IGF Binding Protein 1 Predicts Cardiovascular Morbidity and Mortality in Patients With Acute Myocardial Infarction and Type 2 Diabetes

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OBJECTIVE — There are indications that the IGF system is related to both type 2 diabetes and cardiovascular disease (CVD). We tested the hypothesis that low IGF-I and high IGF-binding protein (IGFBP)-1 predict future cardiovascular mortality and morbidity in patients with acute myocardial infarction (AMI) and type 2 diabetes.

RESEARCH DESIGN AND METHODS — The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Trial recruited 1,253 patients with type 2 diabetes and AMI, of whom 575 were enrolled in a biochemical program with repeated blood sampling. Primary and secondary end points included adjudicated cardiovascular mortality and a composite of cardiovascular events (cardiovascular death, reinfarction, or stroke). Multiple Cox proportional hazard regression was used to study the relationship between the end points and the variables. Admission variables were used for the survival analysis and for blood glucose, and A1C updated mean values during follow-up were also available.

RESULTS — During a median follow-up period of 2.2 years, 131 (23%) patients died from all-cause mortality and 102 (18%) from CVD, whereas 175 patients (30%) suffered from at least one cardiovascular event. The independent predictors for cardiovascular death in the Cox regression model were (as hazard ratio [HR] [95% CI]): ln updated mean blood glucose (12.2 [5.8–25.7]), age (+5 years) (1.5 [1.4–1.7]), ln IGFBP-1 (1.4 [1.1–1.8]), and ln serum creatinine at admission (2.4 [1.3–4.2]). The model predicting cardiovascular events contained the same variables (ln IGFBP-1 at admission, 1.2 [1.0–1.4]).

CONCLUSIONS — High levels of IGFBP-1 at admission are associated with increased risk for cardiovascular mortality and morbidity in type 2 diabetes patients with AMI.

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Patients with type 2 diabetes have an increased risk for cardiovascular disease (CVD) (1). The prognosis after an acute myocardial infarction (AMI) does, indeed, already deteriorate at glucose levels in the upper normal range (2,3). The importance is underlined by the high prevalence of AMI patients with previously undetected glucose abnormalities (4–6). The increased cardiovascular risk cannot be completely explained by traditional risk factors, and mechanisms amplifying their impact are not fully understood (7). Thus, the search for novel risk factors linking type 2 diabetes and CVD is important (8).

The IGF-I system has been related to poor glucose control, and low levels of IGF-I have been related to future type 2 diabetes (9). In addition, the IGF-I system and especially low IGF-I, low IGF binding protein (IGFBP)-1, and high IGFBP-3 relate to increased cardiovascular risk (10,11). Thus, it is of interest to explore the IGF-I system as a potential novel risk factor and as a possible link between type 2 diabetes and subsequent cardiovascular complications (12). The hepatic production of IGFBP-1 is downregulated by insulin (13). Accordingly, in the general population, there is a correlation between low levels of IGFBP-1 and hyperinsulinemia, and these findings may link to an increased cardiovascular risk (14,15). However, IGFBP-1 concentrations rise during the development of type 2 diabetes, despite persisting hyperinsulinemia, indicating increased hepatic insulin resistance during disease progression (16,17). These observations were supported by van den Berghe et al. (18), who demonstrated that patients admitted to the intensive care unit with elevated levels of IGFBP-1 presented a poor prognosis regarding mortality, a finding that related to acute hepatic insulin resistance. Furthermore, there is a correlation between high levels of IGFBP-1 and cardiovascular mortality in elderly men (19), which is a finding that is in accordance with trends observed in a recently published study on AMI patients without previously known type 2 diabetes (20).

This study tests the hypothesis that low levels of IGF-I and high levels of IGFBP-1 predict future cardiovascular mortality and morbidity in patients with AMI and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2, a prospective randomized trial, compared three different management strategies in patients with type 2 diabetes and suspect AMI. An extensive description of the study design has been presented elsewhere (21). In brief, 1,253 patients were randomized to one of three study arms

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Abbreviations: AMI, acute myocardial infarction; CVD, cardiovascular disease; DIGAMI, Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction; IGFBP, IGF binding protein; RIA, radioimmunoassay.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical and biochemical characteristics of the DIGAMI 2 patients divided into availability of biochemistry*

