Markedly Reduced Insulin-Like Growth Factor-1 in the Acute Phase of Myocardial Infarction

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OBJECTIVES

We investigated whether insulin-like growth factor-1 (IGF-1) is reduced in the early phase of acute myocardial infarction (AMI) and whether such a decrease might influence prognosis. Although insulin resistance has been reported in AMI, IGF-1 levels have not been investigated.

BACKGROUND

Insulin-like growth factor-1 protects against insulin resistance and apoptosis. Although adverse outcomes. Reduced IGF-1 preceding the rise of myocardial necrosis markers suggests a possible cardioprotective role. A compensatory increase in IGF-1 appears to occur by one year.

METHODS

We measured serum IGF-1 in 23 patients with AMI within 24 h of symptom onset and in 11 matched controls. In the first 12 patients and controls, we also measured fasting insulin, diurnal growth hormone (GH) and insulin sensitivity (assessed as glucose disappearance or T/2 after an insulin bolus), and repeated IGF-1, insulin and GH after one year. In all patients, 90-day cardiovascular death, recurrent ischemia, reinfarction, revascularization and late malignant arrhythmias were assessed.

RESULTS

The AMI patients versus controls showed markedly reduced IGF-1 (115 ± 112 vs. 615 ± 300 ng/ml, p < 0.0001) and slower T/2 (−0.98 ± 1.5 vs. −2.57 ± 1.0 mg/dl/min, p = 0.01). Low IGF-1 often preceded the rise of myocardial necrosis markers. Patients with 90-day events (n = 12) versus those without had lower IGF-1 (47 ± 54 vs. 189 ± 110 ng/ml, p < 0.0001). Acute phase GH and insulin concentrations did not differ significantly from controls. After one year, the patients' IGF-1 values had risen to 460 ± 242 ng/ml (p = 0.1 vs. controls, p < 0.0005 vs. acute phase), whereas GH levels were lower (0.2 ± 0.2 vs. 2.5 ± 2.3 ng/ml, p = 0.01) and insulin levels higher (12.5 ± 2.0 vs. 3.9 ± 2.6 μU/ml, p < 0.0001) compared with controls.

CONCLUSIONS

In the early phase of AMI, serum IGF-1 levels are markedly reduced and may contribute to adverse outcomes. Reduced IGF-1 preceding the rise of myocardial necrosis markers suggests a possible pathogenetic role. The AMI patients versus controls showed markedly reduced IGF-1 (115 ± 112 vs. 615 ± 300 ng/ml, p < 0.0001) and slower T/2 (−0.98 ± 1.5 vs. −2.57 ± 1.0 mg/dl/min, p = 0.01). Low IGF-1 often preceded the rise of myocardial necrosis markers. Patients with 90-day events (n = 12) versus those without had lower IGF-1 (47 ± 54 vs. 189 ± 110 ng/ml, p < 0.0001). Acute phase GH and insulin concentrations did not differ significantly from controls. After one year, the patients' IGF-1 values had risen to 460 ± 242 ng/ml (p = 0.1 vs. controls, p < 0.0005 vs. acute phase), whereas GH levels were lower (0.2 ± 0.2 vs. 2.5 ± 2.3 ng/ml, p = 0.01) and insulin levels higher (12.5 ± 2.0 vs. 3.9 ± 2.6 μU/ml, p < 0.0001) compared with controls.

Insulin-like growth factor-1 (IGF-1) is synthetized mainly by the liver and kidneys but also, in a paracrine and autocrine way, by endothelial and vascular smooth muscle cells and by cardiac myocytes (1,2). The main factors stimulating IGF-1 secretion are insulin and growth hormone (GH), whereas interleukin-1 and cortisol are known to inhibit its secretion (3–5). Expressed in ventricular myocytes and coronary vessels (1,2), IGF-1 can promote coronary arteriolar dilation through activation of potassium channels (6), induce the production of nitric oxide by vascular endothelium (7,8) and substantially reduce intracellular calcium (9) and infarct size in different models of myocardial ischemia (10–12). Both endogenous and exogenous IGF-1 are known to increase myocardial contractility in the short and long term (10,13,14). In healthy subjects, IGF-1 enhances insulin sensitivity and increases plasma glucose disappearance and tissue glucose utilization (15). Thus, substantial evidence suggests a possible cardioprotective role for IGF-1.

