Circulation

Insulin-Like Growth Factor-1 as a Vascular Protective Factor

Elena Conti, Cinzia Carrozza, Ettore Capoluongo, Massimo Volpe, Filippo Crea,
Cecilia Zuppi and Felicita Andreotti

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

http://circ.ahajournals.org/cgi/content/full/110/15/2260

Subscriptions: Information about subscribing to Circulation is online at
http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/reprints

Insulin-Like Growth Factor-1 as a Vascular Protective Factor

Elena Conti, MD, PhD; Cinzia Carrozza, MD; Ettore Capoluongo, BSc; Massimo Volpe, MD; Filippo Crea, MD, FESC; Cecilia Zuppi, MD; Felicita Andreotti, MD, PhD, FESC

Recent advances in cardiology have focused on proliferation and regeneration as potential cardiovascular defense mechanisms. Within this framework, growth factors are acquiring increasing importance; insulin-like growth factor-1 (IGF-1) emerges among them for its versatile pleiotropic actions. This review provides a current perspective on IGF-1 and vascular disease.

I. Insulin-Like Growth Factor-1 and Vascular Disease: Friend or Foe?

The IGF-1 system is dynamic and complex,[1,2] involving at least 6 IGF-1–binding proteins (IGFBP-1 through -6) and several binding protein–related proteases,[1] including pregnancy-associated plasma protein-A (PAPP-A). The latter promotes IGF-1 bioavailability by cleaving IGFBP-4 and -5.[3] Acute coronary syndromes have been associated with raised PAPP-A concentrations in blood, leading to the interpretation that PAPP-A may enhance the risk of coronary artery disease through increased IGF-1 in vascular tissues.[4] Recent results, however, suggest a different relation between IGF-1 and ischemic syndromes.

II. IGF-1: Vascular Detrimental Factor?

Indirect data have supported the concept that IGF-1 may be atherogenetic because it can induce vascular smooth muscle cell (VSMC) proliferation in vitro.[5] Early studies on VSMCs from human and rabbit atherosclerotic arteries showed enhanced staining for IGF-1 and its receptor[6,7] compared with normal tissues,[7] with further enhancement after experimental angioplasty.[7] Thus, IGF-1 has been considered a promoter of arterial obstructive lesions[8]; an alternative possibility, however (consistent with the higher IGF-1 expression after angioplasty), is that IGF-1 initiates a survival pathway aimed at compensating local vascular cell apoptosis (see sections III.C.3 and III.C.4).

Randomized trials of the somatostatin analogue, angiopeptin, have been performed in the setting of postangioplasty restenosis and heart transplant vasculopathy to assess the possible benefits of lowering IGF-1 levels.[9] Somatostatin analogues, however, have multiple actions: They reduce growth hormone (GH) release and the serum concentrations of other growth factors (epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor [VEGF]) in addition to IGF-1,[10,11] while increasing the concentrations of IGFBP-1,[12] a possible partial IGF-1 agonist.[2] GH and IGF-1 exhibit divergent effects on glucose and lipid metabolism and on endothelial function (see section III.B.3). Thus, the interpretation of these trials is complex.

In patients undergoing coronary angioplasty, the administration of angiopeptin has yielded inconsistent results. Two smaller studies of 80 and 455 patients[13,14] have been inconclusive, whereas a larger study of 1246 patients[15] showed no significant effect on clinical events and restenosis rates. Where somatostatin analogues exhibit real benefit is in the setting of heart transplant vasculopathy[16,17]; here, however, the drug's efficacy may rely on the distinct, largely immunomediated, pathogenesis of graft versus host arterial disease,[18] involving a reduction of the immunoenhancing actions of IGF-1- and VEGF.[19,20]

On balance, the available experimental and clinical data do not provide strong, direct, and consistent evidence in support of a specific, proatherogenetic role of IGF-1 in native arteries.

III. Evidence for IGF-1 as a Vascular Protective Factor

A. IGF-1 and Vascular Effects

1. IGF-1 and Preserved Endothelial Function

Endothelial dysfunction is considered an initial step in the development of atherosclerotic lesions, through activation of a suicidal pathway that leads to endothelial cell apoptosis.[21,22] Indeed, experimental induction of endothelial apoptosis favors atherogenesis.[22] IGF-1 can directly oppose endothelial dysfunction in a number of ways: by interacting with high-affinity endothelial binding sites that lead to nitric oxide (NO) production,[23] by promoting insulin sensitivity[24] and potassium-channel opening,[25] and by preventing postprandial dyslipidemia.[26] IGF-1 can additionally contrast endothelial dysfunction through anti-apoptotic[22] and antiinflammatory[27] properties. IGF-1 also induces vasodilation[28–31] (thereby contributing to the regulation of vascular tone and arterial blood pressure) and preserves coronary flow reserve.[28,29]

(*Circulation.* **2004;110;2260-2265.**)

