TOPIC FOR DISCUSSION

The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: is prevention possible?

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Abstract

The incidence of peripheral, cerebro- and cardiovascular disease (CVD) in patients with type 2 diabetes mellitus is approximately twice as high as in the non-diabetic population. Conventional cardiovascular risk factors such as plasma lipids, lipoproteins and hypertension only partially explain this excessive risk of developing atherosclerosis and CVD. Meta-analysis of studies performed in non-diabetic populations indicates that the risk of CVD increases continuously with glucose levels above 4.2 mmol/l. The glucose hypothesis suggests that treatment which normalizes glucose levels prevents or delays the long-term complications of diabetes mellitus. However, the outcome of the UK Prospective Diabetes Study demonstrates that glucose control does not completely prevent CVD. In healthy subjects, serum IGF-I levels peak in early adulthood, after which they gradually decrease with increasing age. Several observations suggest that there is a premature and progressive age-related decline in serum IGF-I bioactivity in type 2 diabetics, which eventually results in a (relative) IGF-I deficiency. In type 2 diabetics, close relationships have been demonstrated between glycaemic control and serum IGF-I levels, with worse control being associated with lower IGF-I levels. Several studies (in non-diabetics) suggest that lowered circulating IGF-I levels account for a poor outcome of CVD. We previously observed in a population-based study that a genetically determined lowered IGF-I expression increases the risk of myocardial infarction with type 2 diabetes.

This genetic approach overcomes the problem that cross-sectional studies cannot distinguish whether changes in IGF-I levels are a cause or a consequence of a disease. IGF-I is an important metabolic regulatory hormone. In addition, IGF-I suppresses myocardial apoptosis and improves myocardial function in various models of experimental cardiomyopathy. Compared with other growth factors, the 'survival' effect of IGF-I on myocardium seems rather unique.

Therefore, we hypothesize that the premature and progressive decline in serum IGF-I bioactivity in ageing patients with type 2 diabetics is an important pathophysiological abnormality. It contributes not only to elevated glucose and lipid levels, but also to the progression and the poor outcome of CVD. If this hypothesis is proven to be right, treatment with IGF-I as an adjunct to insulin offers great potential and might not only improve metabolic control but also reduce the incidence and prevalence of CVD in type 2 diabetes patients. However, there is as yet no experimental evidence that long-term (replacement) treatment with IGF-I prevents, delays or reduces CVD in type 2 diabetes patients. Clinical trials are necessary to prove that long-term IGF-I treatment, preferably in the form of a better-tolerated IGF-I/IGF-binding protein-3 complex, improves the overall cardiovascular risk in type 2 diabetes.

European Journal of Endocrinology **146** 467–477

Introduction

The incidence of cardiovascular disease (CVD), particularly coronary heart disease (CHD), cerebrovascular, and peripheral vascular disease is approximately twice as high in patients with type 2 diabetes as in age-matched controls without diabetes (1–4). The risk of these complications increases with the duration of diabetes and with age (5–7). In subjects with type 2 diabetes, CVD is associated with a higher mortality rate than in non-diabetic subjects (8, 9). Conventional cardiovascular risk factors such as plasma lipids, lipoproteins and hypertension only partially explain this excessive risk of developing atherosclerosis and CVD in individuals with type 2 diabetes (6, 10). In addition, despite a marked decline in the rate of CVD over the past 35 years in the overall population, this beneficial trend has not been observed for subjects with type 2 diabetes (11).

Another important manifestation of CVD in diabetic patients is heart failure (HF). The special role of diabetes in the development of congestive HF was

firmly established in the Framingham Study (12). In this study the risk of HF was increased 2.4-fold in diabetic men and 5-fold in diabetic women. Diabetes predicted HF independently of coexisting hypertension or CHD. HF is sometimes due to a diabetic cardiomyopathy, which is now recognized as a distinct entity (13). Diabetic cardiomypathy appears to be independent of macrovascular/microvascular disease and contributes significantly to CVD morbidity and mortality, especially in those diabetics with coexistent hypertension (14). Abundant literature evidence supports the concept of myocardial dysfunction separate from epicardial coronary disease in diabetic individuals (15, 16).