Although impaired insulin sensitivity has been described in patients with acute or healed myocardial infarction and in postischemic hibernation (16–19), the levels of IGF-1 in the early phase of acute myocardial infarction (AMI) have not been investigated. We hypothesized that IGF-1 might be decreased in the acute phase of infarction and that such a decrease might influence prognosis. Therefore, we assessed circulating IGF-1 and its main stimulants (GH and insulin), together with insulin sensitivity, in patients with AMI and in controls, and we reexamined a subgroup of patients after one year.

METHODS

Patients and controls. The study was approved by the University Ethics Committee. Inclusion criteria were age <80 years, AMI diagnosed by World Health Organization criteria, left ventricular ejection fraction on admission ≥45% and sampling for IGF-1 <24 h from symptom onset. Exclusion criteria included Killip class III or IV, body mass index >30 kg/m², systemic hypertension, diabetes mellitus (limited to the first 12 patients tested for insulin sensitivity), acromegaly, chronic inflammatory diseases, women of child-bearing potential, washout of calcium-channel blockers and <48 h for beta-adrenergic receptor blockers, treatment with drugs possibly interacting with IGF-1 and GH secretion (i.e., angiotensin-converting enzyme inhibitors, opiates, benzodiazepines, carbamazepine, sex steroids, glucocorticoids, spironolactone, bromocriptine, metoclopramide, clonidine, alpha2 or beta2 agonists, anti-
histamines, thyroxine, L-dopa, piridostigmine, sulfonylureas and their derivatives, indomethacin and insulin.

Twenty-three patients (mean age 60 ± 10 years; 17 men) admitted to our Coronary Care Unit satisfied the inclusion/exclusion criteria and were enrolled. Four of the 23 patients had type II diabetes. Thirteen received systemic thrombolysis (seven with accelerated rt-PA, six with streptokinase), three underwent primary coronary angioplasty with stenting, whereas seven did not have acute revascularization procedures for contraindications (n = 1), presentation beyond 6 h from symptom onset (n = 3) or spontaneous resolution of pain (n = 3). Clinical and laboratory data were recorded on predefined forms. Holter monitoring and two-dimensional echocardiography were done before discharge. Exercise testing was performed in all but three patients (one died in the hospital, one could not exercise and another had recurrent angina). Coronary angiography was available in all but four patients (one died and three were lost to follow-up). All patients were followed for 90 days to record the incidence of cardiovascular death, recurrent ischemia, reinfarction, late malignant arrhythmias. In controls, IGF-1, insulin and diurnal GH were measured on the same day and insulin sensitivity on the following day. Samples were centrifuged without delay at 2,000 g for 20 min; serum aliquots were deep-frozen and stored at −80°C until assayed.

**Insulin sensitivity.** Insulin sensitivity was assessed by Bonora’s insulin tolerance test (20), which offers reliable results and shows good correlations with euglycemic/hyperinsulinemic clamp values (20). The test is useful when complex clamp measurements are not feasible (e.g., in large population studies or in critical patients). For each test, an amount <5 ml of whole blood is necessary. Briefly, between 7:30 and 8:30 AM, fasting subjects received an intravenous bolus injection of regular insulin (Humulin R, Eli Lilly, Florence, Italy: 0.1 IU/kg body weight). Blood samples of 0.5 ml were drawn at 0, 3, 6, 9, 12, 15, 18, 20 and 30 min after the insulin bolus to determine glycemias. Thirty milliliters of 33% glucose in saline was administered intravenously 20 min after the insulin bolus. Insulin sensitivity was measured as blood glucose disappearance rate (T/2) between the 3rd and 15th min (mg/dl/min) (20). Glycemias were measured in real time using the “one-touch-hospital” reflectometer (Ortho-Clinical Diagnostics, Monza, Italy), previously validated by standard gluco-oxidase methods (21,22).

