Review article

Insulin-like Growth Factor-1 and the cardiovascular system

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Abstract: *The insulin-like growth factor -1 axis has been extensively studied at the molecular level, where IGF-1 seems to play a protective role against atherosclerosis and insulin resistance. Thus, low levels of IGF-1 in healthy populations have been prospectively associated with increased occurrence of cardiovascular disease and diabetes mellitus. In diabetic patients, IGF-1 concentrations appear reduced, probably contributing in part to the elevated cardiovascular morbidity of this group of patients. Herein we review the experimental research that has elucidated the molecular actions of IGF-1, as well as the relevant clinical studies, confirmatory or not of the above. Whether IGF-1 can play a role in cardiovascular risk stratification is discussed. Hippokratia 2006; 10(2): 68-74*

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Insulin-like Growth Factor -1 (IGF-1) and its biochemical axis have been studied for years in the field of Endocrinology, whereas its plasma levels have been of use in the differential diagnosis of disturbed Growth Hormone (GH) secretion. During the past 15 years, however, IGF-1 has attracted wider medical attention, as it has been associated with certain malignancies (prostate, breast, colorectal, and lung cancer), osteoporosis, dementia, and cardiovascular disease. More than a decade ago the involvement of IGF-1 in the pathogenesis of atherosclerosis was first suggested[1] and thereafter extensively studied. Especially in patients with Diabetes Mellitus (DM), relatively decreased concentrations of IGF-1 have been found and implicated in the increased cardiovascular morbidity and mortality of this group of patients.

Components of the IGF-axis

The IGF system consists of two major proteins, IGF-1 and IGF-2, with similar morphology and function to insulin[2]; the receptors that mediate their intracellular actions, mainly IGF-1R and IGF-2R (but also the insulin receptor and the hybrid insulin/IGF-1 receptor); the family of IGF-binding proteins (IGFBPs, -1 to -6), that regulate circulating levels of IGF-1; and, finally, the proteases of IGFBPs that determine the availability of the latter[3].

Molecular structure and actions of IGF-1

Insulin-like growth factor-1 is a single peptide chain of similar structure to proinsulin. Its secretion is affected by GH, the nutritional status, hepatic function, and insulin itself[4]. It is produced constitutively in the liver, under the action of GH, and then secreted into the circulation (endocrine action). However, it is also produced by other cells that release IGF-1 locally (paracrine/ autocrine action). Although the major inducer of the production of IGF-1 is GH, an important and independent role is played by insulin[5], which has been found to up-regulate IGF-1 mRNA in cultured hepatocytes[6], while at the same time to sensitize hepatic receptors to the action of GH[7].

Circulating IGF-1 is bound up to 99% with its binding proteins (75-80% with IGFBP-3) and only 1% represents the free fraction, which is considered to be the bioactive one. The IGF-1 produced by peripheral tissues does not possess such high affinity with IGFBPs as the hepatically produced, therefore circulating IGF-1 is mainly of hepatic origin[8]. Regarding IGF-1 actions, it could be outlined that IGF-1 is an important mediator of cell growth, differentiation and transformation, as it augments the uptake of aminoacids and glucose, and induces protein-synthesis, while it regulates the mitotic cycle of the cell. It stimulates bone development - subsequently linear body growth-, and affects body composition[4]. It is the second most potent glucose-lowering agent (after insulin). The metabolic actions of IGF-1 are complementary to those of insulin, but apart from that, IGF-1 increases insulin sensitivity, decreases hepatic glucose disposal, and improves lipid profile[9]. It is regarded as one of the most efficient anabolic factors in human physiology[4].

IGF-1 gene and receptors

The gene encoding IGF-1 is located on chromosome 12q21, between loci 106 and 113 cM. A great scientific interest has grown regarding the polymorphisms of this gene: recently, a microsatellite polymorphism, in the form of cytosine-adenosine repeats, was discovered in the proximity of the promoter of the IGF-1 gene (approximately 1000 base pairs away) and might have clinical significance. Ten different alleles of this region

were found, one of which appears to prevail in frequency (88,4%), thus representing the wild type of the allele (consisting of 192bp and 19C-A repeats)[10]. According to this polymorphism, individuals could be divided into homozygotes for the 192bp allele, heterozygotes, and those completely lacking it.