Glucose control, insulin treatment and CVD in the UK Prospective Diabetes Study (UKPDS)

The glucose hypothesis suggests that treatment that normalizes glucose levels prevents or delays the long-term complications of diabetes mellitus. Based on the UKPDS it has been suggested that the benefits of strict glycaemic control in type 2 diabetes are less than those of tight blood pressure control (17). Although in the primary analysis of the UKPDS no significant reduction in the risk of CVD was observed after strict glycaemic control, mean glycosylated haemoglobin (HbA1c) levels achieved in the UKPDS did not reach the non-diabetic (normal) range. In addition, epidemiological subanalysis of the UKPDS data suggested that a reduction of HbA1c levels by 1% was associated with a 14% reduction in myocardial infarctions and a 12% reduction in strokes (18). These epidemiological data show that glucose-directed therapy which is sufficient to lower glucose levels to normal produces a 'normal' population risk for macrovascular problems. Nevertheless, the overall outcome of the UKPDS makes clear that CVD cannot be completely prevented by the common methods of blood glucose control which are clinically available today (19).

Impaired glucose tolerance (IGT), hyperinsulinaemia, insulin resistance and CVD

It has long been known that even IGT is associated with an increased risk for CVD, while progression from IGT to type 2 diabetes is not necessary in order to cause CVD (20). The Whitehall study, the Honolulu Heart Study and the Rancho Bernardo Study have prospectively followed large cohorts of non-diabetic subjects for cardiovascular outcomes (21–23). In these three studies a continuous increase in the risk for CHD was observed with increasing serum glucose levels. In accord, a meta-analysis of various cohort studies in non-diabetic populations demonstrated that the

increased risk of CVD increased continuously with glucose levels above 4.2 mmol/l (24). All these studies suggest that long-term hyperglycaemia is an important risk factor for CVD, without evidence of a threshold effect and independently of other common risk factors for CHD. Furthermore, subjects with insulin resistance who are not diabetic, e.g. patients with the metabolic syndrome X characterized by hypertriglyceridaemia, hypertension and abdominal obesity, are also at increased risk of CVD (25).

Insulin-like growth factor-I (IGF-I), insulin and the IGF-binding proteins (IGFBPs)

In man there are two important glucose-regulating hormonal systems, insulin and IGF-I (26). In the human body, IGF-I is after insulin the second most powerful naturally occurring peptide with glucose-lowering effects (27). The effects of IGF-I and insulin are complementary. Insulin stimulates the constitutive secretion of IGF-I from the liver (28). IGF-I in turn, suppresses insulin secretion even in euglycaemic conditions (29). IGF-I increases insulin sensitivity and peripheral glucose uptake, decreases hepatic glucose production, and improves the lipid profile (30, 31). IGF-I is probably the most potent anti-catabolic and anabolic hormone in the body (32).

At least six IGFBPs and several proteases modulate the bioavailability of IGF-I to the tissues (33). In the blood, where IGF concentrations are 1000 times higher than those of insulin, IGFBP-3 (the major form of the IGFBPs in the circulation) binds in healthy subjects at least 80% of IGFs as 140 kDa complexes, which do not cross the capillary endothelium and therefore prevent the insulin-like action of IGFs (34). Under normal circumstances less than 1% of IGF-I circulates in the free form (35). Nevertheless, these circulating IGF reserves may be mobilized in response to metabolic and other needs via limited proteolysis of IGFBP-3 by serine proteases (36).

Ageing, glucose metabolism and insulin resistance

Ageing is characterized by progressive alterations in glucose metabolism, including resistance to insulin-mediated glucose disposal, impaired glucose-induced insulin release and altered hepatic glucose output (37). The progression from normal glucose tolerance via IGT to diabetes is a consequence of a further decline in insulin secretion by the β-cell and/or an increase in insulin resistance with ageing (38). In addition, changes in body composition, as well as physical fitness, may contribute to a further reduction of insulin resistance with ageing.

Is there a progressive IGF-I deficiency in type 2 diabetes with ageing?