	Biochemistry available	Biochemistry not available
n	575	678
Age (years)	69.6 (60.3–76.7)	69.7 (61.2–77.0)
Male sex	385 (67)	451 (67)
BMI (kg/m^2)	27.6 (25.1–30.7)	27.7 (25.3–31.1)
Diabetes duration (years)	5.3 (0.6–12.3)	6.1 (1.1–11.9)
Blood pressure (mmHg)		
Systolic	130 (116–150)	130 (120–150)
Diastolic	73 (62–84)	80 (70–88)
Previous medical history		
Myocardial infarction	192 (33)	230 (34)
Angina pectoris	266 (46)	296 (44)
Heart failure	103 (18)	117 (17)
Hypertension	289 (50)	318 (47)
Hyperlipidemia	180 (31)	215 (32)
Current smoker	139 (24)	160 (24)
Medication prior to admission		
Insulin	182 (32)	208 (31)
Metformin	141 (25)	167 (25)
Glibenclamide	143 (25)	131 (19)
β-Blockers	208 (36)	248 (37)
Aspirin (75 mg)	159 (28)	170 (25)
ACE inhibitor	178 (31)	211 (31)
Lipid lowering	160 (28)	188 (28)
Randomized treatment group		
Group 1	211 (37)	263 (39)
Group 2	223 (39)	250 (37)
Group 3	141 (25)	164 (24)
Biochemistry at admission		
Blood glucose (mmol/l)	11.9 (9.4–15.1)	12.6 (10.0–15.3)
A1C (%)	7.0 (6.1–8.4)	7.0 (6.1–8.3)
Serum creatinine (mmol/l)	91 (79–112)	98 (83–118)
Serum cholesterol (mmol/l)	5.0 (4.3–5.9)	5.2 (4.3–5.9)
Serum triglycerides (mmol/l)	1.7 (1.2–2.6)	1.7 (1.2–2.6)

Data are *n* (%) or median (quartile 1–quartile 3). All biochemistry refers to admission values if not otherwise stated.

and received *1*) a 24-h insulin-glucose infusion followed by subcutaneous insulin-based long-term glucose control (group 1, $n = 474$), *2*) the same initial treatment followed by a glucose-lowering treatment according to local practice (group 2, $n = 473$), or *3*) a glucose-lowering treatment according to local practice (group 3, $n = 306$). The objective was to compare total mortality and morbidity between these management strategies. There was no significant difference in the primary (total mortality) or secondary (mortality, nonfatal myocardioal infarction, or stroke) end point. Increasing mean plasma glucose during follow-up was, however, an independent predictor of fatal outcome but could not explain all morbidity (21).

A total of 575 of the DIGAMI 2 patients participated in a biochemistry program, with repeated blood sampling at admission before initiation of the glucose-insulin infusion and fasting at discharge and after 3 and 12 months. Blood glucose and A1C were collected at admission (blood glucose also after 24 h), after 3 and 6 months, and thereafter every 6 months during the follow-up. The median study duration was 2.1 years (quartile 1, 1.0; quartile 3, 3.0), and no patient was lost to follow-up.

Laboratory analyses

Blood glucose was analyzed locally as whole blood glucose in millimoles per liter, whereas A1C was analyzed in a core laboratory (Department of Laboratory Medicine, Malmö Hospital, Malmö, Sweden) by high-performance liquid chromatography on capillary blood applied on filter paper with an upper normal limit of 5.3% (Boehringer Mannheim Scandinavian, Bromma, Sweden). Concentrations of total serum IGF-I were determined by radioimmunoassay (RIA) in micrograms per liter after separation of IGFs from IGFBPs by acid ethanol extraction and cryoprecipitation. To minimize interference of remaining IGFBPs, des(1–3) IGF-I was used as radioligand (22). IGFBP-1 concentrations in serum were determined by RIA according to the method of Póvo et al. (23). The sensitivity of the RIA was 3 μg/l, and the cardiovascular intra- and interassays were 3 and 10%, respectively.

Events during follow-up

In this analysis, cardiovascular mortality and a composite of cardiovascular events (cardiovascular death, reinfarction, or stroke) served as primary and secondary end points, respectively. An independent adjudication committee composed of experienced cardiologists adjudicated the events. They were provided with death certificates, autopsy reports, hospital and laboratory records, and electrocardiograms but did not have any information on group belongings.

