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ARTICLE

Insulin-like growth factor I: a predictor of long-term glucose abnormalities in patients with acute myocardial infarction

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Abstract
Aims/hypothesis Low levels of IGF-I are associated with increased risk of cardiovascular disease and type 2 diabetes. The aim of this study was to investigate the IGF-I system in patients with acute myocardial infarction (AMI) without previously known diabetes.
Materials and methods One hundred and sixty-eight AMI patients were classified before hospital discharge by means of an OGTT as having NGT, IGT or newly detected type 2 diabetes. Age- and sex-matched subjects from the background population (n=185) served as the control group. The associations between fasting levels of IGF-I and IGF binding proteins 1 and 3 (IGFBP-1, IGFBP-3) and glucose metabolism during a follow-up period of 12 months were studied.
Results At hospital discharge, age-adjusted IGF-I (IGF-I SD) was significantly lower in patients with abnormal glucose tolerance (AGT=IGT or type 2 diabetes) compared with patients with NGT (p=0.014) and control subjects (p<0.001). IGF-I was strongly correlated with IGFBP-3 (r=0.730, p<0.001), which was significantly lower in patients with AGT compared with patients with NGT (p=0.009) and control subjects (p<0.001). Fasting levels of IGFBP-1 did not differ significantly between patients with NGT and AGT or between patients and control subjects. In a multiple logistic regression analysis in patients, IGF-I at hospital discharge was a significant predictor of AGT at discharge and after 12 months (adjusted odds ratio 0.29, p=0.022, and adjusted odds ratio 0.29, p=0.034, respectively).
Conclusions/interpretation Low levels of IGF-I may be a useful predictor of abnormal glucose metabolism in patients with AMI.

Keywords Acute myocardial infarction · Glucose tolerance · IGF-I · IGFBP-1 · IGFBP-3 · Insulin-like growth factor

Abbreviations

AGT	abnormal glucose tolerance
AMI	acute myocardial infarction
GAMI	Glucose Tolerance in Patients with Acute Myocardial Infarction
HOMA-IR	homeostasis model assessment of insulin resistance
hs-CRP	high-sensitivity C-reactive protein
IGFBP	IGF binding protein
IGF-I SD	Age-standardised IGF-I score
IGI	insulinogenic index
PAI1	plasminogen activator inhibitor 1

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Introduction

Even at levels below the threshold for the diagnosis of diabetes, fasting and postprandial hyperglycaemia are risk factors for cardiovascular morbidity and mortality [1]. In recent years attention has been devoted to the increased risk of subsequent cardiovascular mortality and morbidity in patients with acute myocardial infarction (AMI) and

disturbed glucose metabolism [2], a condition that is common in such patients [3, 4]. In previous studies we have seen that a substantial proportion of patients with AMI and glucose abnormalities do not have fasting blood glucose or HbA_{1c} above the threshold for type 2 diabetes and would consequently have been missed if not investigated by OGTT [3, 4].

Such observations make it of great importance to find novel and easily used markers of early stages of glucose abnormalities that may be helpful in future attempts to prevent cardiovascular events and mortality in AMI patients.

There is strong evidence that the IGF system plays an important role in glucose homeostasis [5] and low levels of IGF-I have recently been related to the development of type 2 diabetes [6]. Furthermore, clinical studies have shown that low levels of IGF-I and IGF binding proteins 1 and 3 (IGFBP-1 and IGFBP-3) are related to AMI or angiographically assessed coronary heart disease [7–10]. However, the findings are not consistent as previous studies also have shown that patients with coronary heart disease have increased levels of both IGF-I [11] and IGFBP-1 [12] and patients with low circulating IGF-I levels in combination with high IGFBP-3 levels had a significantly increased risk of developing ischaemic heart disease during a 15-year follow-up period [13].

Circulating IGF-I is primarily synthesised in the liver but also, in response to growth hormone, in every tissue, with insulin and amino acids as coactivators. IGF-I has a variety of functions in the regulation of growth and metabolism. The best characterised effects are linked to cell proliferation and accumulating knowledge suggests that IGF-I also is important for glucose homeostasis, lipolysis and protein oxidation. Glucometabolic effects of IGF-I include enhanced glucose uptake and improved insulin sensitivity [14]. The activity of IGF-I is regulated by its association with binding proteins, especially IGFBP-1 and IGFBP-3. IGFBP-3 binds IGF-I and functions together with the acid-labile subunit as a means of storing IGF-I in the circulation. IGFBP-1 has been described as the only acute regulator inhibiting the bioactivity of IGF-I in serum [15].