Circulation is available at http://www.circulationaha.org   DOI: 10.1161/01.CIR.0000144309.87183.FB
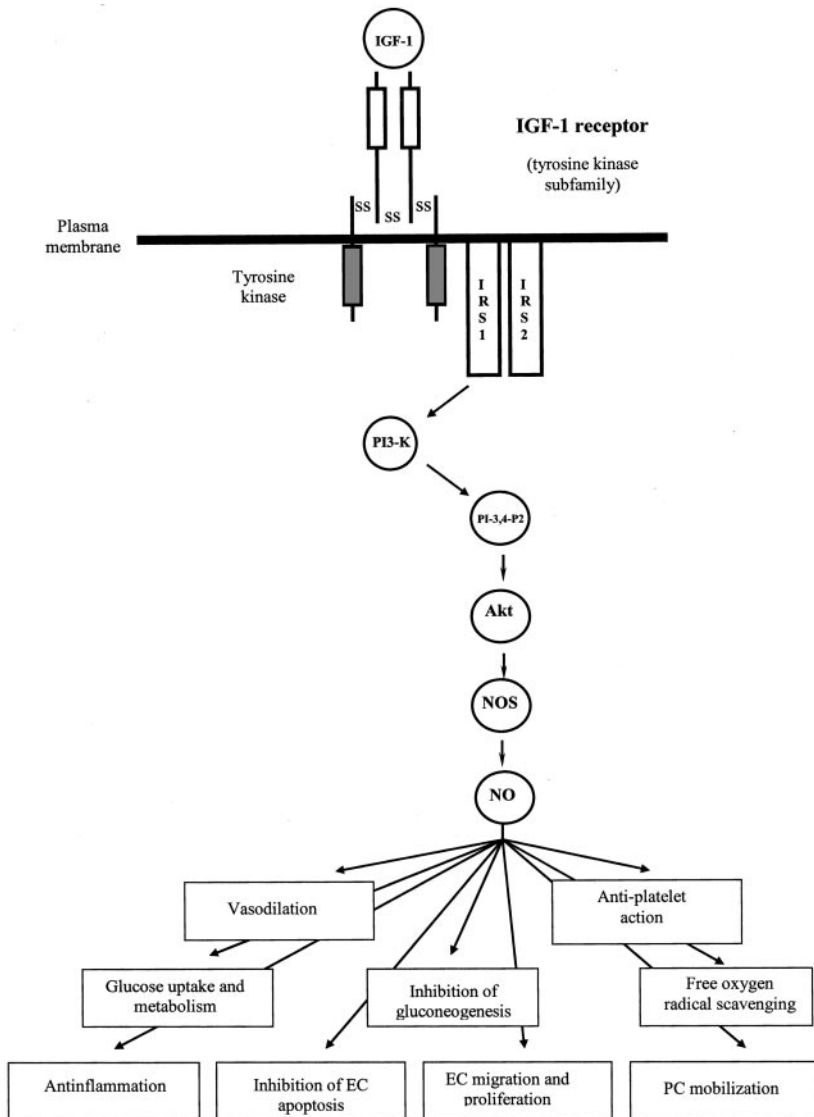
Figure 1. IGF-1 signal transduction leading to NO synthesis. Interaction between IGF-1 and its receptor causes (via insulin receptor substrates 1 and 2) phosphorylation of PI3-K, which converts phosphatidylinositol 3-phosphate into phosphatidylinositol 3,4-diphosphate (PI3,4-P2). This messenger activates the serine/threonine kinase Akt, which phosphorylates constitutive NOS, leading to NO production. NO activates vasodilator, antiaggregatory, angiogenetic, vasculogenetic, and glycometabolic pathways.[35] EC indicates endothelial cell; PC, progenitor cell.

2. IGF-1, Vasodilation, and NO Synthases

Vasodilation by IGF-1 requires NO synthase (NOS)[30] and/or potassium channel activity,[31] dependent on vessel size.[25] In both endothelial cells and VSMCs,[32,33] IGF-1 increases NOS activity by interacting with a tyrosine kinase membrane receptor linked to the insulin receptor substrate 1 and 2.[34] This receptor complex activates phosphatidylinositol 3-kinase (PI3-K), which activates the serine/threonine kinase Akt signaling pathway.[32,33] These cascades are downregulated by angiotensin II.[33] Constitutive NOS activity produces a slow, sustained release of NO, with multiple metabolic and vascular-protective effects (Figure 1). These include, in addition to vasodilation, enhanced glucose uptake; reduced gluconeogenesis; antiplatelet actions; free oxygen radical scavenging; endothelial cell migration, proliferation, and survival; and progenitor cell mobilization[35] (Figure 1).

While increasing constitutive NOS, IGF-1 inhibits inducible NO[23,26]; the latter causes large bursts of NO that promote apoptosis and depress myocardial function.[23,36]

B. IGF-1 and Metabolic Effects

1. IGF-1 and the Metabolic Syndrome

The presence of 3 or more of the following conditions defines the metabolic syndrome, an increasingly recognized cluster of factors related to cardiovascular risk, in which insulin resistance plays a central role[37]: hypertension, hyperglycemia, hypertriglyceridemia, reduced HDL cholesterol, and abdominal obesity. A cross-sectional study of 268 healthy men and women reported a strong and independent inverse relation between circulating total and free IGF-1 concentrations and markers of insulin resistance, such as serum leptin, waist-hip ratio, and body mass index.[38] A large prospective study identified an independent association between low serum IGF-1 levels and the future development of diabetes as assessed by the oral glucose tolerance test.[39] In skeletal muscle cells of type II diabetic patients, IGF-1 was found to be a more potent stimulant of glucose transport than insulin itself.[40] The administration of recombinant human IGF-1 to diabetic patients can reduce insulin dose requirement by 50% and serum glucose levels by 23%[41] while improving glucose tolerance, hyperinsulinemia, and hypertriglyceridemia.[42,43] Even in normal volunteers,

recombinant human IGF-1 enhances insulin sensitivity, suppresses plasma free fatty acid levels, reduces fasting plasma triglyceride concentrations, and increases oxidative and non-oxidative glucose metabolism.[44] Some of these effects are a consequence of IGF-1–mediated activation of endothelial constitutive NOS.[23,36]

