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Prognostic role of the glucometabolic status assessed in a metabolically stable phase after a first acute myocardial infarction: the SHEEP study

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Abstract. Janszky I, Hallqvist J, Ljung R, Ahlbom A, Hammar N (Karolinska Institute, Stockholm, Sweden, Institute of Behavioural Sciences, Semmelweis University, Budapest, Hungary, Stockholm Centre for Public Health, Stockholm; Karolinska Institute, Stockholm; Karolinska Institute, Stockholm; and AstraZeneca R&D, Mölndal; Sweden). Prognostic role of the glucometabolic status assessed in a metabolically stable phase after a first acute myocardial infarction: the SHEEP study. *J Intern Med* 2009; **265**: 465–475.

Objectives. Our objective was to examine fasting glucose and insulin levels in patients surviving 3 months after a first AMI in relation to long-term prognosis.

Design. A total of 1167 consecutive patients between 45 and 70 years with a first nonfatal AMI underwent a standardized clinical examination and were followed for a mean of 8 years for total and cardiac mortality and hospitalization for nonfatal cardiovascular disease. Impaired fasting glucose (IFG) was defined as fasting glucose between 5.6 and 7 mmol L^{-1} and a level ≥7 mmol L^{-1} as newly detected diabetes. Patients with a fasting glucose level <5.6 mmol L^{-1} and without a history of diabetes were classified as normoglycemic (NG). An estimate of insulin resistance was calculated using the homeostasis model assessment (HOMA).

Results. We recorded 219 deaths, 121 deaths from cardiac causes, during the follow-up period. After adjustment for several potential confounders, hazard ratios for total mortality were 1.36 (95% confidence interval 0.93–1.99, $P = 0.11$), 2.27 (1.26–4.09, $P = 0.006$) and 2.15 (1.43–3.21, $P < 0.001$) for patients with IFG, newly detected diabetes and history of diabetes when compared to the NG group. Cardiac mortality, risk of hospitalization for recurrent nonfatal AMI, stroke or heart failure generally showed a similar pattern to that of total mortality. Insulin level and HOMA values were also associated with increased risk for recurrent events.

Conclusions. We confirmed that both known and newly detected diabetes is a strong prognostic factor in AMI. In addition, our findings suggest that glucose levels below the diabetes cut off value might also predict poor long-term prognosis when assessed in a metabolically stable phase.

Keywords: acute myocardial infarction, diabetes, glucose, HOMA, insulin, prognosis.

Introduction

Diabetes mellitus predicts coronary heart disease (CHD) morbidity and mortality in initially healthy populations and adverse outcomes in existing CHD [1–4]. Diabetic patients without previous acute myocardial infarction (AMI) have as high a risk of AMI as nondiabetic patients with previous myocardial infarction [5, 6]. It was also established that the relationship between glucose levels and cardiovascular risk in population based studies extends below the diabetic threshold [2]. In AMI, increased admission glucose level or increased fasting glucose level shortly after the onset of symptoms seems to predict prognosis even in nondiabetic patients [7–14]. However, it is not clear whether the elevated glucose level in the early, instable phase of the myocardial infarction reflects abnormal glucose metabolism or is a marker of stress and/or severity of myocardial damage [7]. Although, it has been demonstrated that oral glucose test at hospital discharge predicts the long-term glucometabolic state [15], the prognostic importance of impaired fasting glucose (IFG) evaluated at a metabolically stable phase after an AMI is not known. Detection of a possible relationship between IFG and prognosis in a stable phase would highlight the importance of even moderate disturbances in the glucose metabolism in AMI patients. On the other hand, a failure to detect such a relationship would indicate that glucose elevation below the diabetic threshold in the acute state is more related to the extent of the myocardial damage than to glucose homeostasis. Moreover, information on the possible role of insulin and insulin resistance after an AMI is sparse. In this study, we examined the role of fasting glucose, insulin levels, newly detected and known diabetes in patients surviving at least 3 months after a first AMI and follow-up for 8 years.