Statistical analyses and calculations

BMI was calculated as the weight in kilograms divided by the square of the height in meters. Updated mean blood glucose was calculated as a simple mean value of all samples available (a maximum of nine occasions: at admission, at 24 h, and at 3, 6, 12, 18, 24, 30, and 36 months) during the complete period of follow-up until an event occurred. As IGF-I decreases with age, a standardized IGF-I score was also calculated, as previously described (24). Continuous variables are presented as median (quartile 1 and quartile 3) and categorical variables as percentages. Differences between groups were compared by the Jonckheere-Terpstra's test or the χ^2 test. Multiple Cox proportional hazard regression was applied to investigate relations between candidate predictors from Table 2 with a P value <0.2 and the end point. All possible combinations of predictors were fitted into a best-subset analysis, and the models were compared using the Akaike information criterion. To limit the influence of extreme values, all continuous variables were log transformed before analysis. A two-sided P

Table 2—*Clinical and biochemical characteristics of patients divided into tertiles of IGFBP-1 at admission*

	IGFBP-1 tertiles (μg/l)			
	3.0–24.0	25.0–42.0	43.0–677	*P*
n	165	169	167	
Age (years)	65.3 (57.3–73.3)	68.8 (60.5–75.6)	73.0 (65.9–79.6)	<0.001
Male gender	121 (73.3)	123 (72.8)	101 (60.5)	0.017
BMI (kg/m^2)	29.0 (26.7–32.2)	27.5 (25.4–30.2)	26.5 (23.7–29.4)	<0.001
Diabetes duration (years)	5.2 (1.2–12.4)	5.4 (0.7–12.5)	5.1 (0.4–13.5)	NS
Blood pressure (mmHg)				
Systolic	134 (120–150)	130 (116–145)	125 (112–145)	0.002
Diastolic	76 (67–85)	72 (65–82)	70 (60–80)	<0.001
Current smoker	36 (21.8)	48 (28.4)	34 (20.4)	NS
Medication prior to admission				
Insulin	53 (32.1)	54 (32.0)	53 (31.7)	NS
Metformin	54 (32.7)	45 (26.6)	24 (14.4)	<0.001
Glibenclamide	46 (27.9)	41 (24.3)	44 (26.4)	NS
β-Blockers	63 (38.4)	69 (40.8)	54 (32.3)	NS
Aspirin (75 mg)	50 (30.3)	52 (30.8)	38 (23.4)	NS
ACE inhibitor	51 (30.9)	53 (31.4)	45 (27.0)	NS
Lipid owering	53 (32.1)	48 (28.4)	41 (24.6)	NS
Randomized treatment group				
Group 1	62 (37.6)	54 (32.0)	66 (39.5)	NS
Group 2	65 (39.4)	70 (41.4)	59 (35.3)	NS
Group 3	38 (23.0)	45 (26.6)	42 (25.2)	NS
Biochemistry admission				
Blood glucose (mmol/l)	11.4 (9.0–14.0)	11.8 (9.3–14.6)	12.8 (10.0–16.8)	<0.001
A1C (%)	6.8 (6.1–8.1)	7.0 (6.1–8.3)	7.2 (6.0–8.4)	NS
Serum creatinine (mmol/l)	84 (75–97)	94 (81–109)	100 (84–130)	<0.001
Serum cholesterol (mmol/l)	5.1 (4.2–5.8)	5.0 (4.3–6.0)	5.0 (4.3–6.0)	NS
Serum triglycerides (mmol/l)	2.1 (1.4–3.0)	1.7 (1.1–2.5)	1.6 (1.1–2.3)	<0.001
Serum IGF-I (μg/l)	141 (112–169)	124 (93–154)	106 (74–131)	<0.001
Serum IGF-I (SD)	0.0 (−1.1 to 0.9)	−0.4 (−1.6 to 0.5)	−1.0 (−2.1 to 0.08)	<0.001

Data are *n* (%) or median (quartile 1–quartile 3). *P* values are based on Jonckheere-Terpstra's test or χ^2 test. NS, not significant.

value <0.05 was regarded as statistically significant. No adjustments for multiple testing have been performed. All analyses were done using SAS (version 9.1.3; SAS Institute) and Statistica 7.0 (StatSoft).

The study conformed to good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment.