The higher prevalence of insulin resistance and the metabolic syndrome in older compared with younger individuals may be attributable, at least in part, to the decline of serum and tissue IGF-1 concentrations with advancing age,[44] because reduced IGF-1 levels are independently associated with glucose intolerance,[39] diabetes,[39] abdominal obesity,[38,45] and atherogenic dyslipidemia.[26]

Overall, these data suggest an important and independent role of IGF-1 in protecting against the development of the metabolic syndrome. The uncommon coexistence of hyperinsulinemia and elevated free IGF-1 concentrations[46] may represent a compensatory rise in IGF-1, aimed at restoring insulin efficacy.

2. IGF-1 and Flow–Metabolism Coupling

One explanation for the concomitant insulin-sensitizing and vasodilator properties of IGF-1, relying on the enzymatic activities of PI3-K and Akt, is provided by the flow–metabolism coupling theory, commonly applied to insulin.[47] According to this theory, IGF-1 and insulin are responsible, through enhanced NO release, for vasodilation, antiplatelet effects, and glucose uptake,[47] in a linearly related and colocalized fashion.[48] The triple action of IGF-1 (on vascular recruitment, platelet inhibition, and glucose disposal) may be crucial in linking the metabolic syndrome to clinical ischemic events.

3. IGF-1 and GH

IGF-1 is synthesized and released mainly by the liver and kidneys but also by endothelial cells, VSMCs, and cardiomyocytes, as a result of a GH–GH receptor interaction.[49] IGF-1, in turn, regulates GH secretion through a negative feedback loop on the hypothalamic–pituitary axis.[50] Acromegaly, the clinical prototype of increased GH, has been associated with a state of insulin resistance because GH inhibits insulin's action, especially in the liver.[51] GH, however, also increases IGF-1 levels, which tend to maintain insulin sensitivity (especially in skeletal muscles), promote normal carbohydrate and lipid metabolism,[51] and inhibit GH's effects on glucose levels.[52] Although GH inhibits, IGF-1 enhances the action of PI3-K, a key enzyme for NO synthesis, with consequent glucose transport in muscle and fat and inhibition of hepatic gluconeogenesis.[53]

The biological model of adult-onset GH deficiency (associated with low serum IGF-1 concentrations) has failed to show a reduced atherosclerotic risk profile, exhibiting, conversely, an increased rate of restenosis, accelerated atherosclerosis, and increased cardiovascular morbidity and mortality.[54,55] Carotid intimal-medial thickness (IMT) in acromegalic patients has been found to be *lower* than in nonacromegalic subjects matched for atherosclerotic risk factors, and the lowest IMT among acromegalic patients was associated with highest IGF-1 levels.[56]

These data suggest that acromegalic patients may not be particularly prone to atherothrombotic diseases and that the increased IGF-1 levels in such patients may counteract GH-related insulin resistance, hypertension, and dyslipidemia.[56]

C. IGF-1 and Cardiovascular Disease

1. IGF-1 as Negative Predictor of Arterial Thickening and Ischemic Events

A cross-sectional study of 122 young subjects found low circulating IGF-1 associated with angiographically documented coronary artery disease.[57] Another cross-sectional study of 400 elderly men identified an inverse linear relation between free IGF-1 levels and carotid IMT.[58] A prospective, nested, case-control study of >600 initially healthy individuals followed up for 15 years found lower circulating IGF-1 levels to be independently associated with increased risk of ischemic heart disease.[59] Another prospective study of 1185 men and women followed up for about 12 years found serum IGF-1 and IGFBP-1 to be both inversely and independently related to fatal ischemic heart disease.[60] In patients with acute myocardial infarction, serum IGF-1 levels on admission to hospital were markedly reduced compared with healthy controls and were significantly lower in those with a worse prognosis, independent of infarct size.[49]

These observations uniformly support the possibility that IGF-1 deficiency may contribute to atherothrombotic diseases (Figure 2, left).

2. IGF-1 and Cardiac Protection Against Ischemia and Aging

Ischemic preconditioning and ischemia/reperfusion damage are considered important modulators of outcome in patients with ischemic syndromes.[61] In experimental models, IGF-1 has been found to enhance ischemic preconditioning[62] and to reduce ischemia/reperfusion damage[62] through its antiapoptotic and K+ channel–opening activities. Overexpression of IGF-1 in mice can protect from cardiomyocyte death after infarction; attenuate ventricular dilation, wall stress, and cardiac hypertrophy; and reduce the detrimental impact of nonocclusive coronary artery constriction on the heart.[63,64] IGF-1 can additionally recruit cardiomyoblasts in the aging murine heart, compensating for cell death and preventing ventricular dysfunction.[65] IGF-1 may thus represent a key pathway contrasting myocyte senescence and cardiomyocyte damage after an ischemic insult (Figure 2, left). The prospective, community-based Framingham Heart Study supports the above experimental data, showing an inverse and independent relation between serum IGF-1 levels and the risk of congestive heart failure in elderly men and women.[66]