The primary aim of this study was to test the hypothesis that concentrations of IGF-I obtained early in the course of an AMI will identify lasting glucometabolic abnormalities. A secondary aim was to investigate the potential relationship between IGF-I, IGFBP-1, IGFBP-3 and future cardiovascular events.

Subjects and methods

A detailed description of the patients and control subjects from the Glucose Tolerance in patients with Acute Myocardial Infarction (GAMI) study has been presented elsewhere [3, 16]. Patients admitted for AMI were included if they fulfilled the following criteria: no previously known diabetes, baseline capillary blood glucose <11.1 mmol/l, serum creatinine <200 μmol/l and age ≤80 years. A total of 181 participants were enrolled, of whom 168 were characterised by means of an OGTT before hospital discharge as having NGT, IGT or type 2 diabetes.

A control group, described in detail elsewhere [16], was recruited by the use of local population registries that included all inhabitants of the two counties corresponding to the catchment areas of the participating hospitals. Five subjects matched for age and sex were randomly chosen as potential control subjects for each patient. The total number of control subjects was 185 persons without a prior diagnosis of diabetes mellitus or cardiovascular disease other than hypertension.

Study protocol

Blood glucose was measured upon arrival at the coronary care unit and each morning until the day of hospital discharge (day 4 or 5). HbA_{1c} was measured on the first morning following admission. On the day of hospital discharge a standardised OGTT (75 g glucose in 200 ml water) was performed and blood glucose was measured at 0, 15, 30, 60 and 120 min. Plasma concentrations of insulin and proinsulin were analysed in fasting samples taken on the first morning after admission and during the OGTT at 0, 30 and 120 min. In addition, IGFBP-1 was analysed before and 120 min after the glucose load. The following biochemical parameters were analysed in fasting conditions on day 2 and at the day of hospital discharge: IGF-I, IGFBP-1, IGFBP-3, total cholesterol, HDL- and LDL cholesterol, triglycerides, highly sensitive C-reactive protein (hs-CRP) and cortisol. NEFA, plasminogen inhibitor activator 1 (PAI1) and fibrinogen were measured at discharge. Three and 12 months after hospital discharge, OGTT and all biochemical analyses were repeated together with collection of clinical data. All patients were followed regarding future cardiovascular events for a median period of 34 months.

The diagnosis of type 2 diabetes and IGT was based on the 1998 World Health Organization classification [17]. In the present report the presence of either of these two conditions is presented as abnormal glucose tolerance (AGT). AMI was defined according to the joint recommendations by the European Society of Cardiology and the American College of Cardiology [18].

Laboratory tests

Concentrations of IGF-I were determined in serum by RIA after separation of IGFs from IGFBPs by acid ethanol extraction and cryoprecipitation. To minimise interference

by remaining IGFBPs, des(1-3)IGF-I was used as radioligand [19]. The intra- and interassay CVs were 4 and 11% respectively. IGFBP-1 concentrations in serum were determined by RIA according to the method of Povoa et al. [20]. The sensitivity of the RIA was 3 μg/l and the intra- and interassay CVs were 3 and 10% respectively. IGFBP-3 was quantified in heparinised plasma using Immulite 2000 IGFBP-3 (DPC, Bad Nauheim, Germany), which is a solid-phase, enzyme-labelled chemiluminescent immunometric assay. The analytical sensitivity was 0.1 mg/l and the intra- and interassay CVs were 4 and 7%, respectively. A detailed description of other laboratory methods has been presented elsewhere [16].

Calculations and statistical analyses

Because IGF-I decreases with age, a standardised IGF-I score (IGF-I SD) was calculated as follows:

$$\text{IGF-I SD} = (\log[\text{IGF-I}] + 0.00625 \times \text{age} - 2.555)/0.104$$

The equation for IGF-I SD originates from the regression line of IGF-I values in 247 healthy adult subjects [21]. In Fig. 1 the IGF-I SD is converted back to the IGF-I scale by applying a common age (mean: 64 years) for the whole study population.