Methods

We followed individuals enrolled as nonfatal AMI cases in the Stockholm Heart Epidemiology Program (SHEEP), a population-based case–control study of incident AMI [16]. The study base comprised all Swedish citizens living in the Stockholm County, 45–70 years of age, free of previous clinically diagnosed AMI. Male cases were identified during a 2-year period (1992–93) and female cases during 3 years (1992–94). Cases were identified through a special organization at the ten emergency hospitals in the region. Criteria for AMI included (i) certain symptoms according to case history information, (ii) specified changes in blood levels of the enzymes CK and LD, (iii) specified ECG-changes and (iv) autopsy findings. The diagnosis 'acute myocardial infarction' required two of the criteria (i–iii) to be met *or* that autopsy findings showed myocardial necrosis of an age compatible with the time of disease onset. Later comparison with a population-based incidence register indicated close to complete ascertainment of all first AMIs [17].

A questionnaire was administered in the in-hospital period. In a stable metabolic phase, 3 months after the AMI onset, a health examination measuring blood pressure, height and weight with a blood sampling was undertaken.

Assessment of the glucometabolic status

Glucose and insulin levels were determined from fasting blood samples collected at the health examination as described earlier [16, 18]. An estimate of insulin resistance was calculated using the homeostasis model assessment (HOMA) as follows: insulin resistance = fasting glucose*fasting insulin/22.5 [18]. *Impaired fasting glucose* (IFG) was defined according to the current ADA recommendation [19], i.e. fasting glucose between 5.6 and 7 mmol L^{-1}. Patients with fasting glucose ≥7 mmol L^{-1} were classified as having *newly detected diabetes*. Subjects were classified as having a *history of diabetes* if case history information from the questionnaire stated a diagnosis of diabetes with insulin or drug treatment or diet control. Patients with a fasting glucose level <5.6 mmol L^{-1} and without a history of diabetes were classified as *normoglycemic* (NG). Insulin and HOMA values were categorized as quartiles in the subsequent analyses. A total of 1167 patients surviving 3 months had valid data on the glucometabolic status.

Covariates

Lipids, coagulation factors and inflammatory markers were determined from blood samples undertaken during the health examination as previously described elsewhere [16, 18]. *Hypertension*. Hypertension was defined as (i) being on antihypertensive drug therapy, for the reason of hypertension, when included in the study; (ii) a history of regular antihypertensive drug therapy during the last 5 years (or a part of that time); (iii) a systolic blood pressure ≥170 mmHg or a diastolic blood pressure ≥95 mmHg. Blood pressure values were the mean of two readings in supine position after 5 min rest. *Obesity*. Subjects over 30 kg m^{-2} were classified as being obese. *Physical inactivity*. Questions about physical activity included conditions at work, household and homework and leisure time activities. In the present paper, subjects who reported inactive leisure time including occasional walks, during the last 5–10 years were categorized as 'exposed' to physical inactivity. *Smoking*. Subjects who had never smoked regularly (i.e. for at least 1 year) were considered as never-smokers. Subjects, who smoked when included into the study, or had stopped smoking within the last 2 years, were classified as smokers. Subjects, who had stopped smoking for more than 2 years before inclusion, were classified as ex-smokers. *Socio-economic position*. As a measure of socio-economic position, we classified educational attainment as mandatory school only versus high school, college or university.

Follow-up

The centralized health care system in Sweden provides virtually complete follow-up information for all patients by matching their unique ten digit person identification numbers to health care registers. The average follow-up from the AMI was 8 years. All-cause and cardiac mortality was used as a primary end-point as provided by the National Cause-of-death Register. Patients were also followed for nonfatal AMI using the Swedish Myocardial Infarction Register [20]. Information on hospitalization for heart failure (ICD-9 and 10 codes were 428, I50 respectively) and stroke (431, 434, I64, I63, I61) was derived from the national Swedish Hospital Discharge Register [21–23]. Follow-up was closed on December 1st 2001.

Statistics

We used un-, gender/age- and multivariable-adjusted Cox proportional hazard models to examine the prognostic role of the glucometabolic status. Patients with a history of diabetes, newly detected diabetes or IFG were compared to normoglycemic patients. Insulin and HOMA were analyzed as quartiles with the lowest quartile as the reference category. Selection of covariates in the multiadjusted models was based (i) on previous knowledge about their potential relationship with the measures of glucometabolic status and outcome and (ii) on the change in the point estimate strategy [24]. Proportionality of hazards was investigated visually by log–log curves and by formal tests of interaction with time. We found no evidence against the assumption that the risks associated with different levels of the glucometabolic status are stable over time. Statistical analyses were performed using SAS 9 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 presents the characteristics of patients with NG, IFG, newly detected diabetes and history of diabetes respectively. Patients with newly detected diabetes were the youngest and patients with history of diabetes were the oldest. Patients with NG had lower BMI and, in general, a more favourable lipid profile, lower prevalence of sedentary lifestyle and hypertension, higher education and lower levels of fibrinogen, CRP, insulin and HOMA than patients in the rest of the groups. Overall, these values were the highest amongst patients with newly detected or old diabetes and IFG was an intermediate group.