3. IGF-1, PAPP-A, and Plaque Stability

In advanced atherosclerotic lesions, IGF-1 and IGF-1 receptor expression are significantly lower in VSMCs of intimal regions with macrophage infiltration than in regions without macrophage infiltration or in the media.[67] The inflammatory mediator tumor necrosis factor-α, which is upregulated in atherosclerotic plaques, reduces IGF-1 expression in VSMCs while increasing expression of IGFBP-3.[68] Plaque-derived VSMCs, compared with normal VSMCs, show enhanced sensitivity to apoptosis, through a reduction of IGF-1 receptor expression, IGF-1 surface-binding, and IGF-1–mediated survival signaling.[69] VSMC apoptosis, in turn, may contribute to plaque instability.[67,69]

Recent data suggest that both IGF-1 and PAPP-A contribute to plaque stability. Among 64 asymptomatic hyperlipidemic men and 25 normolipidemic subjects, those with hyperecho-

genic or isoechogenic carotid lesions had significantly higher serum PAPP-A concentrations compared with those with hypo-echogenic plaques and with normolipidemic controls.[70] Because hyperechogenic and isoechogenic lesions are more stable than hypoechogenic ones and less prone to evolve toward clinical complications, greater IGF-1 availability, produced by higher PAPP-A levels, may play an important role in stabilizing atherosclerotic plaques (Figure 2, left).

4. IGF-1, PAPP-A, and Early Response to Ischemia

Raised PAPP-A levels have been found to predict adverse events among patients with suspected acute coronary syndromes but without cardiac troponin I elevation.[71] Several,[72,73] though not all,[4] studies have reported a significant correlation between circulating PAPP-A and cardiac troponin T or creatine kinase-MB after myocardial infarction, indicating a relation between PAPP-A concentrations and extent of tissue damage. After experimental injury, PAPP-A protein expression in vascular cells is increased.[74] The expression of IGF-1 also is enhanced after experimental infarction in surviving cardiomyocytes.[75] These data suggest activation of the PAPP-A/IGF-1 system as part of a very early response to ischemia[76] aimed at increasing delivery of IGF-1 to jeopardized tissues.[77]

D. IGF-1 and Cardiovascular Risk Factors

1. IGF-1 and Traditional Risk Factors

Traditional cardiovascular risk factors are considered promoters of ischemic diseases by causing endothelial dysfunction, endothelial apoptosis, and impaired endothelial-dependent vascular reactivity.[78] These effects may be mediated, at least in part, by concomitant reductions of IGF-1 (Figure 2, right). Indeed, many cardiovascular risk factors, including circulating oxidized LDL,[79] insulin resistance,[24,26,38] diabetes,[39] obesity,[38,45] waist-hip ratio,[38] reduced coronary flow reserve,[29] smoking,[80] sedentary life,[81] and psychological distress,[82] have been associated with low serum IGF-1 levels (Figure 2, right). Additionally, oxidized LDL but not native LDL markedly reduce IGF-1 and IGF-1 receptor mRNA and protein expression in VSMCs.[79]

Conversely, LDL apheresis has been shown to increase IGF-1 and VEGF serum concentrations in patients with peripheral ischemia.[83]
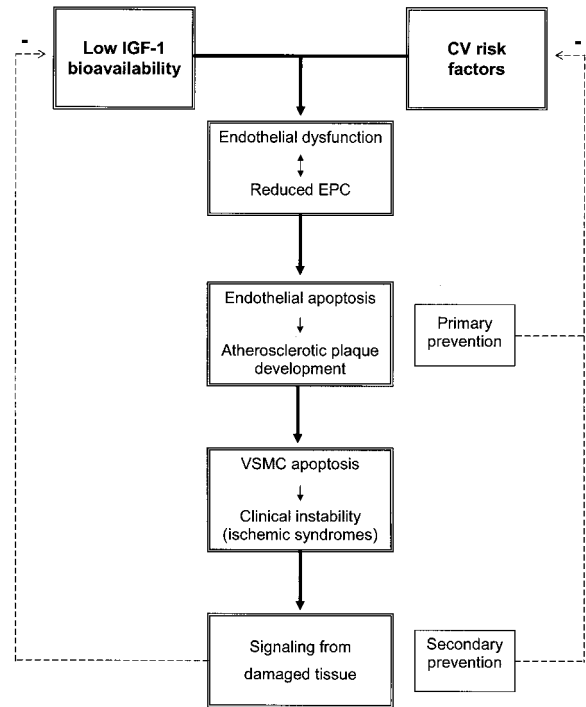

Figure 3. Proposed involvement of IGF-1 deficiency in promoting endothelial damage and ischemic syndromes. CV indicates cardiovascular; EPC, endothelial progenitor cells.

2. IGF-1 as an Independent Risk Factor

The relation between serum IGF-1 levels and protection against heart disease (identified in several prospective studies)[59,60,66] remains significant even after adjustment for body mass index, smoking, cholesterolemia, menopause, alcohol intake, physical activity, sex, age, social class, previous diabetes, family history of ischemic heart disease, self-evaluated health, use of antihypertensive agents, and circulating IGFBP-3 levels (which lower IGF-1 bioavailability).[59,60,66] Low IGF-1 may thus represent an additional independent risk factor for cardiovascular disease.

