglyceride (0.02 ± 0.97 SDS) levels had significantly higher IGF1 levels than those with hypercholesterolemia (-0.88 ± 1.16 SDS, $P<0.0001$) or hypertriglyceridemia (-1.13 ± 1.18 SDS, $P<0.0001$); these latter were similar to each other. IGF1 SDS was significantly correlated with total cholesterol ($r=-0.32$, $P<0.0001$) and triglyceride ($r=-0.34$, $P<0.0001$) levels. IGF1 SDS did not independently predict total cholesterol ($t=-1.41$, $P=0.17$) nor triglyceride ($t=-1.80$, $P=0.073$) levels.

Prevalence of hypertension and diabetes according to zSDS of IGF1

The subjects were grouped according to zSDS of IGF1 < -1.0, $-1.0-1.0$, or >1.0 (Table 3). The prevalence of mild or severe hypertension, impaired glucose fasting, and diabetes was significantly higher in the subjects with a zSDS IGF1 < -1.0 than in the other two groups. By the ROC curve, a zSDS IGF1 -0.86 cutoff point predicted severe hypertension and diabetes mellitus (Table 4).
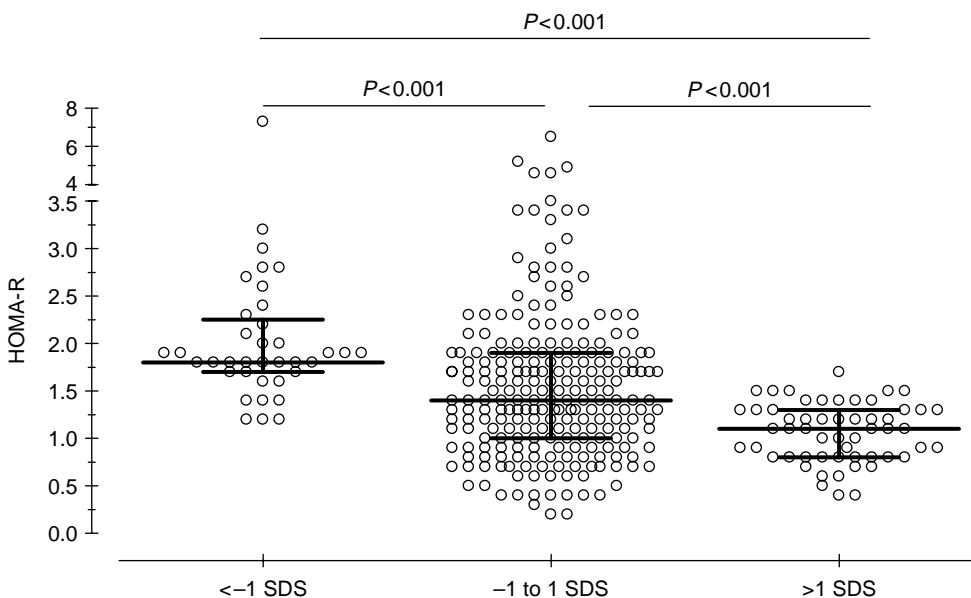

Figure 3 Individual values of HOMA-R in patients with normal glucose tolerance according to categories of IGF1 levels expressed as SDS. Normal glucose level was considered when below 5.6 mmol/l at fasting (20).

Table 3 Prevalence of hypertension, and glucose and lipid abnormalities according to zSDS of insulin-like growth factor-1 (IGF1) in the population of women and men as a whole.

	zSDS of IGF1 < −1.0	zSDS of IGF1 −1.0 to 1.0	zSDS of IGF1 > 1.0	*P*
No.	82 20.3%	262 65.1%	60 14.6%	
Mild hypertension	38 (46.3)	45 (17.1)	3 (15.3)	<0.0001
Severe hypertension	12 (14.6)	10 (3.8)	0 (0)	<0.0001
Impaired fasting glucose	25 (30.5)	24 (9.1)	4 (6.8)	<0.0001
Diabetes mellitus	20 (24.4)	7 (2.7)	2 (3.4)	<0.0001

Data are expressed as the number of subjects affected and percentage of the total subjects.

