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Original Contributions

Serum Total IGF-I, Free IGF-I, and IGFBP-1 Levels in an Elderly Population

Relation to Cardiovascular Risk Factors and Disease

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Abstract

Abstract—Recently, a method to measure free insulin-like growth factor-I (IGF-I) levels has been developed. Free IGF-I levels may have greater physiological and clinical relevance than total (bound and free) IGF-I. The associations between the circulating IGF-I/IGF binding protein (IGFBP) system and cardiovascular disorders was studied. In a cross-sectional study of 218 healthy persons (103 men, 115 women) aged 55 to 80 years, fasting serum (total and free) IGF-I and IGFBP-1 levels, lipid profile, insulin, and glucose were measured. In addition, blood pressure, body mass index (BMI), and waist-hip ratio (WHR) were measured. Ultrasonography of both carotid arteries was performed to investigate the presence of atherosclerotic lesions. A history of angina pectoris, the presence of a possible or definite myocardial infarction on the ECG, and plaques in the carotid arteries were used as indicators of presence of cardiovascular signs and symptoms. Free IGF-I was inversely related to serum triglycerides ($P=.04$, adjusted for age and sex). Mean free IGF-I levels in subjects without signs or symptoms of cardiovascular diseases were significantly higher than in those with at least one cardiovascular symptom or sign ($P=.002$, adjusted for age and sex). Free IGF-I levels were also higher in subjects who had no atherosclerotic plaques in the carotid arteries ($P=.02$, adjusted for age and sex) and who had never smoked ($P=.02$, adjusted for age and sex). IGFBP-1 showed an inverse relation with insulin, BMI, and WHR and a positive relation with HDL cholesterol. The associations between IGFBP-1 levels and HDL cholesterol, WHR, and BMI remained significant after adjustment for fasting insulin levels. High fasting serum free IGF-I levels are associated with a decreased presence of atherosclerotic plaques and coronary artery disease and lower serum triglycerides, whereas high fasting IGFBP-1 levels are associated with a more favorable cardiovascular risk profile. The findings suggest that the IGF-I/IGFBP system is related to cardiovascular risk factors and atherosclerosis.

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Key Words: free IGF-I • IGFBP-1 • atherosclerosis • cardiovascular risk factors • elderly

Introduction

A possible involvement of circulating IGF-I and IGFBP in the pathogenesis of cardiovascular disorders has recently been suggested.¹ Total IGF-I levels are lower in patients with an atherogenic lipid profile and may contribute to the development of atherosclerosis.² Many in vitro studies have shown proliferation of vascular smooth muscle cells after stimulation with IGF-I.^{3 4} Moreover, IGF-I has also been shown to be an important regulator of vascular function by stimulating nitric oxide release from cultured vascular endothelium.⁵

The commonly measured total extractable IGF-I in serum provides only a crude estimate of biologically active IGF-I, due to the wide interindividual variation in IGFBP.⁶ Free IGF-I, by analogy with sex and adrenal steroids and thyroid hormones, may have greater physiological and clinical relevance and accounts for only 1% of total IGF-I.⁷ Recently, a method has been developed to measure free IGF-I levels.⁸

The six IGFbps comprise a family of structurally homologous proteins that prolong the half-life of IGF-I in the circulation and modulate IGF-I action at its target cells.^{9 10} IGFBP-1, one of these IGFbps, is not restricted to the circulation and is considered to function as a transport protein that shuttles IGF-I from the intravascular space through the endothelial walls of the capillaries.^{11 12}

IGFBP-1 has been proposed as an acute regulator of IGF-I bioactivity and might simultaneously both inhibit and potentiate IGF-I action at different sites.¹³ Recent evidence even suggests that IGFBP-1 has intrinsic mitogenic and metabolic activity.¹⁴ Consequently, it seems desirable to distinguish bound and unbound components of IGF-I when studying the IGF-I/IGFBP system.

To broaden our understanding of a possible role of the IGF-I/IGFBP system in the development of cardiovascular disorders, we studied the relationship of fasting serum circulating levels of (free and total) IGF-I and IGFBP-1 with the presence of cardiovascular risk factors and diseases in an elderly population.

Methods

Subjects

For the present study, a sample of participants from the Rotterdam Elderly Study was invited for an additional examination. The Rotterdam study is a population-based cohort study of the determinants of chronic disabling diseases in the elderly. All approximately 10 000 inhabitants of a suburb of Rotterdam, aged 55 years and over, were invited to participate, as described elsewhere.¹⁵ Overall, 7983 participants were examined (response rate 78%).