Cardiovascular and metabolic correlates of IGF-1	
CORRELATE OF RAISED IGF-1	**REF**
Reduced incidence of IHD	(59,60)
Reduced incidence of diabetes mellitus	(39)
Reduced infarct size and LV dysfunction	(63-66)
Reduced IMT	(58,70)
Increased insulin sensitivity	(39,41-44)
Decreased blood pressure and vascular tone	(28-31)
Large and small vessel dilation through nitric oxide and potassium-channel signaling	(25,30, 31)
Increased flow-metabolism coupling	(47,48)
Antinflammatory action	(27)
Increased endothelial cell survival	(21,22)
Increased VSMC survival	(67,69)
Plaque stability	(67-70)
Increased progenitor cell output	(84)

Association between IGF-1 and cardiovascular risk factors		
RISK FACTOR	**IGF-1 BIOAVAILABILITY**	**REF**
Diabetes mellitus	↓	(39)
Insulin-resistance	↓	(38)
Oxidized LDL	↓	(79)
Smoking	↓	(80)
Reduced coronary flow reserve	↓	(29)
Obesity	↓	(38,45)
Increased waist-hip ratio	↓	(38)
Sedentary life style	↓	(81)
Worse quality of life score	↓	(82)
Reduced psychological well-being	↓	(82)

Figure 2. Cardiovascular and metabolic correlates of IGF-1 (left). Association between IGF-1 and cardiovascular risk factors (right). IHD indicates ischemic heart disease; LV, left ventricular.

3. IGF-1 and Progenitor Cells

Endothelial cell apoptosis and reduced reendothelialization promote experimental neointima formation,[22] whereas VSMC apoptosis has been associated with plaque instability.[67,69] Progenitor cells may serve to replace vascular apoptotic cells.[84] IGF-1 has the potential to expand progenitor cell production[84] and therefore may favor endothelial and parenchimal[84] regeneration at sites of tissue damage.

IV. Conclusions

Until recently, IGF-1 was considered a mediator of vascular disease.[4,5,6,8] Increasing evidence indicates, instead, that IGF-1 protects against endothelial dysfunction, atherosclerotic plaque development, the metabolic syndrome, clinical instability, and ischemic myocardial damage (Figure 3). Some of these effects are related to the induction, by IGF-1, of constitutive NO production. Experimental and clinical data suggest that signaling from ischemic tissues causes changes in IGF-1's regulatory system, including compensatory increases in PAPP-A, presumably aimed at expanding tissue IGF-1 concentrations.

Measurement of circulating IGF-1 may add valuable information to the current assessment of cardiovascular risk. Individuals with traditional cardiovascular risk factors but normal or elevated IGF-1 may be protected, at least in part, against disease. With reduced IGF-1 levels, instead, vascular risk factors may fully exert their detrimental effects, through unopposed endothelial dysfunction, endothelial apoptosis, and development of unstable plaques (Figure 3).[21,22,67,69] Those with markedly reduced IGF-1 might develop disease even in the absence of traditional risk factors. It is worth noting that healthy centenarians have high serum IGF-1 concentrations.[85]