In patients with type 2 diabetes, serum IGF-I levels are dependent on the degree of metabolic control, with near normal IGF-I levels in well-controlled diabetics, whereas they tend to decrease in poorly controlled diabetics (39–41). It has also been suggested that lowered serum IGF-I concentrations predict worsening of insulin-mediated glucose uptake in older people (42). In healthy subjects, serum total IGF-I levels peak in early adulthood and then start to decline to 50% of adolescent values in the fifth and sixth decades of life (43). In type 2 diabetes this progressive age-dependent decline of total IGF-I levels is even greater than that observed in healthy controls. Tan & Baxter (44) reported that circulating total IGF-I levels are lowered in type 2 diabetic patients even after age was taken into consideration.

Although the mechanism for the progressive reduction of circulating IGF-I levels with ageing in patients with type 2 diabetes has remained obscure until now, it has been suggested that this decrease is at least in part a result of decreased IGF-I production through lowered growth hormone (GH) concentrations and/or an uncoupling of the GH induction of IGF-I generation by insulin resistance (45). Another explanation might be central inhibition of the GH/IGF-I axis. Increased demands for IGF-I with ageing, resulting in accelerated metabolic clearance rate of IGF-I by displacement of IGF-I from circulating IGFBP-3 and transport of IGF-I to peripheral tissues may also contribute to the progressive decrease of circulating IGF-I concentrations. It has been speculated that increased serum IGFBP-3 protease activity, as observed in insulin-resistant states and type 2 diabetes, is an endogenous compensatory mechanism to increase IGF-I bioavailability at the tissue level in order to restore insulin sensitivity, glycaemic control and other IGF-I-dependent effects (46–48).

It has also been reported that subjects with insulin resistance have initially decreased serum levels of IGFBP-1 in comparison with those without insulin resistance (49, 50). Although the biological significance of reduced circulating IGFBP-1 levels in insulin-resistant/hyperinsulinaemic states is unknown, it has been suggested that low circulating IGFBP-1 concentrations might be another endogenous mechanism to increase IGF-I bioavailability at the tissue level in an attempt to stimulate glucose uptake in muscles and other insulin-resistant tissues (51). However, ageing and frank type 2 diabetes are both associated with a reduction of insulin secretory rate as a consequence of a progressive loss of β-cell function and this results in an increase in IGFBP-1 levels (50, 52–55). Increased IGFBP-1 levels are associated with a decreased IGF-I bioactivity in diabetic serum (56) and *in vivo* data in animals have shown that increased levels of IGFBP-1 can both inhibit IGF-I action and induce mild hyperglycaemia (57). All these findings together suggest that in type 2 diabetes during ageing there is a premature and progressive decline in serum IGF-I bioactivity, resulting in the development of a progressive (relative) IGF-I deficiency, especially in those with a poor metabolic control (see also Table 1).

Age, genetic susceptibility, IGF-I and type 2 diabetes

Age-related changes interact with the genetic background and may explain the increasing prevalence of

Table 1 Schematic time course of changes in circulating insulin, IGF-I/IGFBP levels and IGF-I bioactivity during the progression from impaired glucose tolerance (IGT) to overt type 2 diabetes. Blood glucose levels rise at first, resulting in IGT, and finally in overt type 2 diabetes. Initially, insulin secretion increases to overcome insulin resistance, but reaches a plateau and then falls. IGFBP-1 levels are thought to modulate the free fraction of IGF-I. IGFBP-1 levels are negatively regulated by insulin. It has been suggested that low IGFBP-1 concentrations might increase the free IGF-I concentration in an attempt to stimulate glucose uptake in muscles and other insulin-resistant tissues. The progression from IGT to frank type 2 diabetes is associated with a (relative) increase in IGFBP-1 levels and as a consequence IGF-I bioactivity decreases. Increased IGFBP-3 proteolysis has been reported to occur in insulin-resistant states and type 2 diabetes. It has been speculated that this increased protease activity in insulin-resistant states and diabetes is another compensatory mechanism to attenuate the decrease in free IGF-I concentrations in order to restore insulin sensitivity and glycaemic control. The physiological age-dependent decrease of IGF-I bioactivity is superimposed on the changes in circulating insulin and IGF-I/IGFBP levels during the progression from IGT to overt type 2 diabetes (see also text).