The population for the present study included subjects aged 55 to 80 years who had completed the baseline visit of the Rotterdam study not more than 6 months earlier. Subjects with psychiatric or endocrine diseases, including diabetes mellitus treated with medication, were not invited. From these subjects, a random sample of 218 persons was examined. Compared with the other participants of the Rotterdam study of the same age without known diabetes mellitus, there were no differences in age and sex distribution, mean blood pressure, use of antihypertensive medication, echocardiographic evidence of atherosclerotic plaques in the carotid arteries, and electrocardiographic abnormalities. From all subjects, informed consent was obtained, and the study was approved by the medical ethics committee of Erasmus University Medical School.

Cardiovascular Assessment

A resting standard 12-lead ECG was made with an ACTA Gnosis IV (EsaoteBiomedica), and an automated diagnostic classification system of the Modular Electrocardiogram Analysis System (MEANS) was used.^{16 17} The presence of a possible or definite myocardial infarction on the ECG was used as an indicator of presence of coronary artery disease.¹⁸

Information on medical history of myocardial infarction, medical history, drug use, and smoking was obtained by a trained research assistant using a computerized questionnaire, which includes a Dutch version of the Rose questionnaire to determine the presence of angina pectoris and intermittent claudication.¹⁹

To measure carotid artery intima-media thickness, ultrasonography of the left and right common carotid artery, the carotid bifurcation, and the internal carotid artery was performed with a 7.5-MHz linear array transducer (ATL Ultramark IV, Advanced Technology Laboratories). Following the Rotterdam study ultrasound protocol, a careful search was performed for all interfaces of the near end and far wall of the distal common carotid artery.^{20 21 22} The actual measurements of the intima-media thickness were performed off line.

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This procedure has been described previously.²³

The common carotid artery, carotid bifurcation, and internal carotid artery were also evaluated for the presence (yes/no) of atherosclerotic lesions on both the near and far wall of the carotid arteries. Plaques were defined as a focal widening relative to adjacent segments, with protrusions into the lumen composed of only calcified deposits or a combination of calcification and noncalcified material.²⁴ The size or extent of the lesions was not quantified. The presence of plaques was used as an indicator of presence of atherosclerosis.

Subjects were categorized into groups of current smokers, former smokers, and those who had never smoked. BMI was defined as weight divided by the height squared [$\text{kg}/(\text{m})^2$], and body fat distribution was estimated using the ratio of waist and hip circumferences (WHR) in centimeters. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion was used in the analyses. Hypertension was defined as a systolic blood pressure of ≥ 160 mm Hg or a diastolic pressure of ≥ 95 mm Hg or the use of antihypertensive drugs.²⁵

Biochemical Measurements

Fasting blood samples were taken by venipuncture between 8 and 9 AM and allowed to coagulate for 30 minutes. Subsequently, serum was separated by centrifugation and quickly frozen in liquid nitrogen. Dissociable free IGF-I was measured with a commercially available noncompetitive two-site immunoradiometric assay (Diagnostic System Laboratories Inc; intra-assay and interassay CV: 10.3% and 10.7%, respectively).⁸ The free IGF-I assay used needs no initial sample extraction as part of the standard procedure to measure IGF-I. Samples are added directly to tubes containing a dense coating of high-affinity free IGF-I antibody, incubated for 2 hours at room temperature, washed, incubated with ¹²⁵I-labeled antibody directed to a second epitope, washed, and counted. Assay standards are rhIGF-I: 0.04 to 2.6 nmol/L; the minimal detection limit is 0.004 nmol/L. There is no cross-reactivity with IGF-II, and no residual IGFBP-1 or IGFBP-3 is detectable after the first wash. It is likely that the free IGF-I fraction measured with the free IGF-I assay is a combination of the true free IGF-I and the fraction that can be readily dissociated from IGFBP under the specific assay conditions.⁸ Addition of pure IGFBP-1 and -3 to an IGF-I-containing buffer caused a dose-related decrease in measurable free IGF-I.⁸ Total IGF-I was determined by a commercially available radioimmunoassay (Medgenix Diagnostics; intra-assay and interassay CV: 6.1% and 9.9%) after an acidification/neutralization step. The purpose of this step is to convert the different forms of IGF-I present into free IGF-I. A commercially available immunoradiometric assay was also used for measurement of IGFBP-1 (MW 25.3 kD; Diagnostic System Laboratories Inc; intra-assay and interassay CV: 4.0% and 6.0%). Insulin was determined by a commercially available radioimmunoassay (Medgenix Diagnostics, intra-assay and interassay CV: 8.0% and 13.7%). Serum glucose, creatinine, cholesterol, HDL cholesterol, and triglyceride levels were determined with standard laboratory methods.