Discussion

This study indicates that lower IGF1 levels, age-normalized as zSDS, are associated with increased prevalence of severe hypertension and diabetes mellitus in a population of control subjects without pituitary or cardiovascular diseases used to represent the general - population. These results extend and support previous reports suggesting that low circulating IGF1 are associated with an increased cardiovascular risk, in particular to develop ischemic heart disease (11–13), stroke (14–16), and atherosclerosis (17, 18). Cardiovascular disease is the leading cause of death in developed and developing countries. Despite some biologically plausible mechanisms, relatively few epidemiologic studies have so far focused on potential relationships between circulating IGF1 levels and cardiovascular risk factors or cardiovascular disease.

The regulation of circulating levels of IGF1 is complex as it is modified by binding proteins that in turn are under influence and control of GH and nutritional factors. IGF1 and IGFBP1, -2, and -3 are considered components of two axes: the GH/IGF1 axis, including IGF1 and IGFBP3, and the obesity–insulin resistance axis, including IGFBP1 and -2. IGFBP1 and -2 are inversely correlated with insulin and BMI, and are expectedly to be negatively associated with components of insulin resistance syndrome, namely, hypertension, diabetes, and dyslipidemia (24, 25). Conversely, the role of IGF1 is less clear.

IGF1 levels and hypertension

In vitro and *in vivo* experiments showed that IGF1 has vasodilator properties (26). Part of the vasodilator effect of IGF1 is mediated through stimulation of nitric oxide (NO) synthesis by endothelial and vascular smooth muscle cells (SMCs) (26, 27). NO can blunt the effect of vasoconstrictors (e.g., norepinephrine) and mediate the relaxation induced by some vasodilators (acetylcholine and bradykinin). Despite its vasodilation properties, IGF1 seems to be also involved directly in the pathogenesis of hypertension, through its inotropic and growth effects on the heart and endothelium (28) and its ability to stimulate vascular SMCs migration and proliferation (29). These mechanisms appear to have, however, opposite effects on the risk of developing hypertension. Moreover, investigators of two studies with middle-aged participants suggested that BP affects IGF1 levels (30, 31). Acromegalic subjects are at increased risk of hypertension, and IGF1 mediates some of the effects of elevated GH levels that may be related to increased BP, such as increased left ventricular mass, stroke volume, cardiac output, and diastolic peak velocity (32). It is clinically relevant to understand the relationships between IGF1 levels and hypertension since arterial hypertension is a major risk factor of stroke and myocardial infarction. Hunt *et al.* (33) studied 715 men and women aged 30–62 years, who participated in the Västerbotten Intervention Project cohort. They found that IGF1 quartile was associated inversely with 2-h glucose and DBP levels. There was a stepwise inverse-graded association between increasing IGF1 quartile and hypertension, with an odds ratio of 0.51 (95% confidence interval, 0.29–0.90) for hypertension comparing the fourth IGF1 quartile with the first so concluding that IGF1 level may be related inversely to prevalent hypertension (33). The authors also acknowledged that part of the inverse association of IGF1 levels with hypertension they found (33) could reflect the hyperinsulinemic profile of subjects with hypertension (higher insulin and lower IGFBP1 and -2 levels). The relationships with insulin levels and metabolic profile are relevant and have been still poorly understood, but in our multiple regression model IGF1 SDS have found to be independently predictive of hypertension so that insulin secretion does not have a prominent role. Besides, the existence of an inverse relationship between IGF1 levels and BP was also demonstrated by Capoluongo *et al.* (34) in patients

Table 4 Cutoff points determined by a receiving-operator characteristics (ROC) curve analysis.