	Age ⟶		
	Normo-glycaemia ⟶	IGT ⟶	Overt type 2 diabetes
Insulin	N	↑	↓ or ↓↓
IGFBP-1	N	↓	N or ↑
Total IGF-I	N	N, ↓	↓
Free IGF-I	N	N, ↓	↓↓
Intact IGFBP-3*	N	N, ↓	↓↓
IGFBP3 protease activity	N	↑	↑↑
IGF-I bioactivity	N	N, ↓	↓↓

N = normal; ↑ = increased; ↓ = decreased.
* Measured by Western ligand blotting.

type 2 diabetes and diabetic complications during the ageing process (37, 58).

Recently we observed in a population-based study of elderly subjects higher circulating total IGF-I levels in carriers of a genetic polymorphism in the promoter region of the IGF-I gene than in non-carriers (59). This study suggested that this IGF-I gene polymorphism is functionally related to circulating IGF-I levels (59). However, the main finding of this study was that both the risk of type 2 diabetes and myocardial infarction were significantly increased in non-carriers of this polymorphism when compared with carriers, suggesting that a genetically determined exposure to relatively low IGF-I levels plays a role in the pathogenesis of type 2 diabetes and myocardial infarction (59).

IGF-I, diabetes and atherosclerosis

GH and IGF-I deficiency in non-diabetic humans are associated with premature and increased atherosclerosis (60–63). It was observed in hypophysectomized rats that after vascular endothelial injury the proliferation of vascular smooth muscle is markedly delayed, suggesting an impaired adaptive response in the process of healing of the injured arterial wall, when compared with healthy control animals (64).

Atherosclerosis is also a major cause of morbidity and mortality in patients with diabetes mellitus. Imbalance between cell death and survival may substantially affect the cellularity and integrity of the blood vessel and contributes to the pathogenesis of atherosclerosis (65). IGF-I is a potent survival factor preventing apoptosis of vascular smooth muscle cells (VSMCs) (66) as well as stimulating the proliferation (67) and migration
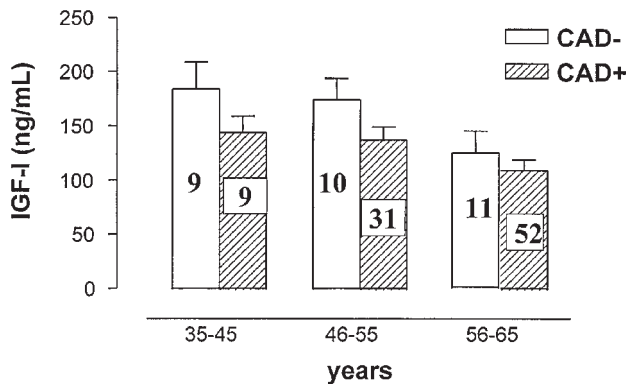
of VSMCs (68). Thus, IGF-I may contribute in different ways to the balance between apoptosis and survival in atherosclerotic lesions (65).

IGF-I accumulation is found at the site of ischaemic injury and VSMC proliferation is an important part of the arterial response to injury (69). In an experimental animal model it has been observed that vascular smooth muscle proliferation after endothelial injury is impaired by the diabetic state (69). In this experimental model, IGF-I treatment enhances and normalizes vascular smooth muscle proliferation (69).

Circulating IGF-I levels, like insulin, stimulate nitric oxide (NO) in certain vascular beds (70–74). Reduced NO generation or accelerating NO inactivation may
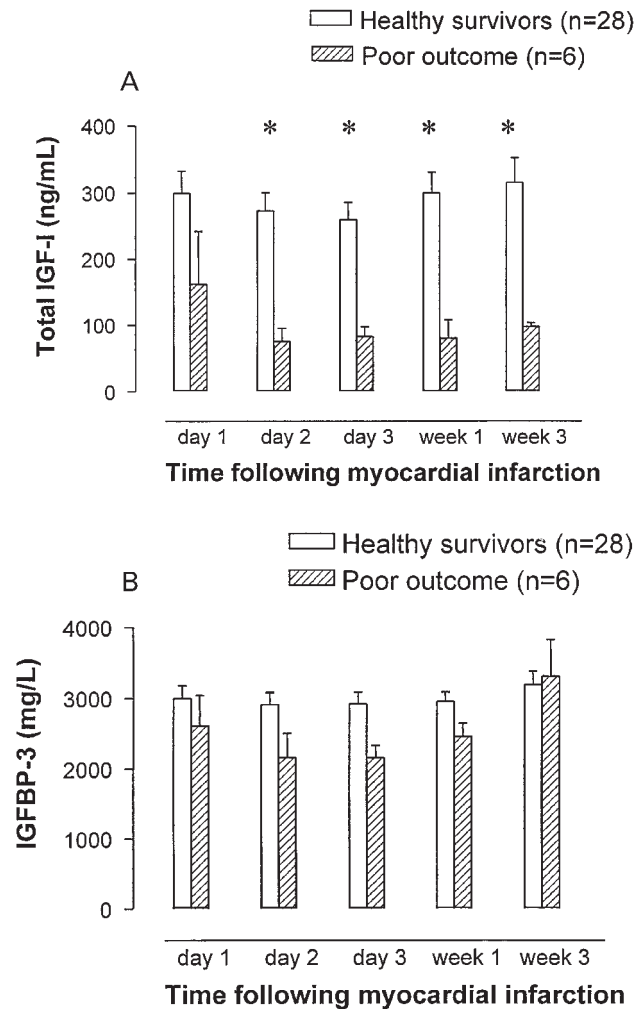