**IGF-1, GH and insulin determinations.** Serum concentrations of IGF-1, GH and insulin were measured by sensitive and specific immunoradiometric and immunoenzymatic assays (Active Non-Extraction IGF-1 IRMA DSL-2800, and Active Growth Hormone IRMA DSL-1900, Diagnostics System Laboratories, Webster, Texas; IMX Insulin Assay, Abbott Laboratories, Pomezia, Italy).

| Table 1. Clinical and Biochemical Variables of Patients and Controls |
|-------------------|-----------------|-----------------|-----------------|
|                   | Patients (n = 23) | Controls (n = 11) | p Value         |
| Age (yrs)         | 60 ± 10          | 54 ± 12          | 0.18            |
| Gender (M/F)      | 17/6            | 8/3             | 0.73            |
| BMI (kg/m²)       | 24.8 ± 2.7       | 22.7 ± 2.8       | 0.06            |
| Fasting glycemia (mg/dl) | 104 ± 37    | 83 ± 10          | 0.07            |
| Fasting insulinemia (µU/ml)* | 7.8 ± 7.7   | 3.4 ± 2.3        | 0.09            |
| Smokers (yes/no)  | 13/10           | 5/6             | 0.81            |
| Parental history of IHD (yes/no) | 7/16      | 4/7             | 0.96            |
| Cholesterolemia (mg/dl) | 199 ± 28  | 180 ± 15         | 0.05            |
| Mean resting blood pressure (mm Hg) | 133/74 | 124/71          | 0.26/0.57       |
| Fibrinogenemia (mg/dl) | 309 ± 106 | ND              |                 |
| C-reactive protein (mg/l) | 25 ± 33    | ND              |                 |
| Free fatty acids (mg/ml) | 0.67 ± 0.29 | ND              |                 |
| Previous angina/MI | 13/2       | 0/0             |                 |
| Infarcted territory (anterior/inferior) | 13/10 | 0/0             |                 |
| Diseased vessels at angiography (1/2/3) | 13/2/4 | 0/0             |                 |
| Ischemia on Holter monitor | 3        | ND              |                 |
| Angina in-hospital | 5          | 0               |                 |
| LV ejection fraction at discharge (%) | 45 ± 8   | ND              |                 |

*First 12 patients.
BMI = body mass index; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; ND = not determined.
The samples were tested in batches and in duplicate. The intrasample variability was <10% for all assays; the interassay coefficient of variation for IGF-1 was <12%.

**Other biochemical variables.** Fasting glycemia, cholesterolemia, fibrinogenemia, serum C–reactive protein and free fatty acids were measured the morning after admission by standard laboratory methods. For controls, glycemic and cholesterolemic values were taken from their clinical records.

**Statistical analyses.** Analyses were performed using GB-Stat 6.5 software (Dynamic Microsystems Inc., Silver Springs, Maryland). Biochemical variables showed a normal distribution by Kolmogorov-Smirnov testing; therefore, mean ± SD values are given. Continuous variables were compared by analysis of variance, and the Newman-Keuls test was used for multiple comparisons. Discrete variables were analyzed by Yates-corrected chi-square test. Relations among variables were tested by linear and multiple regression. Statistical significance was defined by a two-tailed \( p < 0.05 \).

**RESULTS**

**Baseline clinical characteristics.** Patients and controls did not differ significantly in age, gender, body mass index, fasting glycemia or fasting insulinemia (Table 1).

**IGF-1.** Within 24 h of admission, IGF-1 levels were significantly lower in patients compared with controls (115 ± 112 vs. 615 ± 300 ng/ml, \( p < 0.0001 \)). The lowest IGF-1 concentrations were recorded in the two patients who died, one in-hospital [0 ng/ml], the other within one month [1.3 ng/ml], and in three other patients with complications, one who required in-hospital revascularization [1 ng/ml], one who was readmitted for sustained ventricular tachycardia [0 ng/ml], and one whose disease progressed within one month from one to two vessels.
The 12 patients with clinical events at 90 days had lower acute phase IGF-1 (47 ± 54 vs. 189 ± 110 ng/ml, p < 0.0001) and more often values <120 ng/ml (chosen as an arbitrary cutoff, p = 0.002), compared to those with an uneventful course. Patients with and without complications did not differ significantly in age (p = 0.81), time from symptom onset to treatment (p = 0.30) or sampling (p = 0.23), admission (p = 0.32) or peak levels of creatine kinase (CK), number of diseased vessels at angiography (p = 0.22), left ventricular ejection fraction at discharge (p = 0.53), glyceremia (p = 0.21), C-reactive protein (p = 0.88), cholesterolemia (p = 0.11) and triglyceridemia (p = 0.30).