	Cutoff point	Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)
Severe hypertension	−0.86	63.6% (40.7–82.8%)	89.1% (83.3–93.4%)	43.8	94.8
Diabetes mellitus	−0.86	75.9% (56.5–89.7%)	85.7% (81.4–89.3%)	32.4	97.5

Data are expressed as sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values. The 95% coefficient limits are given in parentheses.

with type 1 diabetes mellitus; they found a decrease in free IGF1 and IGFBP3 levels, along with increases in BP, and reported that these alterations significantly influenced the presence of diabetic complications. Furthermore, *in vitro* studies demonstrates that glucose concentrations play a key role in the responsiveness of small muscle cells to IGF1, and that hyperglycemia enhances cell migration and proliferation in response to IGF1 (35). These data could explain the apparent opposite effect of IGF1 at the vascular level.

In our series, we confirm that subjects with hypertension had lower IGF1 levels than those with normal BP. The lowest IGF1 concentrations occurred in subjects with more severe hypertension. Our data are, thus, in line with the hypothesis that low IGF1 levels could play a role in the development of hypertension even if a concurrence of insulin resistance could not be ruled out. In fact, the subjects with IGF1 SDS below -1 had increased prevalence of hypertension and also of impaired GT and diabetes, preventing a differentiation among these conditions.

IGF1 levels and GT

In humans, IGF1 has approximately one-thirteenth the potency of insulin (on a molar basis) for lowering glucose concentrations. The effects of IGF1 are complex when administered to intact animals, as they potentially involve direct stimulation of glucose transport in IGF1 sensitive tissues, an effect that is mediated by binding to either the IGF1 or the IGF1/insulin hybrid receptor and enhancement of insulin actions through suppression of GH secretion, which reduces the anti-insulin-like effect of GH in the liver (36). Previous cross-sectional reports of the association between circulating concentrations of IGF1 and GT have been contradictory (37, 38) but interpretation of these data is difficult because of potential confounding from secondary effects. Early type 2 diabetes and impaired GT are usually characterized by insulin resistance and hyperinsulinemia; insulin suppresses production of IGFBP1 and increases sensitivity of the GH receptor and expression of GH in the liver (1, 37, 39). Since GH is the main positive regulator of the production of IGF1 in the liver (1), raised concentrations of insulin might increase either circulating concentrations of free IGF1 or GH-stimulated synthesis of IGF1 in the liver. Epidemiologic studies suggest that IGF1 contributes to glucose homeostasis in normal subjects. A polymorphism in the promoter of the *IGF1* gene was demonstrated in 12% of Dutch Caucasians resulting in reduced IGF1 secretion (40); these subjects have 40% lower IGF1 levels than those without the polymorphism, are ~ 2.1 cm shorter and have a 2.2-fold increase in the prevalence of type 2 diabetes after 60 years of age (41). This suggests that these individuals have impaired insulin sensitivity. In addition to the increased prevalence of type 2 diabetes,

they also have a 3.4-fold increase in the prevalence of myocardial infarction after 60 years of age.

Similarly, Sandhu *et al.* (10) reported an association between development of impaired GT or type 2 diabetes and IGF1 levels. The odds ratio for risk of impaired GT or type 2 diabetes for participants with IGF1 concentrations above the median (≥ 152 μg/l) compared with those with concentrations below the median (< 152 μg/l) which was 0.50 (0.26–0.95) (10). Our study has no epidemiological value as our cohort cannot be entirely representative of the general population as constituted by subjects coming from a selected group of individuals, but data confirm previous observations; in fact, subjects with NGT had higher IGF1 SDS than those with impaired GT. As expected on the basis of the reported GH resistance in patients with diabetes mellitus (36), these latter had the lowest IGF1 SDS in our series.

A number of issues, however, remain uncertain. For instance, circulating IGF1 interacts with both insulin and GH secretion, and the role of free versus bound IGF1 needs clarification. It is still a distinct possibility that one mechanism whereby IGF1 may decrease cardiovascular risk is by increasing insulin sensitivity. In addition, recent evidence indicates that the effects of GH (and thereby of IGF1) may be U-shaped as, for instance, indicated by the fact that not only low levels induce insulin resistance and cardiovascular disease as seen in GHD and obesity, but also high levels as seen in acromegaly.