The major receptor mediating the interaction between IGF-1 and the cell is the IGF-1 Receptor (IGF-1R). It is expressed in all cell types and it resembles morphologically the insulin receptor (InsR), as it consists of two extracellular a-subunits and two intracellular β-subunits, the latter containing a region with tyrosine-kinase properties, capable of auto-phosphorylation and subsequent activation of the Insulin Receptor Substrate (IRS-1 and -2) and of the following pathways: a) the phosphoinositide 3-kinase (PI3-K) pathway, which activates Akt kinase, a pivotal player in the metabolism of the cell, responsible, among others, of the contractile state, the production of nitric oxide, NO, and of the inactivation of caspases, thus resulting into inhibition of cell apoptosis, and b) pathways stimulating the proliferation and migration of the cell are MEK and Rac, respectively[11] (Figure 1). The second, in terms of significance, receptor of IGF-1 is the hybrid insulin / IGF-1 receptor, which is widely distributed in peripheral tissues, skeletal muscle and adipose tissue included[12]. The concentration of this hybrid receptor on the cell surface depends on the circulating levels of IGF-1 and insulin: low circulating IGF-1 up-regulates IGF-1R; similarly, high circulating insulin, as is the case in insulin resistant states, is

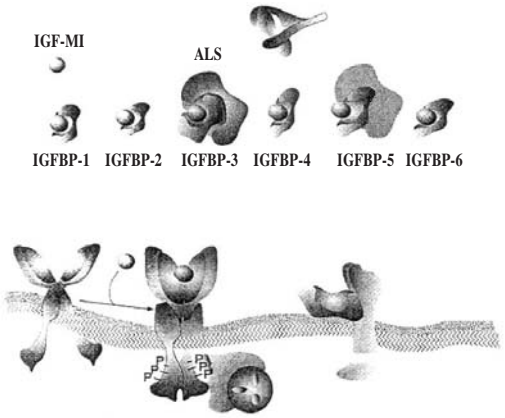

Figure 2. ***Various IGFBPs (IGFBP-3 is depicted forming a complex with Acid Labile Subunit, ALS) and the binding of IGF-1 with IGF-1 Receptor or, alternatively, with the Integrin / Transforming Growth Factor -β receptor. Modified, from Le Roith and Butler[14].***

associated with decreased InsR; both phenomena result in the disturbance of the physiological InsR / IGF-1R ratio, leading to an increased formation of the hybrid receptor, which in turn dislocates InsR from the cell surface, thus contributing to even greater insulin resistance. The above described mechanism[13] that explains the development of insulin resistance at low IGF-1 concentrations, although not fully elucidated, offers a clue to the clinically evident association between IGF-1 deficiency and type 2 Diabetes Mellitus (DM), as well as the Metabolic Syndrome (MetS), conditions