Statistical Analysis

The clinical characteristics are presented as mean (SE). Differences between subgroups with or without cardiovascular symptoms and signs were analyzed by linear regression after adjustment for age and sex. Multiple linear regression analyses were used to further assess the associations of free IGF-I and IGFBP-1 with other parameters. A two-sided probability value of $<.05$ was considered statistically significant. Analyses in which the values were logarithmically transformed yielded similar results to those with untransformed data. Because the interpretation of logarithmic data is difficult, the nontransformed data are presented. Age-adjusted ORs (with 95% CIs) were calculated as an approximation of the relative risk of free IGF-I for the presence of atherosclerotic plaques and coronary artery disease. All statistical analyses were performed with Stata statistical package (Computing Resource Center).

Results

In Table 1⁺, the general characteristics of the study population are presented. The percentage of free over total serum IGF-I varied between 0.14% and 2.77%. Serum free IGF-I increased 0.003 nmol/L per nmol/L total IGF-I (SE 0.0004, $P<.001$, adjusted for age and sex) and decreased 0.013 nmol/L per nmol/L IGFBP-1 (SE 0.004, $P=.003$, adjusted for age and sex). Serum total IGF-I levels decreased 2.766 nmol/L per nmol/L serum IGFBP-1 (SE 0.596, $P<.001$, adjusted for age and sex). Age- and sex-adjusted fasting free IGF-I levels were inversely related to serum triglycerides but showed no relation with most cardiovascular risk factors (Table 2⁺). After further adjustment for insulin, the relation between free IGF-I and serum triglycerides became even stronger: regression coefficient, -3.1 (mmol/L per nmol/L free IGF-I, $P=.01$).

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View this table: **Table 1.** General Characteristics of 218 Subjects (103 Men, 115 Women)
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View this table: **Table 2.** Age- and Sex-Adjusted Associations Between Fasting Free IGF-I and IGFBP-1, Respectively, and Several Cardiovascular Risk Factors in an Elderly Population (Aged 55 to 80 Years)
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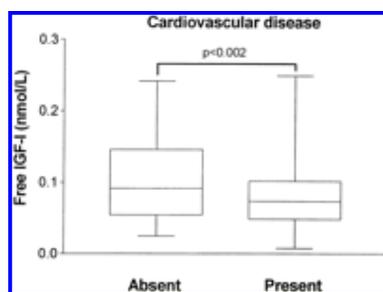
Total IGF-I was positively related to serum glucose: regression coefficient, 0.022 (SE 0.008; mmol/L per nmol/L serum IGF-I, $P=.008$), but not to any of the other investigated cardiovascular risk factors mentioned in Table 2 (data not shown). IGFBP-1 showed an inverse relation with insulin, glucose, BMI, and WHR and a positive relation with HDL cholesterol (Table 2). The associations between IGFBP-1 and HDL cholesterol, WHR, and BMI remained significant after adjustment for fasting insulin levels: regression coefficients per nmol/L IGFBP-1 were, respectively, 0.06 (SE 0.03; mmol/L, $P=.03$); -0.02 (SE 0.01, $P=.009$), and -0.63 (SE 0.27; kg/[m]², $P=.02$), while the association between IGFBP-1 and serum glucose lost statistical significance after this adjustment.

Free IGF-I and Presence of Cardiovascular Diseases

Age- and sex-adjusted mean free IGF-I levels were lower in subjects with at least one plaque in the carotid arteries than in those without plaques: difference, 0.017 nmol/L (SE 0.008, $P=.02$). Free IGF-I levels were also lower in subjects with coronary artery disease than in those without: difference, 0.018 nmol/L (SE 0.009, $P=.04$); Table 3. Age- and sex-adjusted free IGF-I levels were not related to the carotid intima-media thickness: regression coefficient per 0.01 nmol/L IGF-I, 0.0012 (SE 0.0016; mm, $P=.47$). Mean free IGF-I levels were lower in subjects with a history of angina pectoris and higher in subjects with hypertension, but this value did not reach statistical significance after adjustment for age and sex (Table 3). Serum free IGF-I levels were significantly higher in subjects who had never smoked ($P=.02$) than in ever (former and current) smokers.