Serum IGF1 levels and hypercholesterolemia or hypertriglyceridemia

In normoglycemic subjects, Sandhu *et al.* (10) did not find any difference in cholesterol and triglycerides levels according to tertiles of IGF1 levels. However, according to the previously reported data on GT, it is likely that cholesterol and triglycerides follow closely glucose levels. On the other hand, data collected in patients with hypopituitarism and severe GHD clearly demonstrate dyslipidemia, which is considered one of the most important link with mortality for cardiovascular disease reported in these patients subset (42–44). In this study we confirmed that IGF SDS levels did not independently predict lipid levels that, more likely, are only in agreement with GT results. In a previous study we did not find any difference between total cholesterol and triglyceride levels in patients classified as partial GHD after GH-releasing hormone plus arginine test, and the patients with partial GHD had levels of IGF1 in the normal range but significantly lower than controls (45). Thus, the current data suggest that circulating IGF1 levels are also associated with cholesterol and triglycerides levels, but this relationship is likely mediated by the GT.

More recently, higher IGF1 levels as well as vitamin D levels were found to be associated with lower prevalence of metabolic syndrome (46). Additionally, GH and IGF1

levels were found differently associated with metabolic syndrome in women and men, but both in men and women IGF1 were correlated positively with lipids and negatively with obesity/GT (47). In this latter study, data are partially in disagreement with our data on lipid levels and BP levels but the cohort of subjects studied is different (47).

Conclusion

In a large population of control subjects without pituitary and cardiovascular diseases at study entry, IGF1 levels in the lower normal range were correlated with hypertension, reduced GT, and diabetes. Though this study has no epidemiological relevance as the study population is not fully the representative of the general population, it suggests a role of IGF1 levels in determining indirect cardiovascular risk conditions such as hypertension and diabetes.

References

1 Jones JI & Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocrine Reviews* 1995 **16** 3–34.

2 Le Roith D. Insulin like growth factors. *New England Journal of Medicine* 1997 **336** 633–640.

3 Lombardi G, Di Somma C, Rota F & Colao A. Associated hormonal decline in aging: is there a role for GH therapy in aging men? *Journal of Endocrinological Investigation* 2005 **28** (Suppl 3) 99–108.

4 Gatford KL, Egan AR, Clarke IJ & Owens PC. Sexual dimorphism of the somatotrophic axis. *Journal of Endocrinology* 1998 **157** 373–389.

5 Hall K, Johansson BL, Povoa G & Thalme B. Serum levels of insulin-like growth factor (IGF) I, II and IGF binding protein in diabetic adolescents treated with continuous subcutaneous insulin infusion. *Journal of Internal Medicine* 1989 **225** 273–278.

6 Gillespie CM, Merkel AL & Martin AA. Effects of insulin-like growth factor-I and LR3IGF-I on regional blood flow in normal rats. *Journal of Endocrinology* 1997 **155** 351–358.

7 Galderisi M, Caso P, Cicala S, De Simone L, Barbieri M, Vitale G, de Divitiis O & Paolisso G. Positive association between circulating free insulin-like growth factor-1 levels and coronary flow reserve in arterial systemic hypertension. *American Journal of Hypertension* 2002 **15** 766–772.

8 Paolisso G, Tagliamonte MR, Rizzo MR, Carella C, Gambardella A, Barbieri M & Varricchio M. Low plasma insulin-like growth factor-1 concentrations predict worsening of insulin-mediated glucose uptake in older people. *Journal of the American Geriatrics Society* 1999 **47** 1312–1318.

9 Clemmons DR, Moses AC, McKay MJ, Sommer A, Rosen DM & Ruckle J. The combination of insulin-like growth factor I and insulin-like growth factor-binding protein-3 reduces insulin requirements in insulin-dependent type 1 diabetes: evidence for *in vivo* biological activity. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1518–1524.

10 Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB & Wareham NJ. Circulating concentrations of insulin-like growth factor-I and development of glucose intolerance: a prospective observational study. *Lancet* 2002 **359** 1740–1745.

11 Juul A, Scheike T, Davidsen MJ, Gyllenborg T & Jorgensen JO. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case–control study. *Circulation* 2002 **106** 939–944.