Insulin resistance, expressed as the homeostasis model assessment of insulin resistance (HOMA-IR), was calculated in the fasting condition as follows (1.13 converts blood glucose to plasma glucose and 6 converts pmol/l to mU/l) according to Matthews et al. [22]:

$$\text{HOMA-IR} = (\text{plasma insulin} \times \text{blood glucose} \times 1.13)/(22.5 \times 6)$$

The insulinogenic index (IGI) was calculated as the difference between plasma insulin during the OGTT at 0 and 30 min (ΔI30) divided by the difference between the corresponding glucose values (ΔG30). The adjusted IGI was corrected for insulin sensitivity by dividing it by HOMA-IR:

$$\text{Adjusted IGI} = (\Delta\text{I30}/\Delta\text{G30})/\text{HOMA-IR}$$

BMI was calculated as weight/height squared (kg/m^2). Continuous variables are presented as median (quartile 1, quartile 3) and categorical variables as percentages. Differences between groups were compared using the χ^2 test, Kruskal–Wallis test or Jonckheere–Terpstra test.

Differences in the profiles of IGF-I in patients and control subjects with respect to glucose tolerance categories were subjected to a non-parametric test for interactions based on aligned ranks (program written in Fortran) [23]. Spearman's rank correlation was calculated for pairs of continuous variables. Multiple logistic regression analyses were performed with the classification of AGT at discharge and after 12 months as dependent variables and all biochemical variables presented in Table 2, including age, sex and BMI, as candidate predictors. Predictors with a p value <0.2 were entered into a best subset selection. All possible combinations of predictors were then fitted and the models were compared using the Akaike information criterion (AIC), which is −2 times the log likelihood plus a penalty function of two times the number of predictors in the model; the smaller the value of this criterion the better the model. The rationale behind this criterion is that if the only difference between two models is that a chance predictor has been included, the values of the AIC for the two models will not differ much and would rather tend to increase. The AIC is an approximate measure of prediction accuracy.

Cox proportional hazards regression was applied to investigate the relationship between variables from the IGF-I system and a composite endpoint consisting of cardiovascular death or a major cardiovascular event (stroke, re-infarction, severe heart failure). To limit the influence of extreme values, continuous variables were log-transformed prior to analysis if there was a skewed distribution. A two-sided p value <0.05 was regarded as statistically significant. All analyses were made using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Ethical considerations

The study was approved by the regional ethics committee at Karolinska Institute and all patients and control subjects provided written and oral informed consent.

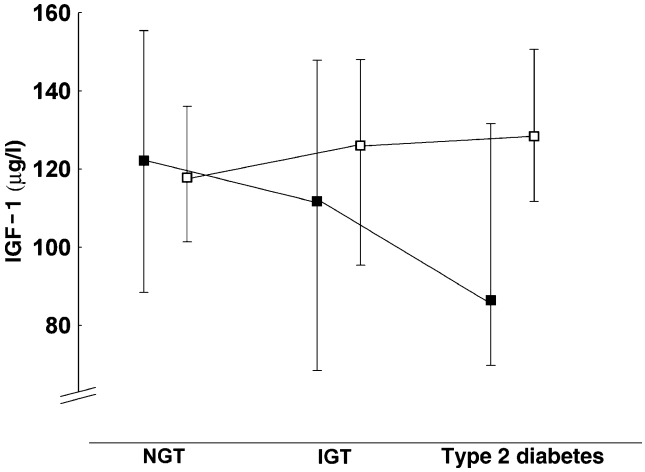

Fig. 1 Glucose tolerance profiles of age-adjusted IGF-I in patients and control subjects. *Plots* show the median (patients, *filled squares*; control subjects, *empty squares*) and interquartile range. p value for interaction <0.001

Results

Clinical and biochemical characteristics

Pertinent clinical and biochemical characteristics of patients at hospital discharge and all control subjects are presented in Table 1. The patients were more frequently smokers, had higher fasting blood glucose, 2-h blood glucose, HbA_{1c}, hs-CRP, triglycerides and proinsulin but lower HDL cholesterol and LDL cholesterol than the control subjects. A detailed discussion of these data has been published elsewhere [16].

At hospital discharge, 55 (33%) patients were classified as having NGT while 113 (67%) had AGT. Clinical and biochemical characteristics of the patients divided into glucose tolerance groups are presented in Table 2. There were no clinical differences between the patients except that those with AGT were older than those with NGT. None of the AGT patients received glucose-lowering drugs or insulin during the period of follow-up.

In patients with AGT, hs-CRP, NEFA, proinsulin and HOMA-IR were all significantly higher while beta cell function, measured as adjusted IGI, was lower compared with patients with NGT.