Figure 1 Circulating total IGF-I levels in patients with significant CAD (CAD+) and in those without (CAD −) stratified by decades of age. Each bar represents the mean±s.e.m. in each group. Values for the number of patients of each subgroup are shown in each box. Mean circulating total IGF-I levels were significantly lower ($P < 0.01$) in CAD+ patients (126 ± 7 ng/ml; $n = 92$) than in CAD− patients (162 ± 15 ng/ml; $n = 30$). When age was taken into account circulating total IGF-I levels were significantly lower in patients with CAD+ (two-way ANOVA, $P < 0.05$). (Reprinted from (62) with permission from Excerpta Medica Inc.)

Figure 2 Circulating total IGF-I (A) and IGFBP-3 (B) levels in healthy survivors and patients with poor clinical outcomes after an acute myocardial infarction. Data are means±s.e.m. Mean total IGF-I levels were significantly lower in patients who died ($n = 2$) or developed severe congestive HF ($n = 4$) during 3 months of post-acute myocardial infarction follow-up (*$P < 0.001$). In those patients with poor outcomes, a borderline reduction of IGFBP-3 was observed on day 2 ($P = 0.086$). (Adapted from (83) with permission from The Endocrine Society.)

cause vascular damage and vascular dysfunction (75). Vascular dysfunction is known to be associated with all major risk factors for atherosclerosis, encompassing hypertension and diabetes mellitus. Because NO is essential for the integrity of the vessel wall, decreased NO production by vascular endothelium, due to low IGF-I levels, might be another pathogenic mechanism responsible for the observed association between low circulating IGF-I levels and atherosclerosis in diabetics and non-diabetics (72). IGF-I can promote vasodilation through the activation of potassium channels, with a consequent reduction in the intracellular calcium concentrations (76–79). In addition, IGF-I can stimulate migration and tube formation by vascular endothelial cells (80), has been shown to promote aortic angiogenesis (81), and inhibits adherence of human peripheral blood monocytes to endothelial cells (82). All these data together suggest a role for IGF-I deficiency *per se* in increasing the atherosclerotic risk in diabetics and non-diabetics.

IGF-I, diabetes and the heart

Low circulating IGF-I levels have been previously associated with angiographically documented coronary artery disease (CAD) in non-diabetics (62) (Fig. 1). Immediately after acute myocardial infarction, lowered circulating IGF-I levels were especially measured in non-diabetic patients with poor outcomes (83) (Fig. 2). Recently Friberg *et al.* (84) reported that non-diabetic patients who died after an acute myocardial infarction from CVD during 2 years of follow-up, had at admission significantly lower IGF-I levels than survivors. In two other studies, non-diabetic patients with myocardial infarction had significantly lower IGF-I levels at admission than age- and sex-matched healthy controls (85, 86). In one of these latter studies older patients with a cardiac condition were less able to maintain their blood IGF-I levels during the recovery period than younger patients (85) (Fig. 3). The authors suggested that this observation may explain why older patients take longer to recover and to heal after a myocardial infarction than younger patients. These human studies all suggest that lowered circulating IGF-I accounts for a poor outcome of CVD.