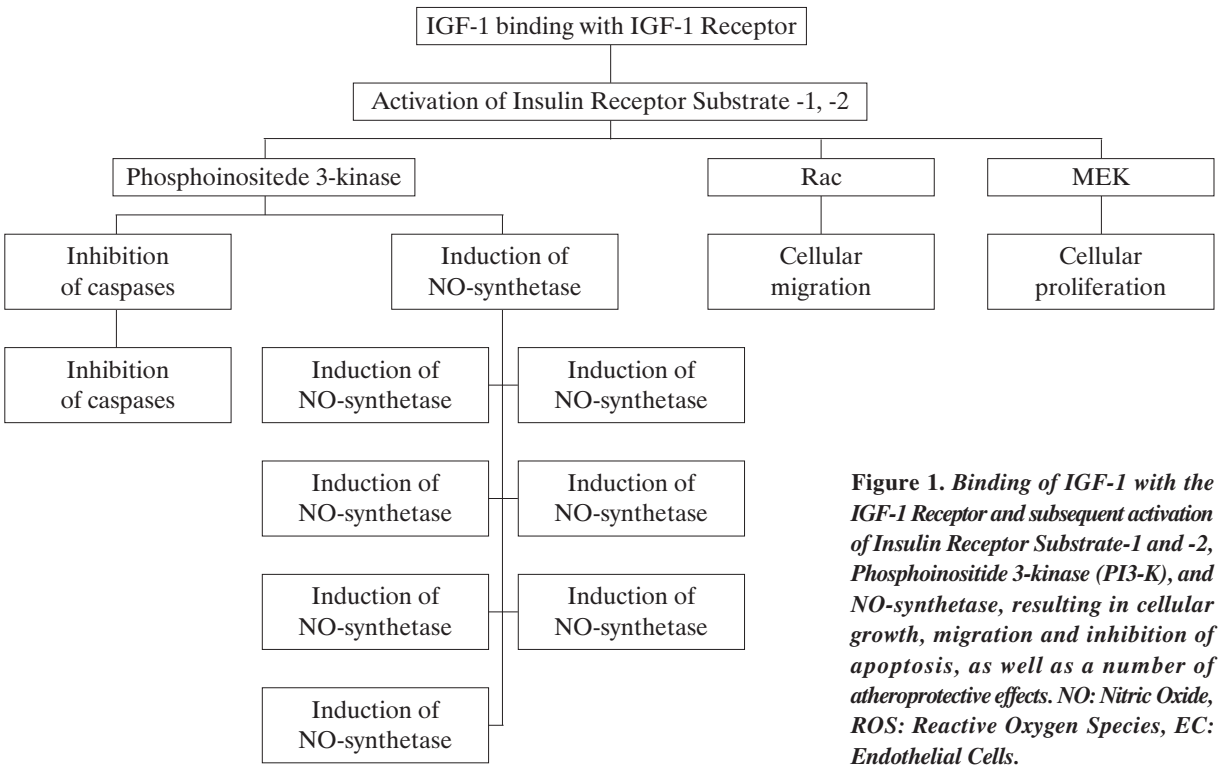

Figure 1. ***Binding of IGF-1 with the IGF-1 Receptor and subsequent activation of Insulin Receptor Substrate-1 and -2, Phosphoinositide 3-kinase (PI3-K), and NO-synthetase, resulting in cellular growth, migration and inhibition of apoptosis, as well as a number of atheroprotective effects. NO: Nitric Oxide, ROS: Reactive Oxygen Species, EC: Endothelial Cells.***

tightly linked to reduced insulin sensitivity. Finally, IGF-1 actions through other receptors have been reported, for example the Integrin / Transforming Growth Factor -β receptor[14] (Figure 2).

The family of IGF-1 Binding Proteins (IGFBPs) -The role of IGFBP-proteases

The IGFBPs are the transport vehicles of IGF-1 within the circulation by forming dimeric (IGF plus an IGFBP) and trimeric (IGF plus an IGFBP plus the Acid Labile Subunit, ALS) complexes (Figure 2). Binding proteins -1, -2, and -4 are capable of crossing the endothelium, thus shuttling IGF-1 to the subendothelial target-tissues. Their main role of IGFBPs, however, is not to just carry IGF-1, but to regulate its free fraction, which is the bioactive one. This regulation is assisted by certain proteases of the IGFBPs, that, through proteolysis of the latter, release IGF-1 either by decreasing IGFBP affinity with IGF-1 or by causing the disintegration of the IGFBP/IGF-1 complexes. Furthermore, IGFBPs undergo phosphorylation, polymerization, and inactivation by the cells or the matrix, all of which ultimately affect the bioavailability of IGF-1 at the tissue level. One of the IGFBP proteases, in particular the protease of IGFBP-4, has been identified as the Pregnancy Associated Plasma Protein A, PAPP-A, a protein bound with zinc that has been studied as a marker of acute coronary events[15].