Among the control subjects, 120 (65%) had NGT and 65 (35%) AGT.

Insulin-like growth factor I

Patients had lower levels of IGF-I compared with control subjects (median [quartile 1, quartile 3]: 117.0 [75.0, 145.0] vs 122.0 [99.0, 143.0] μg/l, p=0.009). Table 3 contains all variables related to the IGF-I system in patients and control subjects and Table 4 contains unadjusted Spearman's rank correlations between IGF-I, IGFBP-1, IGFBP-3 and pertinent variables in patients.

Patients with AGT had lower levels of IGF-I compared with those with NGT (p=0.002) and compared with control subjects, irrespective of glucose tolerance (NGT, p<0.001; AGT, p=0.008). However, patients and control subjects with NGT did not differ in IGF-I levels. When dividing patients with AGT into those with IGT and those with type 2 diabetes and comparing these groups with patients with NGT, there was a significant difference between the three groups; the lowest IGF-I values were in the group with type 2 diabetes (median [quartile 1, quartile 3]: NGT, 128.0 [93.0, 154.0] μg/l; IGT, 99.0 [70.0, 144.5] μg/l; type 2 diabetes, 90.5 [67.0, 125.0] μg/l; p<0.001). Figure 1 presents the glucose tolerance profiles of age-adjusted IGF-I levels in patients and control subjects, which were significantly different (p<0.001 for the interaction).

Insulin-like growth factor binding proteins 1 and 3

Fasting levels of IGFBP-1 did not differ significantly between patients with NGT and AGT or between patients and control subjects (Table 3). The absolute decrease in IGFBP-1 during the OGTT was significantly smaller in patients with AGT than in the control subjects in general (NGT, p<0.001; AGT, p=0.004; Table 3), resulting in significantly higher 120-min IGFBP-1 levels in patients with AGT than in control subjects (NGT, p<0.001; AGT, p=0.048; Table 3).

Table 1 Pertinent clinical and biochemical characteristics of the patients at the time of hospital discharge and of the control subjects

Variables	Patients (n=181)	Control subjects (n=185)	p value
Age (years)	63.0 (57.0, 71.0)	64.0 (58.0, 72.0)	0.395
Sex (female; %)	31	31	0.932
Current smokers (%)	34	11	<0.001
BMI (kg/m^2)	26.2 (23.6, 29.3)	26.0 (23.6, 29.0)	0.989
Fasting blood glucose (mmol/l)	5.2 (4.7, 5.5)	5.0 (4.6, 5.4)	0.061
Blood glucose 120 min (mmol/l)	8.8 (6.9, 11.0)	7.0 (5.9, 8.4)	<0.001
HbA_{1c} at admission (%)	4.9 (4.6, 5.3)	4.6 (4.3, 5.0)	<0.001
hs-CRP (mg/l)	17.8 (8.11, 50.2)	1.7 (1.0, 3.4)	<0.001
HDL cholesterol (pmol/l)	1.0 (0.9, 1.2)	1.2 (1.0, 1.5)	<0.001
LDL cholesterol (pmol/l)	3.1 (2.5, 3.8)	3.9 (3.3, 4.5)	<0.001
Triglycerides (mmol/l)	1.9 (1.6, 2.6)	1.2 (0.9, 1.6)	<0.001
NEFA (mEq/l)	0.49 (0.35, 0.71)	0.54 (0.38, 0.71)	0.324
PAI1 activity (IU/ml)	8.9 (3.5, 18.7)	7.3 (2.6, 16.6)	0.123
Insulin (pmol/l)	53 (35, 84)	47 (32, 74)	0.126
Proinsulin (pmol/l)	5.9 (4.3, 8.9)	2.5 (1.4, 4.6)	<0.001
HOMA-IR (mU mmol/l)	2.3 (1.5, 3.6)	2.0 (1.4, 3.0)	0.071

Values are medians (quartile 1, quartile 3)
p values based on χ^2 or Kruskal–Wallis test

Table 2 Clinical and biochemical characteristics of the patients with normal and abnormal glucose tolerance