12 Vasan RS, Sullivan LM, D'Agostino RB, Roubenoff R, Harris T, Sawyer DB, Levy D & Wilson PW. Serum insulin-like growth factor I and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study. *Annals of Internal Medicine* 2003 **139** 642–648.

13 Laughlin GA, Barrett-Connor E, Criqui MH & Kritz-Silverstein D. The prospective association of serum insulin-like growth factor I (IGF-I) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 114–120.

14 Denti L, Annoni V, Cattadori E, Salvagnini MA, Visioli S, Merli MF, Corradi F, Ceresini G, Valenti G, Hoffman AR & Ceda GP. Insulin-like growth factor 1 as a predictor of ischemic stroke outcome in the elderly. *American Journal of Medicine* 2004 **117** 312–317.

15 Johnsen SP, Hundborg HH, Sorensen HT, Orskov H, Tjonneland A, Overvad K & Jorgensen JO. Insulin-like growth factor (IGF) I, -II, and IGF binding protein-3 and risk of ischemic stroke. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5937–5941.

16 Bondanelli M, Ambrosio MR, Onofri A, Bergonzoni A, Lavezzi S, Zatelli MC, Valle D, Basaglia N & degli Uberti EC. Predictive value of circulating insulin-like growth factor I levels in ischemic stroke outcome. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3928–3934.

17 van den Beld AW, Bots ML, Janssen JAMLL, Pols HAP, Lamberts SWJ & Grobbee DE. Endogenous hormones and carotid atherosclerosis in elderly men. *American Journal of Epidemiology* 2003 **15** 25–31.

18 Colao A, Spiezia S, Di Somma C, Pivonello R, Marzullo P, Rota F, Musella T, Auriemma RS, De Martino MC & Lombardi G. Circulating insulin-like growth factor-I levels are correlated with the atherosclerotic profile in healthy subjects independently of age. *Journal of Endocrinological Investigation* 2005 **28** 440–448.

19 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung & Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Journal of the American Medical Association* 2003 **289** 2560–61.

20 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006 **29** S43–S48.

21 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF & Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985 **28** 412–419.

22 Consensus Conference: treatment of hypertriglyceridemia. *Journal of the American Medical Association* 1984 **251** 1196–1200.

23 Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final reprot. *Circulation* 2002 **106** 3143–3421.

24 Cruickshank JK, Heald AH, Anderson S, Cade JE, Sampayo J, Riste LK, Greenhalgh A, Taylor W, Fraser W, White A & Gibson JM. Epidemiology of the insulin-like growth factor system in three ethnic groups. *American Journal of Epidemiology* 2001 **154** 504–513.

25 Harrela M, Koistinen R, Tuomilehto J, Nissinen A & Seppala M. Low serum insulin-like growth factor-binding protein-1 is associated with an unfavourable cardiovascular risk profile in elderly men. *Annals of Medicine* 2000 **32** 424–428.

26 Sowers JR. Insulin and insulin-like growth factor in normal and pathological cardiovascular physiology. *Hypertension* 1997 **29** 691–699.

27 Walsh MF, Barazi M, Pete G, Muniyappa R, Dunbar JC & Sowers JR. Insulin-like growth factor I diminishes *in vivo* and *in vitro* vascular contractility: role of vascular nitric oxide. *Endocrinology* 1996 **137** 1798–1803.

28 Galderisi M, Vitale G, Lupoli G, Barbieri M, Varricchio G, Carella C, de Divitiis O & Paolisso G. Inverse association between free insulin-like growth factor-1 and isovolumic relaxation in arterial systemic hypertension. *Hypertension* 2001 **38** 840–845.

29 Jones JI, Prevette T, Gockerman A & Clemmons DR. Ligand occupancy of the α-V-β3 integrin is necessary for smooth muscle cells to migrate in response to insulin-like growth factor. *PNAS* 1996 **93** 2482–2487.