IGF-1 as a biological marker

The reliability of IGF-1 as a biomarker has been investigated in a number of clinical studies. Borofsky et al[16] demonstrated that IGF-1 values taken from an individual within a relatively short time period (up to a few years) do not vary considerably, which is extremely useful in studies in human populations. Moreover, IGF-1 levels tend to decrease with age[16,17], and most studies agree on that, with the exception of those with narrow age-limits for the included individuals[18,19]. This age-related decline in IGF-1 is attributed to the parallel decrease of GH-production, although some researchers believe that IGF-1 age-dependency is only found in the homozygotes for the wild type allele[20]. In heterozygotes and individuals completely lacking the 192bp allele, IGF-1 is considered to be less GH-dependent and more subject to regulation by nutritional status, hepatic function, insulin, and corticosteroid hormones[21]. There is also very limited circadian or postprandial fluctuation of IGF-1 concentrations. This finding was confirmed in diabetic patients, who, irrespective of the time elapsed since the last insulin injection, had unchanged IGF-1 levels[22]. Finally, similar concentrations have been demonstrated in men and women by most studies, but not all[23-25].

Insulin-like Growth Factor-1 can be determined in two forms[5], total IGF-1, which has to undergo acid-extraction from its binding proteins, and free IGF-1, the biologically active form. Until recently, only the determination of total IGF-1 was available. Lately, however, reliable, albeit laborious, methods have been developed for the determination of the free fraction. In some settings, e.g. type 1 DM, chronic renal insufficiency and obesity, free IGF-1 shows a better association with GH than total IGF-1, however the latter is still preferred in most experimental and clinical studies.

IGF-1 as a protective factor of the cardiovascular system

Experimental data

Until 5 years ago, researchers seemed to support a detrimental role for IGF-1 in the atherosclerotic process (reviewed in Bayes-Genis et al[3]), underlined mainly by experimental studies in animal models, which had demonstrated a number of unwanted actions of IGF-1: smooth muscle cell hyperplasia[26], increased uptake of LDL-cholesterol by macrophages[27], induction of the production of adhesion molecules by endothelial cells[28], and neoangiogenesis[29]. When added up, however, and critically examined, these data cannot be considered strong and consistent enough to attribute atherogenic properties to IGF-1[30].

At the same time, research has accumulated a significant amount of data in favor of an atheroprotective role of IGF-1. In particular, IGF-1 was found to induce NO synthetase, via the PI3-K/Akt pathway[31], therefore increasing its constitutive production and diminishing its inducible, pulsed secretion[32], causing a number of beneficial effects[30] (Figure 1): vasodilation, facilitation of glucose uptake, inhibition of gluconeogenesis, reactive oxygen species (ROS) scavenging, anti-inflammatory and antiplatelet action, migration and survival of endothelial cells, and mobilization of progenitor endothelial cells, the production of which is also augmented by IGF-1[33]. Furthermore, studies in human atherosclerotic plaques have shown that smooth muscle cells (SMCs) within them demonstrate reduced expression of IGF-1 and increased apoptosis[35, 36]. Oxidized LDL-cholesterol causes a down-regulation of IGF-1 receptors and mRNA, resulting in the loss of the IGF-1 anti-apoptotic effect on SMCs[37]. Moreover, IGF-1 interacts with potassium channels with additive vasodilatory effect[38,39]. Concerning the actions on the myocardium, IGF-1 contributes to the phenomenon of ischemic preconditioning[40] and to the survival of the rat cardiomyocyte after ischemic or reperfusion injury[41], while increased IGF-1 expression in the failing heart delays the progression of cardiomyopathy[42]. The survival benefit arises from the induction of the PI3-K pathway, as it has been proven in transgenic mice overexpressing IGF-1R[43] and in a rat model where angiotensin converting enzyme inhibitors were used[44].