Variables	Normal glucose tolerance (*n*=55)	Abnormal glucose tolerance (*n*=113)	*p* value
Clinical characteristics			
Age (years)	60.0 (54.0, 67.0)	64.0 (57.0, 72.0)	0.007
Sex (female; %)	20	33	0.086
Current smokers (%)	13	33	0.355
BMI (kg/m^2)	26.0 (23.1, 28.3)	26.8 (24.0, 29.7)	0.133
Family history (%)			
Type 2 diabetes	17	25	0.216
Coronary heart disease	56	54	0.810
Previous diseases (%)			
Myocardial infarction	13	22	0.146
Angina pectoris	31	32	0.901
Hypertension (treated)	31	34	0.723
Hyperlipidaemia (treated)	15	17	0.701
Biochemical characteristics			
Fasting blood glucose (mmol/l)	4.8 (4.5, 5.3)	5.3 (4.8, 5.7)	n.a.
Blood glucose 120 min (mmol/l)	6.5 (5.9, 7.1)	10.3 (8.8, 11.9)	n.a.
HbA_{1c} at admission (%)	4.8 (4.5, 5.2)	5.0 (4.6, 5.3)	0.168
hs-CRP (mg/l)	12.7 (5.3, 28.0)	23.0 (9.4, 65.2)	0.002
Total cholesterol (pmol/l)	5.5 (4.6, 6.0)	5.0 (4.4, 5.8)	0.168
HDL cholesterol (pmol/l)	1.0 (0.9, 1.3)	1.0 (0.9, 1.2)	0.912
LDL cholesterol (pmol/l)	3.3 (2.6, 3.9)	3.0 (2.5, 3.6)	0.305
Triglycerides (mmol/l)	2.1 (1.5, 2.6)	1.9 (1.6, 2.6)	0.460
NEFA (mEq/l)	0.39 (0.30, 0.61)	0.57 (0.36, 0.73)	0.010
PAI1 activity (IU/ml)	6.4 (3.1, 14.4)	10.4 (4.0, 20.9)	0.106
Fibrinogen (g/l)	5.1 (4.3, 6.3)	5.4 (4.6, 7.0)	0.207
Cortisol (nmol/l)	486 (408, 609)	476 (395, 602)	0.848
Insulin (pmol/l)	52 (33, 70)	56 (37, 90)	0.113
Proinsulin (pmol/l)	4.9 (3.9, 6.8)	6.8 (4.6, 9.3)	<0.001
HOMA-IR (mU mmol/l)	2.07 (1.34, 2.71)	2.53 (1.52, 3.97)	0.024
Adjusted insulinogenic index (1/mmol^2)[a]	33.5 (21.3, 43.1)	18.7 (9.06, 31.6)	<0.001

Values are presented as median (quartile 1, quartile 3); *p* values are based on the χ^2 or Kruskal–Wallis test; if not stated otherwise, values were obtained at hospital discharge

n.a. Not applicable (used for classification)

[a]Adjusted insulinogenic index=(ΔI30/ΔG30)/HOMA-IR

Fasting levels of IGFBP-3 were significantly lower in patients compared with control subjects (median [quartile 1, quartile 3]: 3.1 [2.4, 3.7] vs 3.7 [3.7, 3.2] mg/l, $p<0.001$). Patients with AGT had lower levels of IGFBP-3 compared with those with NGT ($p=0.009$) and with controls (NGT, $p<0.001$; AGT, $p<0.001$; Table 3).

Table 3 Variables from the IGF-I system in patients and controls divided into glucose tolerance groups

Variable	Patients			Control subjects		
	NGT (*n*=55)	AGT (*n*=113)	*p* value[a]	NGT (*n*=120)	AGT (*n*=65)	*p* value[a]
IGF-I (μg/l)	128.0 (93.0, 154.0)	93.5 (68.5, 138.0)[b]	0.002	122.0 (100.0, 143.0)	124.0 (90.0, 149.0)[b]	0.971
IGF-I SD	−0.66 (−2.00, 0.35)	−1.74 (−3.00, −0.02)[b]	0.014	−0.81, (−1.43, −0.21)	−0.47 (−1.53, 0.22)[b]	0.250
IGFBP-1 baseline (μg/l)	18.0 (10.0, 28.0)	20.0 (12.0, 31.0)	0.400	16.0 (10.0, 26.0)	19.0 (12.0, 26.0)	0.345
2-h IGFBP-1 (μg/l)	10.0 (5.0, 17.0)	11.5 (7.0, 19.0)[b]	0.143	8.0 (5.0, 12.0)	9.0 (6.0, 14.0)[b]	0.155
2-h IGFBP-1/IGFBP-1 baseline	0.52 (0.44, 0.75)	0.63 (0.46, 0.74)[b]	0.218	0.50 (0.43, 0.58)	0.50 (0.44, 0.62)[b]	0.342
IGFBP-3 (mg/l)	3.4 (2.7, 3.9)	2.9 (2.2, 3.6)[b]	0.009	3.6 (3.2, 4.2)	3.8 (3.1, 4.3)[b]	0.546