30 Andronico G, Mangano MT, Nardi E, Mule G, Piazza G & Cerasola G. Insulin-like growth factor 1 and sodium-lithium countertransport in essential hypertension and in hypertensive left ventricular hypertrophy. *Journal of Hypertension* 1993 **11** 1097–1101.

31 Diez J & Laviades C. Insulin-like growth factor-1 and cardiac mass in essential hypertension: comparative effects of captopril, lisinopril and quinapril. *Journal of Hypertension* 1994 **12** (Supplement) S31–S36.

32 Colao A, Ferone D, Marzullo P & Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocrine Reviews* 2004 **25** 102–152.

33 Hunt KJ, Lukanova A, Rinaldi S, Lundin E, Norat T, Palmqvist R, Stattin P, Riboli E, Hallmans G & Kaaks R. A potential inverse association between insulin-like growth factor-I and hypertension in a cross-sectional study. *Annals of Epidemiology* 2006 **16** 563–571.

34 Capoluongo E, Pitocco D, Lulli P, Minucci A, Santonocito C, Manto A, Di Stasio E, Zaccardi F, Zuppi C, Ghirlanda G & Ameglio F. Inverse correlation between serum free IGF-1 and IGFBP-3 levels and blood pressure in patients affected with type 1 diabetes. *Cytokine* 2006 **34** 303–311.

35 Maile LA, Capps BE, Ling Y, Xi G & Clemmons DR. Hyperglycemia alters the responsiveness of smooth muscle cells to insulin-like growth factor-I. *Endocrinology* 2007 **148** 2435–2443.

36 Clemmons DR. Involvement of insulin-like growth factor-I in the control of glucose homeostasis. *Current Opinion in Pharmacology* 2006 **6** 620–625.

37 Frystyk J, Skjærbæk C, Vestbo E, Fisker S & Orskov H. Circulating levels of free insulin-like growth factors in obese subjects: the impact of type 2 diabetes. *Diabetes/Metabolism Research and Reviews* 1999 **1** 314–322.

38 Clauson G, Brismar K, Hall K, Linarsson R & Grill V. IGF-I and IGFBP-1 in a representative population of type 2 diabetics in Sweden. *Scandinavian Journal of Clinical and Laboratory Investigation* 1998 **58** 353–360.

39 Lee PD, Giudice LC, Conover CA & Powell DR. Insulin-like growth factor binding protein-1: recent findings and new directions. *Proceedings of the Society for Experimental Biology and Medicine* 1997 **216** 319–357.

40 Rietveld I, Janssen JA, van Rossum EF, Houwing-Duistermaat JJ, Rivadeneira F, Hofman A, Pols HA, van Duijn CM & Lamberts SW. A polymorphic CA repeat in the IGF-I gene is associated with gender-specific differences in body height, but has no effect on the secular trend in body height. *Clinical Endocrinology* 2004 **61** 195–203.

41 Vaessen N, Heutink P, Janssen JA, Witteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA & van Duijn CM. A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. *Diabetes* 2001 **50** 637–642.

42 Colao A, Marzullo P, Di Somma C & Lombardi G. Growth hormone and the heart. *Clinical Endocrinology* 2001 **54** 137–154.

43 Gola M, Bonadonna S, Doga M & Giustina A. Growth hormone and cardiovascular risk factors. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 1864–1870.

44 Erfurth EM & Hagmar L. Cerebrovascular disease in patients with pituitary tumors. *Trends in Endocrinology and Metabolism* 2005 **16** 334–342.

45 Colao A, Di Somma C, Spiezia S, Rota F, Pivonello R, Savastano S & Lombardi G. The natural history of partial growth hormone deficiency in adults: a prospective study on the cardiovascular risk and atherosclerosis. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2191–2200.

46 Hyppönen E, Boucher BJ, Berry DJ & Power C. 25-Hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008 **57** 298–305.

47 Maison P, Balkau B, Souberbielle JC, Cunin P, Vol S, Macquin-Mavier I, Eschwège E & D E S I R Study Group. Evidence for distinct effects of GH and IGF-I in the metabolic syndrome. *Diabetic Medicine* 2007 **24** 1012–1018.