View this table: **Table 3.** Fasting Free IGF-I and IGFBP-1 Levels (nmol/L) in Subjects With Versus Without Symptoms and Signs of Cardiovascular Diseases
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Mean free IGF-I levels were higher in subjects without any actual sign and symptom of cardiovascular disease (ie, no angina pectoris, no myocardial infarction on the ECG, and no atherosclerotic lesions in the carotid arteries) than in subjects with at least one symptom or sign of cardiovascular disease (ie, angina pectoris and/or myocardial infarction on the ECG and/or atherosclerotic lesions in the carotid arteries): 0.107 nmol/L (SE 0.008) versus 0.086 nmol/L (SE 0.004), $P=.002$, adjusted for age and sex; (see Figure 1). This association remained significant after further adjustment for smoking and hypertension.



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Figure 1. Mean free IGF-I levels (adjusted for age and sex) compared between subjects without signs and symptoms of cardiovascular diseases (left) and subjects with at least one cardiovascular symptom or sign (right). The line in the middle of the boxes represents the 50th percentile of the data. The boxes extend from the 25th percentile to the 75th percentile values, and the whiskers extend from the 5th to the 95th percentile values of each group (difference=0.026 nmol/L [SE 0.008], $P=.002$).

For total IGF-I, lower levels were observed in groups with presence of one cardiovascular disease and/or risk factor than in those without. The difference in total IGF-I levels was significant for angina pectoris; mean total IGF-I in subjects with angina pectoris: 15.0 (SE 2.1) nmol/L and 19.1 (SE 0.6) nmol/L in subjects without angina pectoris (adjusted for age and sex, $P=.04$).

Mean IGFBP-1 levels were not significantly different in subgroups with or without cardiovascular diseases and risk factors, hypertension, or smoking (Table 3⁺).

Age-adjusted multiple logistic regression analysis, performed with the presence of atherosclerotic plaques and the presence of coronary artery disease as dependent variable, respectively, and free IGF-I as independent variable, showed a significant decreased risk for the presence of plaques per 0.01 nmol/L increase in serum free IGF-I level: OR 0.94 (95% CI: 0.89 to 0.99) per 0.01 nmol/L ($P=.03$) and a decreased risk for the presence of coronary artery disease per 0.01 nmol/L increase in serum free IGF-I level: OR 0.91 (95% CI: 0.84 to 0.99) per 0.01 nmol/L ($P=.02$).

Discussion

Mean free IGF-I levels were significantly lower in subjects with atherosclerotic plaques in the carotid arteries and with coronary artery disease. When subjects without symptoms or signs of cardiovascular diseases (ie, no angina pectoris, no myocardial infarction on the ECG, and no atherosclerotic plaques in the carotid arteries) were compared with those with at least one symptom or sign of cardiovascular disease, mean free IGF-I levels were significantly higher in the former group. These findings suggest that lowered free IGF-I levels are associated with a higher prevalence of cardiovascular disease. Low circulating IGF-I levels have been previously associated with angiographically documented coronary artery disease.²⁶ Other investigations have also suggested that low circulating IGF-I levels are associated with premature atherogenesis, cardiovascular morbidity, and mortality.^{27 28 29} However, these latter studies need to be considered with caution because they were retrospective studies; many subjects in these studies also showed deficiencies of other pituitary hormones, which might have been suboptimally replaced.