Values are expressed as median (quartile 1, quartile 3); patient values were obtained at hospital discharge; *p* values are based on the Kruskal–Wallis test

[a]*p* value for the difference between glucose tolerance groups in patients and controls, respectively

[b]$p<0.05$ for the difference between patients and controls in the same glucose tolerance category

Table 4 Unadjusted correlations between IGF-I, IGFBP-1, IGFBP-3 and pertinent variables in patients expressed as Spearman's rank correlations

Variable		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Age	1.000															
2	BMI	−0.143	1.000														
3	Fasting blood glucose (mmol/l)	0.147	0.075	1.000													
4	2-h blood glucose (mmol/l)	0.210[a]	0.064	0.324[a]	1.000												
5	HbA_{1c} (%)	−0.014	0.163	0.184[a]	0.123	1.000											
6	hs-CRP (mg/l)	−0.001	−0.063	0.301[a]	0.315[a]	−0.082	1.000										
7	HDL (pmol/l)	0.124	−0.159[a]	−0.048	−0.109	0.012	−0.177[a]	1.000									
8	LDL (pmol/l)	−0.147	0.062	−0.164[a]	−0.048	0.0146	−0.148	0.108	1.000								
9	Triglycerides (mmol/l)	−0.289[a]	0.394[a]	−0.116	0.015	0.208[a]	−0.151	−0.261[a]	0.245[a]	1.000							
10	NEFA (mEq/l)	0.223[a]	0.109	−0.104	0.345[a]	0.098	−0.036	0.013	0.077	0.091	1.000						
11	Insulin (pmol/l)	−0.139	0.591[a]	0.195[a]	0.122	0.151	0.005	−0.171	0.037	0.336[a]	0.113	1.000					
12	Proinsulin (pmol/l)	0.029	0.432[a]	0.267[a]	0.257[a]	0.153	−0.061	−0.166	0.041	0.337[a]	0.121	0.567[a]	1.000				
13	Adjusted IGI ($1/mmol^2$)	0.045	−0.325[a]	−0.416[a]	−0.464[a]	−0.251[a]	−0.137	0.130	−0.097	−0.112	0.106	−0.551[a]	−0.411[a]	1.000			
14	IGF-I (μg/l)	−0.265[a]	−0.052	−0.140	−0.320[a]	−0.125	−0.268[a]	0.119	0.010	0.006	−0.224[a]	−0.000	−0.068	0.219[a]	1.000		
15	IGFBP-1 (μg/l)	0.303[a]	−0.279[a]	−0.012	−0.017	−0.011	−0.019	0.075	−0.162	−0.210[a]	0.051	−0.319[a]	−0.171[a]	0.047	−0.301[a]	1.000	
16	IGFBP-3 (mg/l)	−0.269[a]	0.109	−0.102	−0.249[a]	0.091	−0.513[a]	0.222[a]	0.228[a]	0.320[a]	−0.130	0.030	0.016	0.115	0.730[a]	−0.269[a]	1.000

[a] $p<0.05$

Prediction of abnormal glucose tolerance

Candidate predictors ($p<0.2$) for AGT at discharge in order of significance were (univariate odds ratio [95% CI], p-value): fasting blood glucose, 2.8 [1.6–5.1], $p<0.001$; ln IGF-I, 0.2 [0.1–0.5], $p=0.001$; ln hs-CRP, 1.5 [1.2–2.0], $p=0.002$; age, 1.1 [1.0–1.1], $p=0.005$; ln proinsulin, 2.5 [1.3–4.7], $p=0.006$; ln HOMA-IR, 1.9 [1.1–3.2], $p=0.014$; ln IGFBP-3, 0.2 [0.1–0.8], $p=0.018$; ln NEFA 2.2 [1.1–4.1], $p=0.020$; ln insulin, 1.7 [1.0–2.8], $p=0.071$; female sex, 1.9 [0.9–4.2], $p=0.089$; HbA_{1c}, 1.7 [0.9–3.1], $p=0.097$; ln PAI1, 1.3 [0.9–1.7], $p=0.110$; and ln fibrinogen, 2.3 [0.8–6.7], $p=0.138$.