Obviously, circulating IGF-I levels can decrease by two mechanisms or their combination: (i) the production of IGF-I is decreased and the efflux from the circulation is unaltered, or (ii) the production is unaltered and the efflux from the circulation is increased, e.g. increased delivery of IGF-I at an injury of the vascular endothelium by an increased proteolysis of circulating IGFBP-3 by specific IGFBP-3 proteases (87). Probably both factors play a role in the reduction of circulating IGF-I.

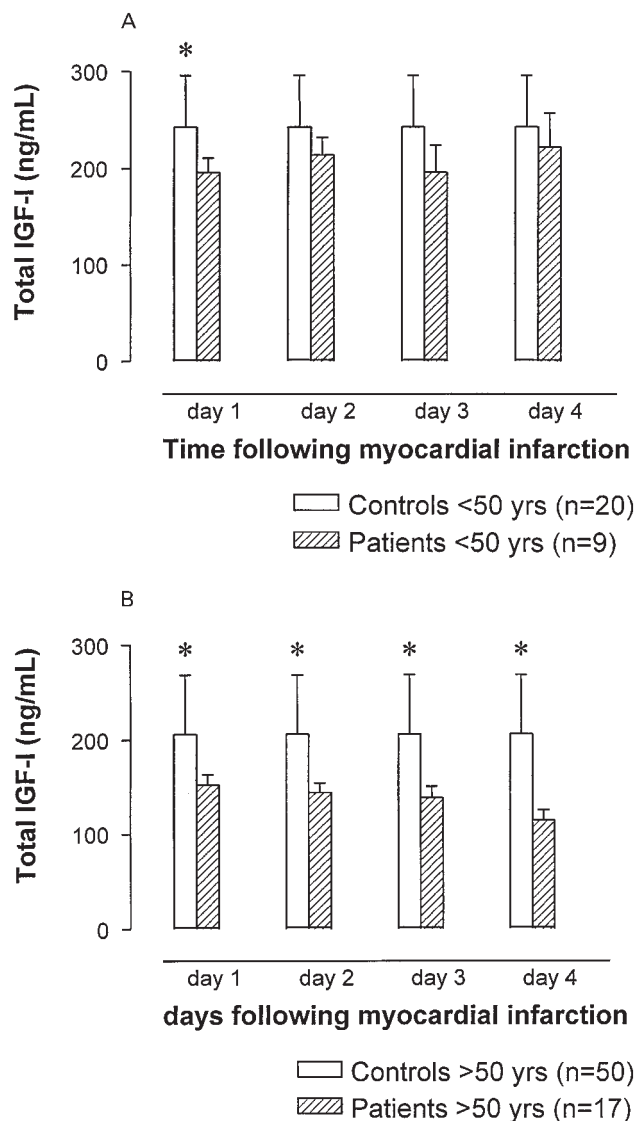However, the most important issue in all these human studies is to what extent low circulating IGF-I

Figure 3 Circulating total IGF-I levels following myocardial infarction compared with age- and sex-adjusted normal adults. Twenty-one males and five females ranging in age from 19 to 71 years were divided into two age groups: the first ranging from 19 to 48 years (nine males) (A) and the second ranging from 50 to 71 years (five post-menopausal females and 12 males) (B). Total IGF-I levels in the older age group (B) showed a significant decline from day 1 to day 4 ($P = 0.001$). Values of the younger age group (A) remained stable from day 1 to day 4 compared with the older group (B). Total IGF-I levels were significantly lower on the first day compared with the age- and sex-adjusted total IGF-I levels of normal adults (controls) aged <50 years (197 ± 44 vs 243 ± 53 ng/ml, $P = 0.03$) (A) and those aged >50 years (151 ± 43 vs 206 ± 62 ng/ml, $P = 0.002$) (B). In contrast to the younger group, values of total IGF-I in the older group (>50 years) remained significantly lower than those of controls on day 2 to day 4. *$P < 0.005$. (Adapted from (85) with permission from Harcourt Publishers Ltd.)

levels are a cause or a consequence of the poor cardiovascular outcome. In our opinion the decrease in circulating IGF-I levels is probably the cause and not the consequence of the poor outcome of CVD. In the section that follows we will give several arguments to support this statement.