Serum free IGF-I is considered an important biologically active IGF-I fraction.⁷ The serum free IGF-I levels in our study lie within the same range as previously reported for the molecular affinity of the IGF-I receptor on both vascular endothelium and vascular smooth muscle cells.^{3 30} Because endothelial cells are continuously exposed to IGF-I in vivo, it is conceivable that endocrine IGF-I might be of importance in both the normal physiology of vascular endothelium and in disease states, eg, atherosclerosis.³¹ Evidence exists that IGF-I does cross vascular endothelium and in this respect might be also comparable to insulin.^{30 32} The importance of circulating (endocrine) IGF-I has been challenged by the autocrine/paracrine concept of IGF-I since most cells implicated in the pathogenesis of atherosclerosis are capable of expressing (autocrine and paracrine) IGF-I, IGF-I receptors, and IGFbps.¹ There are many who even believe that there is no physiological role for circulating IGF-I in atherosclerosis. Some arguments in favor of this view are that the expression of IGF-I in the vessel wall is independent of pituitary growth hormone secretion³³ and that endothelial denudation of blood vessels in rats increases the accumulation of IGF-I in vascular smooth muscles without concomitant changes in hepatic IGF-I mRNA expression and serum total IGF-I levels.³⁴ However, both observations can also be explained by an increased proteolysis of circulating IGFbps by specific IGFBP proteases present in serum (as plasmin and thrombin), contributing to a higher IGF-I delivery at an injury of the vascular endothelium.^{35 36} This mechanism may then result in an increased association of IGF-I with the IGF-I receptor of the vascular smooth muscle cells during repair of injured arterial intima. This response to injury might be reflected in (transiently) lower serum free IGF-I levels as a consequence of consumption. In addition, the frequently immunoreactive techniques used to localize ultrastructurally IGF-I in atherosclerotic plaques cannot demonstrate the origin of IGF-I (locally produced or endocrine). Other arguments for a physiological effect of circulating IGF-I to the vessel wall are that administration of exogenous IGF-I to human retinal vascular endothelium cells in culture causes decreased IGF-I mRNA levels in these cells³⁷; and finally, several studies suggest that the majority of IGF-I secreted by vascular endothelial cells (in contrast to IGFbps) results from IGF-I uptake from serum and not from local de novo synthesis.^{30 38} These studies suggest that intact endothelium serves as a regional storage site for intravascular receptor-bound IGF-I.

Recent data suggest that IGF-I stimulates the production of nitric oxide from both the endothelium and vascular smooth muscles.³⁹ Decreased nitric oxide production by vascular endothelium due to low free IGF-I levels might be a mechanism, which could contribute to the observed relation between free IGF-I levels and the presence of cardiovascular symptoms and signs in our study.⁴⁰

In our study, free IGF-I levels were inversely associated with fasting triglycerides. Indeed, administration of recombinant IGF-I to humans was reported to cause a decrease in triglyceride levels.⁴¹

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Also in our study, no relationships were found between free and total IGF-I and BMI or WHR. The total amount of excess fat on the body is roughly reflected in the BMI, whereas WHR is more strongly associated with the amount of abdominal fat. Several epidemiological studies suggest that abdominal obesity may especially be involved in atherosclerosis⁴² and that a decreased growth hormone secretion is an endocrine characteristic of obesity.⁴³ Growth hormone-dependent IGF-I concentrations would thus be expected to be subnormal in obesity.⁴⁴ However, total IGF-I levels have been reported not to be significantly different between obese subjects and lean control subjects.^{44 45} In this latter study, free IGF-I levels were reported to be higher in obese males, while free IGF-I levels were not significantly elevated in obese females.⁴⁵ The differences between these results and ours are most likely due to difference in age, sex, and degree of obesity in the study group, as the subjects in our study were older, predominantly female, and less obese. Moreover, in our study, another method was used to measure free IGF-I levels.

Higher fasting age-adjusted IGFBP-1 levels were associated with decreased BMI, WHR, insulin, and glucose levels and increased HDL cholesterol levels. In a previous study, it was demonstrated that reduced fasting IGFBP-1 levels correlate with an increased prevalence of cardiovascular risk factors in non-insulin-dependent diabetes mellitus.⁴⁶ Our study shows that this relationship similarly exists in a nondiabetic population and that the reverse is also true, ie, higher IGFBP-1 levels are associated with an advantageous cardiovascular risk profile. Insulin is considered as the main regulator of IGFBP-1 levels, while it also modulates the action of IGFBP-1.¹¹ It also accelerates IGFBP-1 transport from the intravascular space through the endothelial walls of the capillaries to the target cells.^{11 12} However, the associations between IGFBP-1 levels and BMI, WHR, and HDL cholesterol were independent of insulin levels. This observation suggests that a low IGFBP-1 level might be an independent marker for the metabolic disturbances, which are all associated with an increased risk of cardiovascular diseases.