The candidate predictors for AGT after 12 months in order of significance were: HbA_{1c}, 5.8 [2.4–14.1], $p<0.001$; fasting blood glucose, 2.9 [1.5–5.7], $p=0.002$; ln proinsulin, 2.8 [1.3, 5.9], $p=0.006$; ln IGF-I, 0.3 [0.1–0.8], $p=0.017$; ln triglycerides, 3.1 [1.1–8.7], $p=0.034$; ln HOMA-IR, 2.0 [1.1–3.6], $p=0.025$; ln PAI1, 1.4 [1.0–2.1], $p=0.041$; ln insulin, 1.8 [1.0–3.4], $p=0.059$; ln hs-CRP, 1.3 [1.0–1.7], $p=0.067$, BMI, 1.1 [1.0–1.2], $p=0.100$; and ln NEFA, 1.8 [0.8–3.7], $p=0.136$.

The final models, which are presented in Table 5, represent those with the strongest predictive value. The replacement of any of these variables did not improve the predictive power. IGF-I at hospital discharge remained a significant predictor of AGT both at the time of hospital discharge and 12 months later (OR=0.29; $p=0.022$ and OR=0.29; $p=0.034$, respectively, Table 5). Other variables in the final models, in order of significance, were fasting blood glucose, NEFA, proinsulin (predictors for AGT at discharge), HbA_{1c} and triglycerides (predictors for AGT at 12 months).

Relationships to cardiovascular events

During the period of follow-up (median: 34 months) there were a total of 39 major cardiovascular events, including 12 cases of cardiovascular death [2]. Neither IGF-I, IGFBP-1 nor IGFBP-3 at hospital discharge could predict the occurrence of these events, while IGF-I on the first morning after admission presented a hazard ratio of 0.6 (95% CI: 0.3–1.2, $p=0.133$).

Discussion

The main finding in this study was that AMI patients with newly detected AGT have lower levels of IGF-I and IGFBP-3 compared with patients with NGT and controls with NGT or AGT and that IGF-I can be used to predict the subsequent glucometabolic state.

In the present study, in patients, IGF-I was inversely related to the 120-min post-load blood glucose and early insulin secretion but not to fasting blood glucose. This supports the idea that IGF-I is related to the processes that regulate postprandial concentrations of glucose, such as first-phase insulin secretion and glucose uptake.

There was a difference between patients with AMI and normal or abnormal glucose tolerance, indicating that processes related to the acute event by itself are not the likely explanation for the decrease in IGF-I. This assumption is supported by IGF-I remaining lower among AGT patients 3 months after the infarction (median 120.0 vs 144.0 μg/l, $p=0.015$). Because of the loss of patients over time, the data at 3 months were less complete, which is the reason for basing this analysis on data obtained during the hospital phase of the study. Moreover, low levels of IGF-I at discharge predicted the classification of AGT both at discharge and after 12 months in multiple logistic regression models. Fasting blood glucose was a strong predictor of the outcome of the OGTT at discharge; HbA_{1c} did not add any predictive power to this model. In contrast, HbA_{1c} was the strongest predictor of AGT after 12 months whereas fasting blood glucose was not a significant predictor. Interestingly, IGF-I added predictive power to both the short- and the long-term model. Although other known risk factors for diabetes, such as NEFA, triglycerides and proinsulin, were included in the models, IGF-I was the only biochemical variable that remained stable in all models. Moreover, the best subset analyses, which were used to investigate the predictive values of all candidate predictors at the same time, revealed that IGF-I at discharge seemed to be a better predictor of AGT both at discharge and after 12 months compared with traditional risk factors, such as age, HDL cholesterol and LDL cholesterol, hs-CRP, BMI, insulin, proinsulin and HOMA-IR.