RESULTS

Baseline characteristics

As outlined in Table 1, the present study population from DIGAMI 2 (n = 575) was similar to the group where biochemistry was not available (n = 678), apart from slightly lower blood glucose and lower creatinine at admission. In brief, 67% of the patients were men, the median age was 69.6 years (quartile 1, 60.3; quartile 3, 76.7), 24% were smokers, and the median BMI was 27.6 kg/m^2 (quartile 1, 25.1; quartile 3, 30.7). Thirty-three percent of patients had a history of previous AMI, and the median duration of the type 2 diabetes was 5.7 years (quartile 1, 1.1; quartile 3, 12.8).

Baseline characteristics of IGFBP-1 tertiles

Pertinent clinical and biochemical characteristics of the patients divided into tertiles of IGFBP-1 at admission are presented in Table 2. The number of patients in the different tertiles was equally distributed regarding randomized treatment groups. Patients in the highest tertile were older, more frequently female, had a lower BMI, and had lower blood pressure. In addition, they presented higher admission levels of blood glucose and creatinine but lower levels of triglycerides and IGF-I compared with those in the lowest tertiles. Furthermore, the patients in the highest IGFBP-1 tertile were less often treated with metformin before the study.

Prediction models for cardiovascular mortality and morbidity

During the follow-up period, 131 (23%) patients died from all-cause mortality; of these, 102 (78%) patients died from CVD. A total of 175 (30%) patients suffered from at least one cardiovascular event during the follow-up. There were no significant differences in cardiovascular death or the occurrence of cardiovascular events among the three randomized treatment groups.

Univariate survival analysis of the IGF-I system showed that the ln of IGF-I at admission, discharge (days 4–5), 3 months, or 12 months was not related to cardiovascular death (HR_{adm} 0.8, P = 0.206; HR_{dis} 0.9, P = 0.670; HR_{3M} 0.9, P = 0.824; and HR_{12M} 1.0, P = 0.982), whereas levels of ln IGFBP-1 at admission, discharge, and 3 or 12 months were related to cardiovascular death (HR_{adm} 1.9, P < 0.001; HR_{dis} 1.8, P = 0.002; HR_{3M} 1.5, P = 0.059; and HR_{12M} 2.8, P = 0.004).

Table 3—*Multiple prediction models for cardiovascular mortality and morbidity*

	χ^2 test	HR	95% CI	*P*
Cardiovascular death				
Model 1				
Age (+5 years)	44.5	1.6	1.4–1.8	<0.001
IGFBP-1 baseline (+ln)	13.6	1.5	1.2–1.9	<0.001
Creatinine baseline (+ln)	6.3	2.0	1.2–3.6	0.012
Model 2				
Age (+5 years)	44.5	1.5	1.4–1.7	<0.001
Updated mean blood glucose (+ln)	43.9	12.2	5.8–25.7	<0.001
IGFBP-1 baseline (+ln)	8.9	1.4	1.1–1.8	0.003
Creatinine baseline (+ln)	8.4	2.4	1.3–4.2	0.004
Cardiovascular event (cardiovascular death, reinfarction, or stroke)				
Model 1				
Age (+5 years)	39.3	1.3	1.2–1.5	<0.001
Creatinine baseline (+ln)	10.6	2.0	1.3–3.1	0.001
IGFBP-1 baseline (+ln)	4.9	1.2	1.0–1.4	0.028
Model 2				
Updated mean blood glucose (+ln)	60.6	10.2	5.7–18.2	<0.001
Age (+5 years)	39.9	1.3	1.2–1.4	<0.001
Creatinine baseline (+ln)	16.2	2.4	1.6–3.7	<0.001
IGFBP-1 baseline (+ln)	2.8	1.2	1.0–1.4	0.096

All HRs for biochemistry refer to the ln of the variable. Candidate predictor with *P* values <0.2 that were eliminated in the best subset analyses were admission blood glucose, A1C, IGF-I, serum cholesterol, serum triglycerides, BMI, sex, blood pressure, smoking status, and previous coronary disease history.

Analyses of the secondary end point showed that ln IGF-I at admission and 3 months was significantly related to future cardiovascular events but the discharge and 12-month levels were not (HR_{adm} 0.7, $P = 0.026$; HR_{dis} 0.8, $P = 0.190$; HR_{3M} 0.5, $P = 0.012$; and HR_{12M} 0.8, $P = 0.740$). Ln IGFBP-1 was significantly related to cardiovascular events at all occasions (HR_{adm} 1.5, $P < 0.001$; HR_{dis} 1.5, $P = 0.002$; HR_{3M} 1.5, $P = 0.012$; and HR_{12M} 1.7, $P = 0.035$).