Clinical studies

Prospective studies in this field have shown: increased incidence of ischemic heart disease[24] and cardiac death due to coronary heart disease[45] in individuals with low baseline IGF-1 concentrations that were followed for

15 and 9-13 years respectively; acute fall of IGF-1 levels in patients suffering acute myocardial infarction (MI), restoration of normal levels one year post-MI, and a worse prognosis for those patients with the lowest IGF-1 concentrations upon admission[46]; increased incidence of heart failure among participants in the Framingham Study with initially low IGF-1 values[25]; and, finally, greater 2-year mortality and worsened left ventricular systolic function in MI-patients with low admission values of IGF-1[47]. Cross-sectional studies have demonstrated an inverse association of free IGF-1 with carotid intima-media thickness (IMT)[48] and a history of MI and electrocardiographic evidence of coronary heart disease[49]. Similar results were derived from genotype-phenotype association studies, where persons lacking the 192bp wild-type polymorphism were more likely to have suffered an MI compared to 192bp hetero- and homo- zygotes[10]. The same individuals had a 1.5 times greater risk of developing left ventricular dysfunction[50]. Moreover, hypertensive patients lacking the 192bp allele display greater carotid IMT and pulse wave velocity (PWV), both signs of advanced atherosclerosis[51].

IGF-1, Diabetes Mellitus and the Metabolic Syndrome

Experimental data

A common link between the Metabolic Syndrome and type 2 Diabetes Mellitus is insulin resistance, a state characterized by decreased sensitivity of peripheral tissues to the actions of insulin and, clinically, with a propensity towards cardiovascular disease (CVD)[52]. The association of low levels of circulating IGF-1 with insulin resistance has gained much attention lately. From a molecular point of view, IGF-1 exerts beneficial effects on glucose homeostasis, such as increased glucose uptake and inhibition of gluconeogenesis, either with the mediation of NO or not. Furthermore, the development of insulin resistance at low IGF-1 levels has at least two explanations. The one, mentioned above, has to do with the extensive expression of the hybrid insulin/IGF-1 receptor[13]. A second possible mechanism involves unrestricted, because of low IGF-1, hypophysial production of GH, a well-known counter-regulatory hormone of insulin; this has been demonstrated in rats genetically under-expressing IGF-1, where high levels of GH were associated with insulin resistance of muscle tissue[53]. At the same time, a link between low IGF-1 and C-reactive protein (CRP), a known risk factor for the MetS, has been found. It appears that certain proinflammatory cytokines, tumour necrosis factor-α and interleukin-6, that are known to induce hepatic CRP production, tend to decrease IGF-1 levels, both local and circulating[55,56].

Clinical studies

The relation between IGF-1 and the risk of developing insulin resistance and frank DM has been adequately studied: prospectively, high baseline IGF-1 levels were associated with a lower likelihood of developing impaired glucose tolerance and DM in 615 normoglycemic participants followed for 4.5 years[57]. In a recent cross-sectional study[13], low concentrations of IGF-1 proved, in multivariate analysis, to be an independent predictor of insulin resistance and the MetS in individuals with varying degrees of glucose tolerance (non-diabetics, diabetics, subjects with impaired glucose tolerance). In the study of the 192bp IGF-1 polymorphism by Vaessen et al, a higher risk to develop DM was conferred by the total absence of the wild type polymorphism, which determines lower IGF-1 levels[10]. Moreover, the administration of recombinant IGF-1 in patients with type 1 DM caused a 23% and a 49% decrease of glucose levels and insulin requirements respectively[58]. The data mentioned above collectively support the hypothesis of a protective role of IGF-1 regarding insulin sensitivity.