In the first 12 patients, serum levels of GH during the acute phase and at follow-up were 0.8 ± 2.1 and 0.24 ± 2.5 ng/ml, respectively, compared to 2.1 ± 2.5 ng/ml in controls (p values in Fig. 1). The corresponding values for fasting insulin were 7.8 ± 1.4 and 12.5 ± 0.5 μU/ml, compared to 3.4 ± 2.3 μU/ml in controls (p values in Fig. 1). At follow-up, GH levels were significantly lower (p = 0.02) and insulin levels significantly higher (p < 0.0001) than in controls.

Insulin sensitivity in the acute phase of infarction was significantly reduced compared with controls: glucose disappearance was -0.98 ± 1.5 mg/dl/min in patients versus -2.57 ± 1.0 mg/dl/min in controls (p = 0.01; individual curves in Fig. 3).

Correlations. Univariate regression did not reveal any significant correlations between the acute phase levels of IGF-1 and age, body mass index, glyceremia, C-reactive protein (r = -0.07, p = 0.7, Fig. 2B), fibrinogen, triglycerides, free fatty acids, admission or peak levels of CK, CK-MB or troponin T, number of episodes of ST-depression on Holter monitoring, number of anginal episodes in-hospital, echocardiographic left ventricular ejection fraction or percentage of asynergy at discharge, and number of diseased coronary vessels at angiography.

In the first 12 patients and in controls, insulin, GH and T2 values did not show significant correlations with either IGF-1 levels or with the other clinical/biochemical variables considered in the previous paragraph, except for an inverse correlation between IGF-1 and T2 values in patients with acute myocardial infarction (Table 2). The 12 patients with clinical events at 90 days had lower acute phase IGF-1 (47 ± 54 vs. 189 ± 110 ng/ml, p < 0.0001) and more often values <120 ng/ml (chosen as an arbitrary cutoff, p = 0.002), compared to those with an uneventful course. Patients with and without complications did not differ significantly in age (p = 0.81), time from symptom onset to treatment (p = 0.30) or sampling (p = 0.23), admission (p = 0.32) or peak levels of creatine kinase (CK), number of diseased vessels at angiography (p = 0.22), left ventricular ejection fraction at discharge (p = 0.53), glyceremia (p = 0.21), C-reactive protein (p = 0.88), cholesterolemia (p = 0.11) and triglyceridemia (p = 0.30).

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relation between T/2 and body mass index among controls \((r = 0.78, p < 0.01)\). On multivariate regression, this correlation persisted after correction for gender and age \((r = -0.5, p = 0.05)\).

**DISCUSSION**

**Main findings.** This study is the first to demonstrate, in a selected series of patients with AMI, a very marked decrease of serum IGF-1 levels in the very early phase of myocardial infarction, compared with the chronic phase and with healthy controls. Patients with adverse events had significantly lower IGF-1 concentrations compared to those with an uneventful course. After one year, the values of IGF-1 appeared to return within the normal range. Our data also confirm the presence of an insulin-resistant state in patients with AMI (16,17).

In agreement with our findings, a recent investigation (23) found that low IGF-1 levels in patients with AMI were related to mortality over the next two years. Because that study (23) lacked a control group, it cannot otherwise be compared to ours. Another previous study (24) of 122 individuals undergoing coronary angiography reported significantly reduced IGF-1 values in patients with significant coronary disease \((126 \pm 7 \text{ ng/ml})\) compared to those without \((162 \pm 15 \text{ ng/ml})\). The relevance of this finding in connection with our data remains to be clarified.

**IGF-1 and other hormones.** Remarkably, the striking reduction of IGF-1 was not correlated with the most powerful known IGF-1 stimulating factors, insulin and GH. Although this may be a consequence of the small patient number, it is also possible that the reduction in IGF-1 was independent of insulin and GH or was due to a transient resistance to their action.