References

1. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor–binding protein (IGFBP) superfamily. *Endocr Rev*. 1999;20:761–787.
2. Conti E, Pitocco D, Capoluongo E, et al. IGF-1 and macrovascular complications of diabetes. *Diabetes Care*. 2003;26:1653–1654.
3. Laursen LS, Overgaard MT, Soe R, et al. Pregnancy-associated plasma protein-A (PAPP-A) cleaves insulin-like growth factor binding protein (IGFBP)-5 independent of IGF: implications for the mechanism of IGFBP-4 proteolysis by PAPP-A. *FEBS Lett*. 2001;504:36–40.
4. Bayes-Genis A, Conover CA, Overgaard MT, et al. Pregnancy-associated plasma protein A as a marker of acute coronary syndromes. *N Engl J Med*. 2001;345:1022–1029.
5. Pfeifle B, Hamann H, Fussganger R, et al. Insulin as a growth regulator of arterial smooth muscle cells: effect of insulin and IGF-1. *Diabetes Metab*. 1987;13:326–330.
6. Grant MB, Wargovich TJ, Ellis EA, et al. Expression of IGF-1, IGF-1 receptor and IGF binding proteins-1, -2, -4 and -5 in human atherectomy specimens. *Regul Pept*. 1996;67:137–144.
7. Grant MB, Wargovich TJ, Bush DM, et al. Expression of IGF-1, IGF-1 receptor and TGFbeta following balloon angioplasty in atherosclerotic and normal rabbit iliac arteries: an immunocytochemical study. *Regul Pept*. 1999;79:47–53.
8. Bayes-Genis A, Conover CA, Schwartz RS. The insulin-like growth factor axis: a review of atherosclerosis and restenosis. *Circ Res*. 2000;86:125–130.
9. Foegh ML, Ramwell PW. Angiopeptin: experimental and clinical studies of inhibition of myointimal proliferation. *Kidney Int Suppl*. 1995;52:S18–S22.
10. Hayry P, Aavik E, Myllarniemi M. Blockade of growth factor synthesis and growth factor action: two possible sites of interference in allograft vessel disease and coronary bypass or balloon injury. *Metabolism*. 1996;45:101–103.
11. Garcia de la Torre N, Wass JA, Turner HE. Antiangiogenic effect of somatostatin analogues. *Clin Endocrinol (Oxf)*. 2002;57:425–441.
12. Ottesen LH, Frystyk J, Kiszka-Kanowitz M, et al. Effects of octreotide on serum insulin-like growth factor I and insulin-like growth factor binding proteins in patients with cirrhosis. *Scand J Clin Lab Invest*. 2002;62:39–47.
13. Eriksen UH, Amtorp O, Bagger JP, et al. Randomized double-blind Scandinavian trial of angiopeptin versus placebo for the prevention of clinical events and restenosis after coronary balloon angioplasty. *Am Heart J*. 1995;130:1–8.
14. Emanuelsson H, Beatt KJ, Bagger JP, et al. Long-term effects of angiopeptin treatment in coronary angioplasty: reduction of clinical events but not angiographic restenosis. European Angiopeptin Study Group. *Circulation*. 1995;91:1689–1696.
15. Kent KM, Williams DO, Cassagneau B, et al. Double blind, controlled trial of the effect of angiopeptin on coronary restenosis following balloon angioplasty. *Circulation*. 1993;88:I-506.
16. Walhers T, Mugge A, Oppelt P, et al. Coronary vasculopathy following cardiac transplantation and cyclosporine immunosuppression: preventive treatment with angiopeptin, a somatostatin analog. *Transplant Proc*. 1994;26:2741–2742.
17. Motomura N, Lou H, Maurice P, et al. Acceleration of arteriosclerosis of the rat aorta allograft by insulin-like growth factor-1. *Transplantation*. 1997;63:932–936.
18. Chen W, Thoburn CJ, Miura Y, et al. Autoimmune-mediated vasculopathy. *Clin Immunol*. 2001;100:57–70.
19. Krishnaraj R, Zaks A, Unterman T. Relationship between plasma IGF-I levels, in vitro correlates of immunity, and human senescence. *Clin Immunol Immunopathol*. 1998;88:264–270.
20. Reinders ME, Sho M, Izawa A, et al. Proinflammatory functions of vascular endothelial growth factor in alloimmunity. *J Clin Invest*. 2003;112:1655–1665.
21. Dimmeler S, Hermann C, Zeiher AM. Apoptosis of endothelial cells: contribution to the pathophysiology of atherosclerosis? *Eur Cytokine Netw*. 1998;9:697–698.
22. Hutter R, Sauter BV, Reis ED, et al. Decreased reendothelialization and increased neointima formation with endostatin overexpression in a mouse model of arterial injury. *Circulation*. 2003;107:1658–1663.
23. Schini-Kerth VB. Dual effects of insulin-like growth factor-1 on the constitutive and inducible nitric oxide (NO) synthase–dependent formation of NO in vascular cells. *J Endocrinol Invest*. 1999;22:82–88.
24. Conti E, Andreotti F, Sestito A, et al. Reduced levels of insulin-like growth factor-1 in patients with angina pectoris, positive exercise stress test, and angiographically normal epicardial coronary arteries. *Am J Cardiol*. 2002;89:973–975.
25. Oltman CL, Kane NL, Gutterman DD, et al. Mechanism of coronary vasodilation to insulin and insulin-like growth factor-1 is dependent on vessel size. *Am J Physiol Endocrinol Metab*. 2000;279:E176–E181.
26. Twickler MT, Cramer MJ, Koppeschaar HP. Unraveling Reaven's Syndrome X: serum insulin-like growth factor-1 and cardiovascular disease. *Circulation*. 2003;107:e190–e192.
27. Spies M, Nesic O, Barrow RE, et al. Liposomal IGF-1 gene transfer modulates pro- and anti-inflammatory cytokine mRNA expression in the burn wound. *Gene Ther*. 2001;8:1409–1415.
28. Gillespie CM, Merkel AL, Martin AA. Effects of insulin-like growth factor-1 and LR3IGF-1 on regional blood flow in normal rats. *J Endocrinol*. 1997;155:351–358.
29. Galderisi M, Caso P, Cicala S, et al. Positive association between circulating free insulin-like growth factor-1 levels and coronary flow reserve in arterial systemic hypertension. *Am J Hypertens*. 2002;15:766–772.
30. Haylor J, Singh I, el Nahas AM. Nitric oxide synthesis inhibitor prevents vasodilation by insulin-like growth factor-1. *Kidney Int*. 1991;39:333–335.
31. Izhar U, Hasdai D, Richardson DM, et al. Insulin and insulin-like growth factor-1 cause vasorelaxation in human vessels in vitro. *Coron Artery Dis*. 2000;11:69–76.
32. Michell BJ, Griffiths JE, Mitchelhill KI, et al. The Akt kinase signals directly to endothelial nitric oxide synthase. *Curr Biol*. 1999;9:845–848.
33. Isenovic ER, Meng Y, Divald A, et al. Role of phosphatidylinositol 3-kinase/Akt pathway in angiotensin and insulin-like growth factor-1 modulation of nitric oxide synthesis in vascular smooth muscle cells. *Endocrine*. 2002;19:287–292.
34. Withers DJ, Burks DJ, Towery HH, et al. IRS-2 coordinates IGF-1 receptor–mediated β-cell development and peripheral insulin signalling. *Nat Genet*. 1999;23:32–40.
35. Dimmeler S, Zeiher AM. Exercise and cardiovascular health: get active to "AKTivate" your endothelial nitric oxide synthase. *Circulation*. 2003;107:3118–3120.
36. Castrillo A, Bodelon OG, Bosca L. Inhibitory effect of IGF-1 on type 2 nitric oxide synthase expression in Ins-1 cells and protection against activation-dependent apoptosis: involvement of phosphatidylinositol 3-kinase. *Diabetes*. 2000;49:209–217.
37. Grundy SM, Brewer HB Jr, Cleeman JI, et al. Definition of the metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433–438.
38. Gomez JM, Maravall FJ, Gomez N, et al. Interactions between serum leptin, the insulin-like growth factor-1 system, and sex, age, anthropometric and body

composition variables in a healthy population randomly selected. *Clin Endocrinol*. 2003;58:213–219.