In the best subset analysis of predictors at admission (Table 3), ln IGFBP-1 at admission remained significantly related to cardiovascular death (HR 1.5, $P < 0.001$) and to cardiovascular event (HR 1.2, $P = 0.028$). Age and ln creatinine at admission also remained significant. The predictive power of the models increased when updated mean blood glucose was entered into the models as an explanatory variable, and ln updated mean blood glucose was correlated to both cardiovascular death and cardiovascular event (HR 12.2, $P < 0.001$ and HR 10.2, $P < 0.001$). Candidate predictors with *P* values <0.2 not included in the final models were admission blood glucose, IGF-I, BMI, sex, smoking status, and previous coronary disease history.

Survival curves for tertiles of IGFBP-1 adjusted for updated mean blood glucose, age, and creatinine are presented in Fig. 1*A* and *B*.

CONCLUSIONS — The main finding from the present study is that high levels of IGFBP-1 at admission, discharge, and after 3 and 12 months are all related to subsequent cardiovascular morbidity and mortality in patients with AMI and

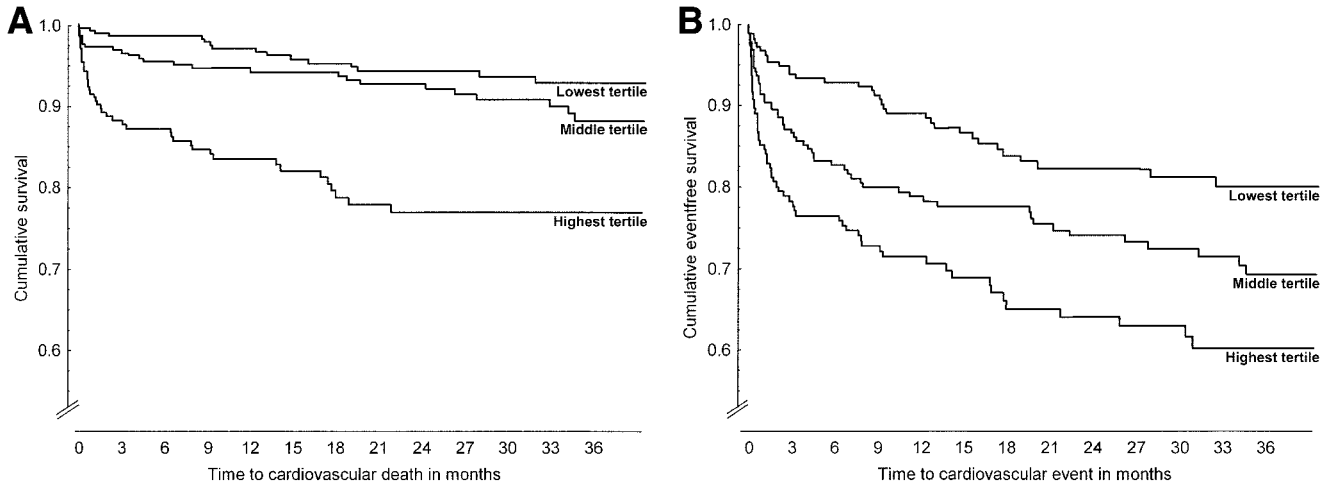

Figure 1— *Kaplan-Meier curves of tertiles of IGFBP-1 during follow-up related to cardiovascular death* (A) *and cardiovascular event* (B) *(cardiovascular death, reinfarction, or stroke). All curves are adjusted for updated mean blood glucose, age, and creatinine.*

type 2 diabetes. Many fatal and other events occurred relatively soon after hospital discharge, with some already during hospitalization. From a clinical point of view, this makes IGFBP-1 at admission an interesting prognostic predictor, which also remained after multiple adjustment.