**Primary or secondary reduction of IGF-1?** Whether the marked reduction of IGF-1 is a primary alteration or is secondary to myocardial necrosis and to the connected neurohumoral environment remains unclear. More than half our patients in whom admission samples were available for IGF-1 showed low values that preceded an increase in CK, raising the possibility of some antecedent cause for the decrease in IGF-1. Given IGF-1’s physiologic circulating half-life of \(~10\) h (25), in these patients a reduction secondary to myocardial infarction seems unlikely. The neurohumoral changes that follow infarction, including elevated cortisol, interleukin-1 and tumor necrosis factor-alpha (which inhibit IGF-1 release) (3–5) or reduced IGF-binding proteins (which can prolong the plasma half-life of IGF-1) (26,27), might have concurred to sustain the decrease in IGF-1. This is suggested by the inverse relation between IGF-1 levels and the delay separating sampling from symptom onset.

Conversely, in our study, we could not find a significant correlation between IGF-1 levels and two systemic indices of inflammation, namely fibrinogen and C-reactive protein, nor between C-reactive protein and prognosis. The latter relation is well established in patients with unstable angina, but it may not be evident in patients with AMI, in whom prodromal symptoms, response to thrombolysis and infarct size influence both C-reactive protein concentrations and clinical outcome, thus confounding the interpretation of C-reactive protein levels.

**IGF-1 and prognosis.** Because IGF-1 can coordinate a pool of actions promoting the survival of cells threatened by ischemia (maintaining cells in a differentiated state [28]; promoting arteriolar dilation [6–8], nitric oxide synthesis [7,8] and potassium-channel opening [6]; favoring glucose metabolism and the elimination of toxic metabolites [15,29,30]; increasing cardiac output [10] and myocardial contractility [13,14]; and improving the response to ischemia [1,11]), reduced IGF-1 levels may impair the recovery of metabolic cell function after AMI. Thus, reduced IGF-1 may represent a negative prognostic factor, as supported by the finding of lower IGF-1 concentrations in our patients with a complicated course.
IGF-1 and insulin sensitivity. The IGF-1 levels have been related to glucose utilization and insulin sensitivity (30,31). In the present study, patients with AMI, compared with controls, showed both reduced IGF-1 levels and decreased glucose disappearance (T/2) after insulin administration. The lack of a significant correlation between IGF-1 and T/2 values is probably a consequence of the relatively small patient population, as this relation has been observed only in considerably larger populations (32). Also, T/2 was inversely correlated with body mass index in controls but not in patients, suggesting that, in AMI, factors other than body mass index (possibly including reduced IGF-1) may contribute to impaired insulin sensitivity.

Patients with AMI showed a trend toward higher insulin values compared with controls (p = 0.09) which achieved statistical significance at follow-up (p < 0.0001); such levels are consistent with an insulin-resistant state, both in the acute (16,17) and chronic phases of infarction (18,19). Conversely, GH concentrations during AMI showed a trend toward lower values compared with controls (p < 0.08), which achieved statistical significance at follow-up (p = 0.02).

IGF-1 and cardiac metabolism. Although our data support a primary reduction of IGF-1, which myocardial necrosis can secondarily sustain, our study also suggests a dynamic relation among IGF-1, insulin and cardiac metabolism: the transient reduction of IGF-1 recorded during the very early phase of infarction might cause an acute worsening of cardiac metabolism and a transient insulin-resistant state. Impaired cardiac metabolism, in contrast, might stimulate a long-term compensatory increase in insulin secretion. Insulin, interacting with IGF-1 receptors, could then enhance IGF-1 secretion (33); as a consequence, in the chronic phase of infarction, increased insulin secretion might determine both normalized IGF-1 values and the maintenance of an insulin-resistant state (initiated during the acute phase by low IGF-1 levels). A negative feedback originating from IGF-1 and/or insulin (34) could explain the low GH levels found at follow-up.

Conclusions. Although the causes of the striking transient reduction of IGF-1 levels in the acute phase of myocardial infarction remain elusive, its frequent occurrence soon after the onset of symptoms and before elevations of myocardial necrosis markers, together with its possible pathogenetic, prognostic and therapeutic implications, deserve further investigation.

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