39. Sandhu MS, Heald AH, Gibson JM, et al. Circulating concentrations of insulin-like growth factor-1 and development of glucose intolerance: a prospective observational study. *Lancet*. 2002;359:1740–1745.

40. Ciaraldi TP, Carter L, Rehman N, et al. Insulin and insulin-like growth factor-1 action in human skeletal muscle: preferential effects of insulin-like growth factor-1 in type 2 diabetic subjects. *Metabolism*. 2002;51:1171–1179.

41. Clemmons DR, Moses AC, McKay MJ, et al. The combination of insulin-like growth factor-1 and insulin-like growth factor binding protein-3 reduces insulin requirements and insulin-dependent type 1 diabetes: evidence for in vivo biological activity. *J Clin Endocrinol Metab*. 2000;85:1518–1524.

42. Kolaczynski JW, Caro JF. Insulin-like growth factor-1 therapy in diabetes. *Ann Intern Med*. 1994;120:47–55.

43. Cusi K, De Fronzo RA. Treatment of NIDDM, IDDM and other insulin resistant states with IGF-1: physiological and clinical considerations. *Diabetes Rev*. 1995;3:206–236.

44. Paolisso G, Tagliamonte MR, Rizzo MR, et al. Advancing age and insulin resistance: new facts about an ancient history. *Eur J Clin Invest*. 1999;29:758–769.

45. Rasmussen MH, Hvidberg A, Juul A, et al. Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor-I levels in obese subjects. *J Clin Endocrinol Metab*. 1995;80:1407–1415.

46. Cordain L, Eades MR, Eades MD. Hyperinsulinemic diseases of civilization: more than just Syndrome X. *Comp Biochem Physiol*. 2003;136:95–112.

47. Baron AD. The coupling of glucose metabolism and perfusion in human skeletal muscle: the potential role of endothelium-derived nitric oxide. *Diabetes*. 1996;45:S105–S109.

48. Utriainen T, Nuutila P, Takala T, et al. Intact insulin stimulation of skeletal muscle blood flow, its heterogeneity and redistribution, but not of glucose uptake in non insulin-dependent diabetes mellitus. *J Clin Invest*. 1997;100:777–785.

49. Conti E, Andreotti F, Sciahbasi A, et al. Markedly reduced insulin-like growth factor-1 in the acute phase of myocardial infarction. *J Am Coll Cardiol*. 2001;38:26–32.

50. Clemmons DR. Roles of insulin-like growth factor-1 and growth hormone in mediating insulin resistance in acromegaly. *Pituitary*. 2002;5:181–183.

51. Yakar S, Setser J, Zhao H, et al. Inhibition of growth hormone action improves insulin sensitivity in liver IGF-1–deficient mice. *J Clin Invest*. 2004;113:96–105.

52. Clemmons DR. The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity. *J Clin Invest*. 2004;113:25–27.

53. Dominici FP, Cifone D, Bartke A, et al. Loss of sensitivity to insulin at early events of the insulin signaling pathway in the liver of growth hormone transgenic mice. *J Endocrinol*. 1999;161:383–392.

54. Pfeifer M, Verhovec R, Zizek B, et al. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *J Clin Endocrinol Metab*. 1999;84:453–457.

55. Serri O, Li L, Maingrette F, et al. Enhanced lipoprotein lipase secretion and foam cell formation by macrophages of patients with growth hormone deficiency: possible contribution to increased risk of atherogenesis? *J Clin Endocrinol Metab*. 2004;89:979–985.

56. Otsuki M, Kasayama S, Yamamoto H, et al. Characterization of premature atherosclerosis of carotid artery in acromegalic patients. *Clin Endocrinol*. 2001;54:791–796.

57. Spallarossa P, Brunelli C, Minuto C, et al. Insulin-like growth factor-1 and angiographically documented coronary artery disease. *Am J Cardiol*. 1996;77:200–202.

58. van den Beld AW, Bots ML, Janssen JA, et al. Endogenous hormones and carotid atherosclerosis in elderly men. *Am J Epidemiol*. 2003;157:25–31.

59. Juul A, Scheike T, Davidsen M, et al. Low serum insulin-like growth factor-1 is associated with increased risk of ischemic heart disease: a population-based case-control study. *Circulation*. 2002;106:939–944.

60. Laughlin GA, Barrett-Connor E, Criqui MH, et al. The prospective association of serum insulin-like growth factor-1 (IGF-1) and IGF-binding protein-1 levels with all cause and cardiovascular disease mortality in older adults: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 2004;89:114–120.

61. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. *Circulation*. 2001;104:2981–2989.