In a rabbit model, acute administration of IGF-I just before and during early cardial ischaemia improves glucose uptake and tolerance to ischaemia in hypertrophied hearts (88). IGF-I has been shown to have beneficial acute and long-term cardiovascular effects in several other experimental studies. Potentially beneficial effects of IGF-I observed in these experimental studies are reduction in afterload through vasodilation, positive inotropy, prevention of apoptosis, increased calcium sensitivity of cardiac myofilaments, improved recovery of cardiac function after myocardial infarction and during reperfusion after global ischaemia (88–92).

In a previous study, as already discussed above, we were able to confirm an increased risk for myocardial infarction in diabetic and non-diabetic subjects with genetically determined low IGF-I expression (59). A genetic approach overcomes the problem that cross-sectional studies cannot distinguish whether IGF-I levels are a cause or a consequence of disease. The increased risk for myocardial infarction in diabetics with low IGF-I expression may thus for a large part be explained by the interaction of low IGF-I availability and coronary atherosclerosis. The study of Conti *et al.* (86) supports this possibility. In this study low IGF-I levels preceded the increase of creatine phosphokinase in the very early phase of an acute myocardial infarction, which suggests also that some antecedent cause and not the acute myocardial infarction was the reason for the lowered IGF-I levels (86). In the same study, patients with acute myocardial infarction showed a trend toward higher insulin levels compared with controls, which achieved statistical significance at 1 year follow-up (86). The authors suggested that these insulin levels were consistent with an insulin-resistant state, in both the acute and chronic phases of myocardial infarction.

Experimental evidence for IGF-I effects on the heart

Effects on CHD

The importance of IGF-I as an anti-apoptotic factor is also supported by the observation in different animal models of myocardial ischaemia that IGF-I administration decreased myocardial apoptosis and thereby the size of myocardial infarction (89, 93). When the coronary artery was ligated to create an experimental myocardial infarction in mice, transgenic mice overexpressing IGF-I in the myocardium showed decreased cell death and less ventricular dilation and wall stress (94). GH-deficient dwarf rats, with reduced circulating IGF-I levels but normal myocardial IGF-I mRNA levels, developed in an experimental model of myocardial infarction more pathological left ventricular remodelling and functional loss than did controls (95). In another experimental model of myocardial infarction a marked reduction in capillarization and a blunted cardiac remodelling response following myocardial infarction were observed in IGF-I-deficient mice, as compared with controls (96).

Diabetic cardiomyopathy

In most forms of cardiomyopathy there is an initial upregulation of myocardial IGF-I and IGF-I receptor expression, which may be a transient, compensatory remodelling response (97). In contrast, diabetic cardiomyopathy is a unique myopathic state and differs from other cardiomyopathies in that a decrease in both myocardial IGF-I content and IGF-I receptors has been observed (98). However, in IGF-I transgenic mice with streptozotocin-induced diabetes, IGF-I overexpression decreased the development of diabetic cardiomyopathy by attenuating p53 function and angiotensin II production (99). IGF-I improves myocardial function in various models of experimental cardiomyopathy and suppresses myocardial apoptosis (100–102). IGF-I administration in animals with experimental cardiac failure promoted a physiological form of myocardial hypertrophy (i.e. there was no increase in extracellular matrix or fibrosis) (101). The myocardial hypertrophy was accompanied by an improved cardiac function (decreased left ventricular end-diastolic volume and increased stroke volume), suggesting a beneficial effect of IGF-I. In another experimental animal model of HF, IGF-I treatment decreased mean arterial pressure, left ventricular end-diastolic pressure and systemic vascular resistance, and increased left cardiac index and stroke volume index (103).

Recently it was shown that basal IGF-I levels are reduced in dilated cardiomyopathy patients with severe left ventricular dysfunction (104) and that serum IGF-I levels are negatively correlated with the severity of the cardiomyopathy (105). IGF-I improves cardiac contractility, cardiac output, stroke volume and ejection fraction by the human heart in the short and long term (91). Adult humans with GH deficiency and low IGF-I levels display slight cardiac dysfunction, which can be reversed by GH replacement therapy (106). IGF-I exerts calcium-dependent positive inotropic effects in the failing human myocardium (107). All these studies together suggest that IGF-I deficiency may contribute to an adverse outcome of CVD.

Is decreased IGF-I a missing link which raises both glucose levels and cardiovascular risk in ageing patients with type 2 diabetes?