Table 5 Results of multiple logistic regression analyses

Variables	Odds ratio	95% CI	p value
Prediction of AGT at discharge			
Fasting blood glucose (mmol/l)	2.93	1.39–6.17	0.005
ln NEFA (mEq/l)	3.01	1.26–7.18	0.013
ln IGF-I (μg/l)	0.29	0.10–0.83	0.022
ln proinsulin (pmol/l)	2.11	0.98–4.59	0.058
Prediction of AGT after 12 months			
HbA_{1c} at admission (%)	6.79	2.08–22.22	0.002
ln triglycerides (mmol/l)	7.05	1.67–29.83	0.008
ln IGF-I (μg/l)	0.29	0.09–0.91	0.034

Odds ratios are for the classification of abnormal glucose regulation after an OGTT at discharge and after 12 months; if not stated otherwise, values were obtained at discharge; variables that were considered as candidate predictors in the multiple regression analyses (univariate p value <0.2) but did not remain significant predictors in the final models were age, sex, BMI, hs-CRP, total, HDL and LDL cholesterol, PAI1, fibrinogen, cortisol, insulin and HOMA-IR

In the present study, population-derived controls with AGT did not differ in IGF-I from controls with NGT. Likewise, patients with NGT had IGF-I values similar to those of controls with NGT.

The subdivision made in the present study of patients into groups with AGT and NGT is justified by the fact that the long-term prognosis as regards new cardiovascular events in the patients included in the present study was considerably better among those with NGT than those with either IGT or newly detected type 2 diabetes [2].

A previous evaluation of the present patients revealed that they had beta cell dysfunction [24]. It has been speculated that the combination of low IGF-I and decreased insulin function makes the patient more prone to developing AGT, causing a high postprandial glucose level [25] which has been shown to be a more apparent predictor of subsequent cardiovascular events than fasting glucose [26].

Another finding of the present study was that patients with AGT had lower levels of IGFBP-3 compared with patients with NGT and controls and that these levels correlated with IGF-I. This correlation was not surprising by itself since it is known that IGFBP-3 binds approximately 95% of total IGF-I in serum, increasing the half-life of IGF-I from a few minutes to 12–15 h. It has been hypothesised that this binding stabilises IGF-I levels in serum, creating a pool of IGF-I available during periods of stress [14]. Previous studies have reported lower levels of IGFBP-3 both in patients with type 2 diabetes [27] and in patients with coronary heart disease [10]. In this context, our findings further emphasise the involvement of the IGF-I system in the pathogenesis of these conditions.

Furthermore, inhibition of IGFBP-1 during the OGTT, measured as the percentage decrease in IGFBP-1, was significantly lower in patients with AGT compared with controls. IGFBP-1, mainly produced in the liver, is inhibited by insulin [28]. Thus, the present findings indicate increased hepatic insulin resistance in patients with AMI and AGT [29].

The adjusted IGI, recently introduced as a simple index for beta cell secretory capacity obtained from the OGTT [30], corresponds to the first-phase insulin response to glucose ingestion adjusted for insulin resistance measured as HOMA-IR. In the present study, IGF-I was related to the adjusted IGI. Furthermore, IGF-I was related to NEFA, a finding which could partly explain the relationship between IGF-I and beta cell function, since increased levels of NEFA are known to have a direct toxic effect on the beta cells [31]. Moreover, many studies have previously shown that IGF-I seems to be important for the survival of beta cells [32].

Circulating levels of IGF-I, IGFBP-1 and IGFBP-3 have been proposed as risk factors for cardiovascular disease in large population studies [9, 13, 33]. In the present study, IGFBP-1 and IGFBP-3 did not correlate to major cardiovascular events, and levels of IGF-I obtained on the first day after admission presented a non-significant trend towards a more dismal prognosis. However, the GAMI population represents a fairly small study (n=181) of patients with early glucose abnormalities and consequently there is a limited number of events (n=39). This limitation may hamper the possibility of predicting the value of IGF-I as a marker of prognosis, because of low power. Accordingly, the survival analysis from the present study needs confirmation in a larger population, possibly of AMI patients.

A limitation of IGF-I as a predictor is the wide normal range and a strong relationship to age, creating difficulties in setting limits for the definition of abnormally low levels. To overcome these difficulties we recommend the use of the standardised IGF-I (IGF-I SD) as presented in this report.

In conclusion, this study provides evidence supporting the importance of IGF-I for glucose homeostasis in patients with AMI. Furthermore, AMI patients with AGT have a lower level of inhibition of IGFBP-1 during an OGTT compared with controls, which could be interpreted as increased hepatic insulin resistance.

IGF-I may be a clinically useful tool for the glucometabolic classification of patients with AMI, allowing early institution of therapeutic modalities directed towards the metabolic disturbance. It deserves further evaluation as regards its prognostic implications.

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