62. Davani EY, Brumme Z, Singhera GK, et al. Insulin-like growth factor-1 protects ischemic murine myocardium from ischemia/reperfusion associated injury. *Crit Care*. 2003;7:417–419.

63. Li Q, Li B, Wang X, et al. Overexpression of insulin-like growth factor-1 in mice protects from myocyte death after infarction, attenuating ventricular dilation, wall stress, and cardiac hypertrophy. *J Clin Invest*. 1997;100:1991–1999.

64. Li B, Setoguchi M, Wang X, et al. Insulin-like growth factor-1 attenuates the detrimental impact of nonocclusive coronary artery constriction on the heart. *Circ Res*. 1999;84:1007–1019.

65. Torella D, Rota M, Nurzynska D, et al. Cardiac stem cell and myocyte aging, heart failure, and insulin-like growth factor-1 overexpression. *Circ Res*. 2004;94:514–524.

66. Vasan RS, Sullivan LM, D'Agostino RB, et al. Serum insulin-like growth factor-1 and risk for heart failure in elderly individuals without a previous myocardial infarction: the Framingham Heart Study. *Ann Intern Med*. 2003;139:642–648.

67. Okura Y, Brink M, Zahid AA, et al. Decreased expression of insulin-like growth factor-1 and apoptosis of vascular smooth muscle cells in human atherosclerotic plaque. *J Mol Cell Cardiol*. 2001;33:1777–1789.

68. Anwar A, Zahid AA, Scheidegger KJ, et al. Tumor necrosis factor-alpha regulates insulin-like growth factor-1 and insulin-like growth factor binding protein-3 expression in vascular smooth muscle. *Circulation*. 2002;105:1220–1225.

69. Patel VA, Zhang QJ, Siddle K, et al. Defect in insulin-like growth factor-1 survival mechanism in atherosclerotic plaque–derived vascular smooth muscle cells is mediated by reduced surface binding and signaling. *Circ Res*. 2001;88:895–902.

70. Beaudeux JL, Burc L, Imbert-Bismut F, et al. Serum plasma pregnancy-associated protein A: a potential marker of echogenic carotid atherosclerotic plaques in asymptomatic hyperlipidemic subjects at high cardiovascular risk. *Arterioscler Thromb Vasc Biol*. 2003;1:e7–e10.

71. Lund J, Qin QP, Ilva T, et al. Circulating pregnancy-associated plasma protein A predicts outcome in patients with acute coronary syndromes but no troponin I elevation. *Circulation*. 2003;108:1924–1926.

72. Qin QP, Laitinen P, Majamaa-Voltti K, et al. Release patterns of pregnancy associated plasma protein A (PAPP-A) in patients with acute coronary syndromes. *Scand Cardiovasc J*. 2002;36:358–361.

73. Khosravi J, Diamandi A, Krishna RG, et al. Pregnancy associated plasma protein-A: ultrasensitive immunoassay and determination in coronary heart disease. *Clin Biochem*. 2002;35:531–538.

74. Bayes-Genis A, Schwartz RS, Lewis DA, et al. Insulin-like growth factor binding protein-4 protease produced by smooth muscle cells increases in the coronary artery after angioplasty. *Arterioscler Thromb Vasc Biol*. 2001;21:335–341.

75. Matthews KG, Devlin GP, Conaglen JV, et al. Changes in IGFs in cardiac tissue following myocardial infarction. *J Endocrinol*. 1999;163:433–445.

76. Conti E, Andreotti F, Zuppi C. Pregnancy associated plasma protein A and suspected acute coronary syndromes. *Circulation*. 2004;109:e211–e212.

77. Bereket A, Wilson TA, Kolasa AJ, et al. Regulation of the insulin-like growth factor system by acute acidosis. *Endocrinology*. 1996;137:2238–2245.

78. Hill JM, Zalos G, Halcox JPJ, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med*. 2003;348:593–600.

79. Scheidegger KJ, James RW, Delafontaine P. Differential effects of low density lipoproteins on insulin-like growth factor-1 (IGF-1) and IGF-1 receptor expression in vascular smooth muscle cells. *J Biol Chem*. 2000;275:26864–26869.

80. Teramukai S, Rohan T, Eguchi H, et al. Anthropometric and behavioral correlates of insulin-like growth factor-1 and insulin-like growth factor binding protein 3 in middle-aged Japanese men. *Am J Epidemiol*. 2002;156:344–348.

81. Trejo JL, Carro E, Nunez A, et al. Sedentary life impairs self-reparative processes in the brain: the role of serum insulin-like growth factor-1. *Rev Neurosci*. 2002;13:365–374.

82. Unden AL, Elofsson S, Knox S, et al. IGF-1 in a normal population: relation to psychosocial factors. *Clin Endocrinol*. 2002;57:793–803.

83. Kobayashi S, Moriya H, Negishi K, et al. LDL-apheresis up-regulates VEGF and IGF-I in patients with ischemic limb. *J Clin Apheresis*. 2003;18:115–119.

84. Dempsey RJ, Sailor KA, Bowen KK, et al. Stroke-induced progenitor cell proliferation in adult spontaneously hypertensive rat brain: effect of exogenous IGF-1 and GDNF. *J Neurochem*. 2003;87:586–597.

85. Paolisso G, Ammendola S, Del Buono A, et al. Serum levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentrations, insulin action, and cognitive function. *J Clin Endocrinol Metab*. 1997;82:2204–2209.