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

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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 atherogenic 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 lesions⁸; 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 patients¹⁵ 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, proatherogenic 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 sensitivity²⁴ and potassium-channel opening,²⁵ and by preventing postprandial dyslipidemia.²⁶ IGF-1 can additionally contrast endothelial dysfunction through anti-apoptotic²² and antiinflammatory²⁷ properties. IGF-1 also induces vasodilation²⁸⁻³¹ (thereby contributing to the regulation of vascular tone and arterial blood pressure) and preserves coronary flow reserve.^{28,29}

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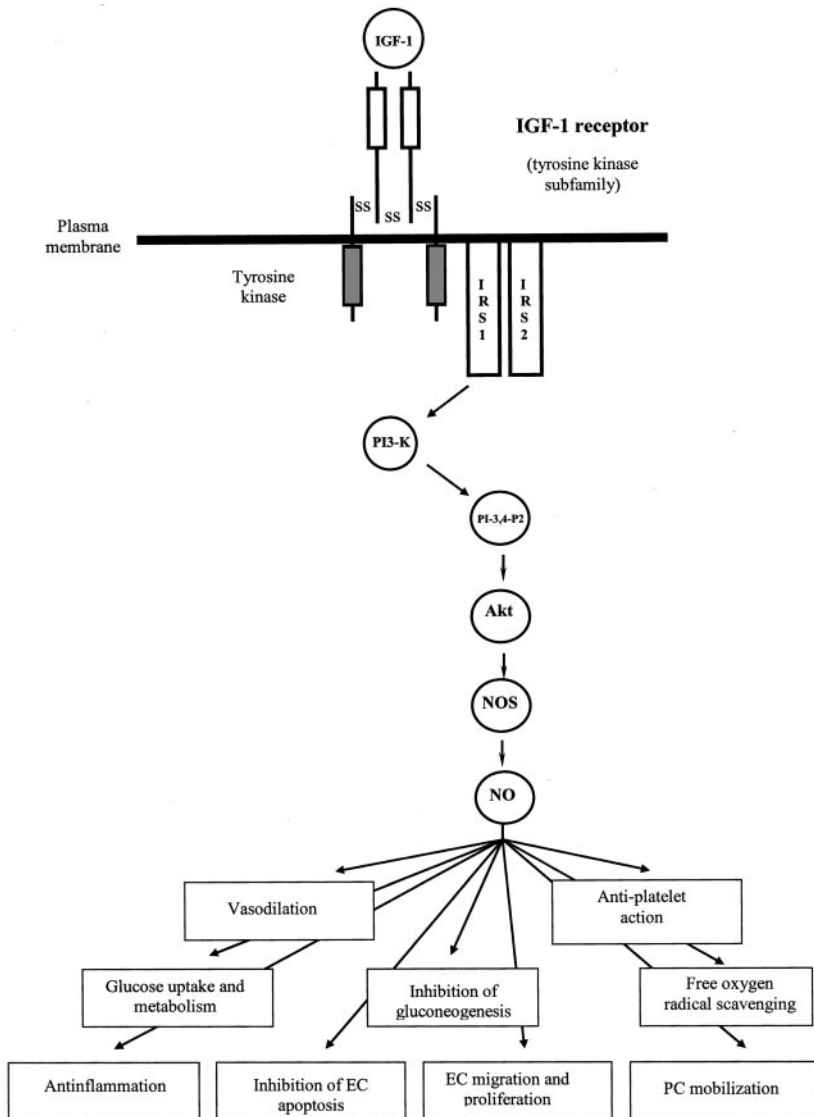


Figure 1. IGF-1 signal transduction leading to NO synthesis. Interaction between IGF-1 and its receptor causes (via insulin receptor substrates 1 and 2) phosphorylation of PI3-K, which converts phosphatidylinositol 3-phosphate into phosphatidylinositol 3,4-diphosphate (PI3,4-P2). This messenger activates the serine/threonine kinase Akt, which phosphorylates constitutive NOS, leading to NO production. NO activates vasodilator, antiaggregatory, angiogenic, vasculogenic, 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; anti-platelet actions; free oxygen radical scavenging; endothelial cell migration, proliferation, and survival; and progenitor cell mobilization³⁵ (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 role³⁷: 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 concentrations⁴⁶ 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 preconditioning⁶² and to reduce ischemia/reperfusion damage⁶² 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 hypercho-

genic or isoechogenic carotid lesions had significantly higher serum PAPP-A concentrations compared with those with hypoechoic plaques and with normolipidemic controls.⁷⁰ Because hyperechogenic and isoechogenic lesions are more stable than hypoechoic 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 ischemia⁷⁶ 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

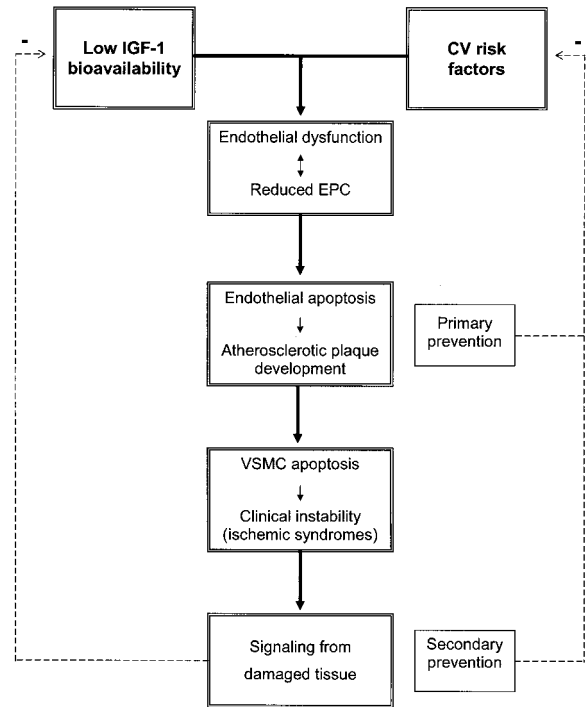


Figure 3. Proposed involvement of IGF-1 deficiency in promoting endothelial damage and ischemic syndromes. CV indicates cardiovascular; EPC, endothelial progenitor cells.

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)
Antiinflammatory 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 production⁸⁴ and therefore may favor endothelial and parenchymal⁸⁴ 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

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