Studies of the biological effect of IGFBP-1 have shown conflicting results. IGFBP-1 is capable of both inhibition and augmentation of IGF-I bioactivity.⁴⁷ These conflicting observations may be explained by the recent findings that differential phosphorylation of IGFBP-1 could significantly alter its affinity for IGF-I and therefore differently modulate IGF-I bioactivity.⁴⁸ The IGFBP-1 assay used in our study cannot discriminate phosphorylated and nonphosphorylated IGFBP-1, but IGFBP-1 normally circulates mainly as a highly phosphorylated form.⁴⁹ This latter form of IGFBP-1 would favor sequestration of IGF-I by IGFBP-1, resulting in a decreased IGF-I release to IGF-I receptors.⁴⁷ The observed lower IGFBP-1 levels in subjects with a disadvantageous cardiovascular risk profile might be thus an adaptive mechanism to increase IGF-I bioactivity at the vascular endothelium.

Although most cells implicated in the pathogenesis of atherosclerosis are capable of expressing autocrine and paracrine IGF-I, IGF-I receptors, and IGFBPs, the results of our study suggest that the measurement of circulating free IGF-I and IGFBP-1 levels may be of clinical relevance and will help to unravel the role of the IGF-I/IGFBP-1 system in atherogenesis.

In conclusion, our findings indicate that low circulating free IGF-I levels are associated with an increased risk of presence of atherosclerotic cardiovascular disease. In addition, higher IGFBP-1 levels are related to a more favorable cardiovascular risk factor profile. These findings lend support to the view that the IGF-I/IGFBP-1 system is related to cardiovascular risk in the elderly population.

Selected Abbreviations and Acronyms

BMI	= body mass index
CI	= confidence interval
CV	= coefficient of variation
IGF-I	= insulin-like growth factor-I
IGFBP	= IGF binding protein
OR	= odds ratio
WHR	= waist-hip ratio

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References

1. Ferns GAA, Morani AS, Anggard EE. The insulin-like growth factors: their putative role in atherogenesis. *Artery*. 1991;18:197–225. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
2. Delafontaine P, Bernstein KE, Alexander RW. Insulin-like growth factor I gene expression in vascular cells. *Hypertension*. 1991;17:693–699. [\[Abstract\]](#)
3. Banskota NK, Taub R, Zellner K, Olsen P, King GL. Characterization of induction of protooncogene *c-myc* and cellular growth in human vascular smooth muscle cells by insulin and IGF-I. *Diabetes*. 1989;38:123–129. [\[Abstract\]](#)
4. Grant MB, Wargovich TJ, Ellis EA, Caballero S, Mansour M, Pepine CJ. Localization of insulin-like growth factor I and inhibition of coronary smooth muscle cell growth by somatostatin analogues in human coronary smooth muscle cells: a potential treatment for restenosis. *Circulation*. 1994;89:1511–1517. [\[Abstract\]](#)
5. Tsukahara H, Gordienko DV, Tonshoff B, Gelato MC, Goligorsky MS. Direct demonstration of insulin-like growth factor-I induced nitric oxide by endothelial cells. *Kidney Int*. 1994;45:598–604. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
6. Ørskov H, Weeke J, Frystyk J, Kaal A, Nielsen S, Skjaerbaek C, Christiansen JS, Moller N, Jorgensen JOL. Growth hormone determination in serum from patients with growth disorders. In: Juul A, Jorgensen JOL, eds. *Growth Hormone in Adults*. Cambridge, UK: Cambridge University Press; 1996:109–121.