IGFBP-1 has been described as the most likely acute regulator of IGF-I actions (25), and the hepatic production of IGFBP-1 is upregulated in response to proinflammatory cytokines (26) and physiological stresses (27) and is downregulated by insulin (13). There are several potential links between high levels of IGFBP-1 and increased cardiovascular risk. One is that the high affinity binding of IGFBP-1 to IGF-I, which prevents the activation of receptor signaling, may attenuate known beneficial effects of IGF-I, such as enhanced glucose uptake, improved insulin sensitivity, and decreased hepatic glucose production (28). Other mechanisms of IGF-I that could be disrupted by the inhibition of IGFBP-1 are the stabilization of atherosclerotic plaques (29) and beneficial effects on arterial blood flow and endothelial function (30). However, IGF-I was not significantly related to the outcome after multivariate analysis. The univariate relationships between IGF-I and cardiovascular events at admission and 3 months could possibly indicate a correlation to age or the glucometabolic state because age and the updated mean value of blood glucose were, by far, the strongest predictors in the multiple analyses.

Although several reports from cohort studies have presented relationships between low IGF-I and CVD, it is only the Danish Monitoring Trends in Cardiovascular Diseases (DAN-MONICA) Study, based on a nationwide population registry in Denmark, that reported a significant relation between coronary heart disease events and IGF-I measured before the event. It was, however, only the combination of a low IGF-I and a high IGFBP-3 that predicted future events (11). We recently investigated patients with AMI with newly detected abnormal glucose tolerance. They had low levels of IGF-I and high levels of IGFBP-3. This combination did not, however, relate to a worse prognosis (20). In addition, although most studies measured total IGF-I and demonstrated relationships to type 2 diabetes (9) and to CVD (11), some studies indicated that the free fraction of IGF-I was the most valuable measure, which also related to an increased cardiovascular risk (31). Free IGF-I was not measured in the present study due to the lack of a reliable commercial method. However, there is a strong inverse correlation between free IGF-I and IGFBP-1 (32). Low levels of free IGF-I would therefore be expected in patients with high levels of IGFBP-1.

IGFBP-1 is a marker for hepatic insulin resistance (33). This can be explained by the fact that when hepatic insulin resistance increases, the hepatic suppression of IGFBP-1 decreases, which causes an increase in IGFBP-1 concentrations. Critically ill patients with elevated levels of IGFBP-1 are unresponsive to administered insulin and have a worse long-term prognosis than patients with low levels of IGFBP-1 (34). Furthermore, patients with severe hepatic cirrhosis have demonstrated high fasting levels of IGFBP-1 that are accompanied by elevated insulin levels. Interestingly, these patients had a less pronounced insulin-mediated suppression of IGFBP-1 during an oral glucose tolerance test (35). A similar pattern has been described in patients with AMI and abnormal glucose tolerance among whom the suppression of IGFBP-1 was significantly decreased during an oral glucose tolerance test, a finding that has been interpreted as increased hepatic insulin resistance (20).

Patients with high levels of IGFBP-1 were less well glucometabolically controlled, as indicated by their higher admission blood glucose and lower levels of IGF-I. In addition, these patients had lower BMI, blood pressure, and triglycerides—correlations already reported on but interpreted as an inverse correlation between IGFBP-1 and cardiovascular risk factors (15).

An adaptation correlation to physiological stress is probably part of the explanation for the present findings. After a 30-min infusion of epinephrine in healthy men, levels of IGFBP-1 increased but returned to basal ~2 h later (36). It is unlikely that the present results may be completely explained by acute stress during the early phase of an AMI since morbidity and mortality continued to relate to the levels of IGFBP-1 during follow-up.

The link between IGFBP-1 and proinflammatory cytokines has recently been demonstrated (26), and because both type 2 diabetes and CVD are conditions with increased inflammatory activity, this correlation must be considered inevitable. We have not analyzed inflammation factors; therefore, we could not adjust for this in the analyses. However, in a recently published (20) study from our group, IGFBP-1 in the acute phase of an AMI did not correlate to C-reactive protein, and as mentioned previously, the risk continues to be higher during follow-up; thus, the acute inflammatory response from the AMI cannot explain the present findings.

Elevated levels of IGFBP-1 may theoretically be a result of chronic insulin deficiency. However, it is likely to assume that patients suffer from various stages of insulin resistance, and one-third of the patients were treated with insulin before the study. Thus, any correlations between insulin levels and IGFBP-1 in the present population would be very difficult to interpret.

In conclusion, this study shows that high levels of IGFBP-1 in AMI patients with type 2 diabetes are related to substantially increased cardiovascular mortality and morbidity. We suggest that this may be due to hepatic insulin resistance and poor metabolic control, and IGFBP-1 could be a novel marker for discovering high-risk patients in this particular group.

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