As for the risk of developing the cluster of metabolic abnormalities known as the MetS, an independent association of IGF-1 with all of its components (as they were defined in the NCEP Adult Treatment Panel III[59]) has been confirmed: 1) hyperglycemia (analyzed above), 2) central obesity: a negative association has been described in the general population between IGF-1 (total and free) with Body Mass Index (BMI) and Waist-to-Hip Ratio (WHR)[13,60], although in men total IGF-1 showed no relation to BMI[60], 3) dyslipidemia: IGF-1 appears positively correlated with HDL-cholesterol in the general population, and negatively with total-, and LDL-cholesterol, as well as triglycerides[13]. Furthermore, low IGF-1 has been associated with post-prandial dyslipidemia, a well-known atherogenic factor[61], 4) arterial hypertension: both in the general population and in type 2 diabetics, IGF-1 has been found to negatively correlate with blood pressure levels[13], but not in all studies. But as a whole, too, the MetS has been associated with low IGF-1 concentrations and, inversely, high CRP levels. In a study of 440 UK inhabitants, members of 3 different ethnic groups, low IGF-1 in combination with high CRP independently predicted the presence of the MetS[62]. Similarly, in the study of Sesti et al, that included individuals with varying degrees of glucose tolerance, participants fulfilling the MetS criteria had lower age- and sex-adjusted IGF-1 values compared to those who did not fall in the MetS definition[13]. In another British study that primarily proved an increased risk for the MetS by high CRP and low IGFBP-1- levels, it was found that individuals with decreased total IGF-1 had a higher prevalence of the MetS[63]. This finding was attenuated in multivariate analysis, but CRP and IGF-1 were indeed inversely correlated in the whole study population. This result is in accordance with our findings[64] in a Greek population with a high prevalence of the MetS, where CRP levels showed a significant and independent of age, gender, smoking status and waist circumference negative correlation with total IGF-1 concentrations, both in the whole study population and the MetS group. It is interesting that both low IGF-1 and high CRP levels demonstrated an almost linear relationship with the number of MetS components

fulfilled by an individual, and that a person in the low tertile of IGF-1 had a 2.9 times excess risk of having the MetS than a subject in the highest IGF-1 tertile.

Studies of IGF-1 in diabetic populations have a special importance in the clinical research involving the IGF-system and CVD. It is known that cardiovascular mortality of diabetic patients is more than that anticipated based on traditional risk factors[65]. One of the possible explanations could be that IGF-1, a now recognized atheroprotective agent, is found decreased in diabetics. This has led to the "IGF-1 deficiency hypothesis"[9], the central idea being that IGF-1 concentrations drop faster and to a greater extent in patients with DM type 1[22, 66, 67] and 2[67] than in age-, and sex-matched normoglycemic individuals, which contributes to their increased cardiovascular morbidity and mortality. Furthermore, it has been proposed that poor glycaemic control, expressed as a high glucosylated hemoglobin concentration (HbA1c), is associated with low circulating IGF-1 levels[9], both total[66] and free[68, 69]. Regarding the complications of DM, one study revealed lower free IGF-1 values in type 2 diabetics with an acute inflammatory process; a history of a micro- or macro-vascular complication (retinopathy, peripheral neuropathy, stroke, MI, limb amputation); or hospitalized for any reason, compared with DM patients free of complications[69]. The finding of low IGF-1 in cases of diabetic retinopathy has been confirmed in another study, where the free IGF-1 fraction was determined[68]. Microalbuminuria, another microvascular complication of DM and a surrogate marker of endothelial dysfunction, has been related to low free and total IGF-1 in young patients with type 1 DM[70]. Patients, however, with end-stage renal disease have demonstrated higher free IGF-1 values than other diabetics with closer to normal renal function[69]. As for the relation of DM treatment with IGF-1, there seems to be no difference in IGF-1 levels among patients treated with diet alone, oral hypoglycaemic agents, or insulin[71, 72].

Conclusions

Insulin-like Growth Factor-1 plays a pivotal role in glucose homeostasis, as it augments the sensitivity of peripheral tissues to insulin. At the same time, it has a beneficial effect on the vessel wall and inhibits the progression of atherosclerosis. An important amount of clinical data, derived from both cross-sectional and prospective studies, supports a protective role for IGF-1 regarding the development of CVD and of several of its risk factors, including DM and the MetS. Especially in diabetic populations, low IGF-1 concentrations compared to healthy controls appear to contribute to their increased cardiovascular burden. However, results are often conflicting, while IGF-1 measurements from various populations are lacking, limiting the generalisability of observations. For these reasons, further research is needed in order to introduce IGF-1 determination in everyday clinical practice for the stratification of CVD risk.

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