Both the prevalence of type 2 diabetes mellitus and CVD are increasing and associated with a very high mortality rate, reduced quality of life and high costs of treatment, despite intensive insulin treatment. New strategies are urgently needed which slow or prevent the development of type 2 diabetes and CVD better than is currently achieved with the available treatment options. Several studies, as discussed above, suggest that the premature and progressive decline in serum IGF-I bioactivity during ageing in patients with type 2 diabetes may result in insufficient protective and regeneration effects of IGF-I on the cardiovascular system. In comparison with other growth factors, these 'survival' effects of IGF-I on the myocardium seem rather unique (108). In addition, IGF-I enhances insulin sensitivity and improves glycaemic control in type 2 diabetic subjects significantly (109). In addition, IGF-I treatment lowers both total and low-density lipoprotein cholesterol and triglyceride levels in type 2 diabetics (110). Lipoprotein(a) (Lp(a)), an important risk factor for CAD, also improved after IGF-I treatment (89). The risk of coronary thrombosis (as measured by plasminogen activator inhibitor-1 and fibrinogen levels) also improved after IGF-I treatment (111). Moreover, IGF-I treatment decreases obesity and improves body composition of type 2 diabetics (109, 112). Taking all the available information together, it becomes increasingly clear that IGF-I is not only an important metabolic regulatory hormone but also produces potent effects on the cardiovascular system (see Table 2 for a summary of potential mechanisms). Therefore, we hypothesize that in patients with type 2 diabetes the accelerated decline in serum IGF-I bioactivity during ageing is an important pathophysiological phenomenon, which not only results in raised glucose and lipid levels but also contributes to the progression and the poor outcome of CVD. However, the 'IGF-I deficiency hypothesis' rests still to a great extent on animal studies, which have been extensively referred to in this manuscript, as well as on circumstantial evidence. The decreased serum IGF-I level observed in subjects with type 2 diabetes mellitus with poor glycaemic control raises the possibility that exogenous recombinant IGF-I acting as a form of 'replacement' therapy might improve glucose tolerance and might inhibit the development of CVD (43). Previous studies have demonstrated that in type 2 diabetes circulating IGF-I levels improve after better glycaemic control (43, 113–115). IGF-I therapy as an adjunct to insulin improved glycaemic control in type 2 diabetes and reduced insulin resistance, a major component of the pathophysiology of type 2 diabetes (31). To date, studies of recombinant IGF-I administration to patients with type 2 diabetes have used free IGF-I doses which were associated with significant side-effects (arthralgias, myalgias, dyspnoea, nerve entrapment, headache and bilateral jaw tenderness) (31). These side-effects were probably caused by the use of free IGF-I in excessive doses. IGF-I administration inhibits GH secretion and may therefore actually further decrease IGFBP-3 and acid-labile subunit levels, which will result in a faster clearance of IGF-I from the circulation and thus more side-effects (116). Most pharmaceutical companies have decided not to develop IGF-I treatment further because of these side-effects (117). Recently, short-term clinical trials using a complex of IGF-I/IGFBP-3 as an adjuvant to insulin therapy in patients with type 2 diabetes caused a rapid fall in plasma glucose concentrations and an improvement in insulin resistance without any side-effects (118). There is as yet no proof that (long-term replacement) therapy with IGF-I as an adjunct to insulin will reduce, delay or even prevent the risk of CVD in patients with type 2 diabetes. Further studies examining the efficacy and the long-term safety of this IGF-I/IGFBP-3 combination should be undertaken in patients with type 2 diabetes, to investigate if this complex can modify the incidence and prevalence of CVD in these patients.

Table 2 Summary of the potential mechanisms by which IGF-I prevents the progression towards CVD (see also text).

(i) Optimization of the metabolic control
(ii) Regulation of endothelium- and non-endothelium-dependent vascular reactivity
(iii) Maintenance of normal NO bioavailability and consequent activation of anti-atherogenic mechanisms
(iv) Stimulation of angiogenesis
(v) Preservation of left ventricular geometry, stress and systolic and diastolic performance
(vi) Activation of anti-apoptic pathways
(vii) Attenuation of vascular risk factors (visceral adiposity, Lp(a), lipids, etc.)

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