7. Frystyk J, Skjaerbaek C, Dinesen B, Orskov H. Free insulin-like growth factors (IGF-I and IGF-II) in human serum. *FEBS Lett*. 1994;384:185–191.
8. Lee PDK, Powell D, Baker B, Liu F, Mathew G, Levitsky I, Gutierrez OD, Hintz RL. Characterization of a direct, non-extraction immunoradiometric assay for free IGF-I. In: Program and abstracts of the 76th annual meeting of the Endocrine Society; June 15–18, 1994:435 Anaheim, Calif. Abstract.
9. Lowe WL. Biological actions of the insulin-like growth factors. In: LeRoith D, ed. *Insulin-like Growth Factors: Molecular and Cellular Aspects*. Boca Raton, Fla: CRC Press; 1991:49–85.
10. Holly JMP. Insulin-like growth factor binding proteins in diabetic and nondiabetic states. In: Flyvbjerg A, Orskov H, Alberti KGMM, eds. *Growth Hormone and Insulin-like Growth Factor I in Human and Experimental Diabetes*. New York, NY: John Wiley & Sons, Inc; 1993:47–76.
11. Hall K, Brismar K, Hilding A, Lindgren B. Insulin-like growth factor-binding protein-1, a marker of insulin production. *Clin Pediatr Endocrinol*. 1993;2(suppl 2):51–55.
12. Bar RS, Clemmons DR, Boes M, Busby WH, Booth BA, Dake BL, Sandra A. Transcapillary permeability and subendothelial distribution of endothelial and amniotic fluid insulin-like growth factor binding proteins in the heart. *Endocrinology*. 1990;127:1078–1086. [\[Abstract\]](#)
13. Lee PDK, Conover CA, Powell DR. Regulation and function of insulin-like growth factor-binding protein-1. *Proc Soc Exp Biol Med*. 1993;204:4–29. [\[Abstract\]](#)
14. Blum WF, Jenne EW, Reppin F, Kietzmann K, Ranke MB, Bierich JR. Insulin-like growth factor I (IGF-I) binding protein complex is a better mitogen than free IGF-I. *Endocrinology*. 1989;125:766–772. [\[Abstract\]](#)
15. Hofman A, Grobbee DE, de Jong PTVM, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol*. 1991;7:403–422. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
16. Van Bommel JH, Kors JA, van Herpen G. Methodology for the Modular Electrocardiogram Analysis System (MEANS). *Methods Inf Med*. 1990;29:346–353. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
17. Willems JL, Abreu-Lima C, Arnoud P, van Bommel JH, Brohet C, Degani R, Debis B, Gehring J, Graham I, van Herpen G, Machado H, Macfarlane PW, Michaelis J, Mouloupoulos SD, Rubel P, Zywiets C. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med*. 1991;325:1767–1773. [\[Abstract\]](#)
18. Savage RM, Wagner G, Ideker E, Podolsky SA, Hackel DB. Correlation of postmortem anatomic findings with electrocardiographic changes in patients with myocardial infarcts: retrospective study in patients with typical anterior and posterior infarcts. *Circulation*. 1977;55:279–285. [\[Abstract\]](#)
19. Rose GA, Blackburn H, Gillum RF, Prineas RJ. *Cardiovascular Survey Methods*. 2nd ed. Geneva, Switz: World Health Organization; 1982.
20. Bots ML, Meurs JHCM, Grobbee DE. Assessment of early atherosclerosis: a new perspective. *J Drug Res*. 1991;16:150–154.
21. Bots ML, Witteman JCM, Grobbee DE. Carotid intima-media thickness in elderly women with and without atherosclerosis of the abdominal aorta. *Atherosclerosis*. 1993;102:99–105. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
22. Bots ML, Mulder PGH, Hofman A, Van Es G-A, Grobbee DE. Reproducibility of carotid vessel wall thickness measurements: the Rotterdam study. *J Clin Epidemiol*. 1994;47:921–930. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
23. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid

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- artery: fundamental principles, and description of a computerized analyzing system. *Clin Physiol*. 1991;11:565–577. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
24. Bots ML, Hofman A, Bruyn AM, De Jong PTVM, Grobbee DE. Isolated systolic hypertension and vessel wall thickness of the carotid artery: the Rotterdam Elderly Study. *Arterioscler Thromb*. 1993;13:64–69. [\[Abstract\]](#)
 25. Joint National Committee on High Blood Pressure. Report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure. *Arch Intern Med*. 1988;148:1023–1038. [\[Abstract\]](#)
 26. Spallarossa P, Brunelli C, Minuto F, Caruso D, Battistini M, Caponnetto S, Cordera R. Insulin-like growth factor-I and angiographically documented coronary artery disease. *Am J Cardiol*. 1996;77:200–202. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 27. Rosen T, Bengtsson B-A. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet*. 1990;336:285–288. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 28. Wuster CHR, Slenczka E, Ziegler R. Erhohte prevalenz von osteoporose und arteriosklerose bei konventionellen substituierter hypophysenvorderlappeninsuffizienz: Bedarf einer zusatzlichen wachstumshormonsubstitution? *Klin Wochenschr*. 1991;69:769–773.
 29. Markussis V, Beshyah SA, Fischer C, Sharp P, Nicolaidis AN, Johnston DG. Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. *Lancet*. 1992;340:1188–1192. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 30. Bar RS, Boes M, Dake BL, Booth BA, Henley SA, Sandra A. Insulin, insulin-like growth factors, and vascular endothelium. *Am J Med*. 1988;85(suppl 5):59–70.
 31. Scott-Burden T, Vanhoutte PM. Regulation of smooth muscle cell growth by endothelium derived factors. *Tex Heart Inst J*. 1994;21:91–97. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 32. Bastian SE, Walton PE, Belford DA. Paracellular transport of insulin-like growth factor-I (IGF-I) across human umbilical vein endothelial cell monolayers. *J Cell Physiol*. 1997;170:290–298. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 33. Khorsandi M, Fagin JA, Fishbein MC, Forrester JS, Cercek B. Effects of hypophysectomy on vascular insulin-like growth factor-I gene expression after balloon denudation in rats. *Atherosclerosis*. 1992;93:115–122. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 34. Khorsandi MJ, Fagin JA, Gianelli Neto D, Forrester JS, Cercek B. Regulation of insulin-like growth factor-I and its receptor in rat aorta after balloon denudation: evidence for local bioactivity. *J Clin Invest*. 1992;90:1926–1931. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 35. Booth BA, Boes M, Bar RS. IGFBP-3 proteolysis by plasmin, thrombin, serum: heparin binding, IGF binding and structure of fragments. *Am J Physiol*. 1996;271:E465–E470. [\[Abstract/Free Full Text\]](#)
 36. Collet-Solberg PF, Cohen P. The role of the insulin-like growth factor binding proteins and the IGFBP proteases in modulating IGF action. *Endocrinol Metab Clin North Am*. 1996;25:591–614. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 37. Grant M, King GL. IGF-I and blood vessels. *Diabetes Metab Rev*. 1995;3:113–128.
 38. Gajdusek CM, Luo Z, Mayberg MR. Sequestration of insulin-like growth factor-I by bovine aortic endothelial cells. *J Cell Physiol*. 1993;154:192–198. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 39. Walsh MF, Barazi M, Pete G, Muniyappa R, Dunbar JC, Sowers JR. Insulin-like growth factor-1 diminishes in vivo and in vitro vascular contractility: role of vascular nitric oxide. *Endocrinology*. 1996;137:1798–1803. [\[Abstract\]](#)
 40. Radomski MW, Salas E. Nitric oxide: biological mediator, modulator and factor of injury: its role in the pathogenesis of atherosclerosis. *Atherosclerosis*. 1995;118(suppl):S69–S80.
 41. Froesch ER, Hussain M. IGFs: therapeutic potential of rhIGF-I in diabetes and conditions of insulin resistance. *J Intern Med*. 1993;234:561–570. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 42. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic disease. *Diabetes Care*. 1991;14:173–194. [\[Abstract\]](#)
 43. William T, Berelowitz M, Joffe SN, Thorner MO, Rivier J, Vale W, Frohman LA. Impaired growth hormone responses to growth hormone-releasing factor in obesity: a pituitary defect reversed with weight reduction. *N Engl J Med*. 1984;311:1403–1407. [\[Abstract\]](#)
 44. Nam SY, Lee EJ, Kim KR, Cha BS, Song YD, Lim SK, Lee HC, Huh KB. Effect of obesity on total and free insulin-like growth factor (IGF)-1, and their relationship to IGF-binding protein (BP)-1, IGFBP-2, IGFBP-3, insulin, and growth hormone. *Int J Obes*. 1997;21:355–359.
 45. Frystyk J, Vestbo E, Skjærbaek C, Mogensen CE, Ørskov H. Free insulin-like growth factors in human obesity. *Metabolism*. 1995;44:37–44. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 46. Gibbson JM, Westwood M, Young RJ, White A. Reduced insulin-like growth factor binding protein-1 (IGFBP-1) levels correlate with increased cardiovascular risk in non-insulin dependent diabetes. *J Clin Endocrinol Metab*. 1996;81:860–863.
 47. Jones JI, Clemmons DR. Insulin-like growth factors and their binding proteins: biological actions. *Endocr Rev*. 1995;16:3–34. [\[Medline\]](#) [\[Order article via Infotrieve\]](#)
 48. Jones JI, d'Ercole AJ, Camacho-Hubner C, Clemmons DR. Phosphorylation of insulin-like growth factor (IGF) binding protein-1 in cell culture and in vivo: effects on affinity for IGF-I. *Proc Natl Acad Sci U S A*. 1991;88:7481–7485. [\[Abstract/Free Full Text\]](#)
 49. Westwood M, Gibbson JM, Davies AJ, Young RJ, White A. The phosphorylation pattern of insulin-like growth factor binding protein-1 in normal plasma is different from that in amniotic fluid and changes during pregnancy. *J Clin Endocrinol Metab*. 1994;79:1735–1741. [\[Abstract\]](#)