Table 2 shows unadjusted proportions of participants who died, sustained nonfatal AMI or were hospitalized for heart failure or stroke during follow-up. All-cause and cardiac mortality gradually increased across the groups of patients with NG, IFG, newly detected and old diabetes. Nonfatal reinfarction

Table 1 Characteristics of the study participants according to their fasting glucose values and diabetic status

Glucose	≤5.6 mmol L^{-1}	5.6–7 mmol L^{-1}	>7 mmol L^{-1}	History of diabetes
n	687	251	68	161
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	59.3 (7.3)	59.6 (7.1)	58.1 (7.6)	60.3 (7.0)
BMI (kg m^{-2})	26.0 (3.8)	27.8 (4.0)	28.3 (4.7)	28.1 (4.7)
Peak CK (ng mL^{-1})	28.7 (28.0)	28.2 (26.3)	27.0 (28.0)	23.1 (24.9)
Serum levels of				
Total cholesterol	6.15 (1.11)	6.38 (1.18)	6.28 (1.52)	6.12 (1.29)
Triglycerides (mmol L^{-1})	1.79 (1.09)	2.21 (1.21)	3.29 (3.51)	2.36 (1.78)
HDL cholesterol (mmol L^{-1})	1.11 (0.31)	1.05 (0.31)	0.99 (0.29)	1.03 (0.28)
Lipoprotein(a) (g L^{-1})	0.31 (0.36)	0.27 (0.34)	0.25 (0.30)	0.28 (0.36)
Apo A (g L^{-1})	1.41 (0.26)	1.39 (0.25)	1.37 (0.30)	1.34 (0.21)
Apo B (g L^{-1})	1.62 (0.37)	1.68 (0.38)	1.75 (0.50)	1.64 (0.48)
Fibrinogen (g L^{-1})	3.68 (0.85)	3.81 (0.91)	3.87 (0.97)	3.93 (0.87)
hsCRP (mg L^{-1})	3.79 (7.18)	4.03 (6.11)	5.13 (7.91)	4.10 (4.58)
Insulin (μU mL^{-1})	9.7 (6.0)	14.7 (9.5)	23.0 (14.7)	23.8 (20.5)
HOMA	2.11 (1.40)	3.99 (2.66)	9.56 (8.34)	9.26 (8.62)
	n (%)	*n* (%)	*n* (%)	*n* (%)
Male gender	474 (69.0)	188 (74.9)	45 (66.2)	107 (66.5)
Hypertension	240 (36.2)	93 (38.6)	23 (41.8)	87 (54.4)
Obesity (BMI > 30 kg m^{-2})	90 (13.1)	62 (24.7)	21 (30.9)	51 (31.7)
Sedentary Lifestyle	274 (41.5)	120 (50.2)	32 (57.1)	83 (51.9)
Cigarette smoking				
Nonsmokers	179 (26.8)	49 (20.3)	9 (16.1)	50 (31.1)
Previous smokers	170 (25.5)	55 (22.7)	10 (17.9)	57 (35.4)
Current smokers	319 (47.8)	138 (57.0)	37 (66.1)	54 (33.5)
High School/College or University	223 (33.6)	74 (30.6)	17 (30.4)	43 (27.2)
Index hospitalization				
Q wave infarction	368 (58.0)	136 (58.6)	39 (60.9)	78 (55.3)
Ventricular tachycardia	57 (8.6)	18 (7.3)	2 (3.2)	9 (5.8)
Killip classification				
1	424 (72.7)	153 (72.2)	44 (72.1)	92 (65.3)
2	133 (22.8)	52 (24.5)	12 (19.7)	39 (27.7)
3	20 (3.4)	7 (3.3)	3 (4.9)	10 (7.1)
4	6 (1.0)	0 (0.0)	2 (3.3)	0 (0)
Regular medication use				
Beta-blockers	549 (79.9)	205 (81.7)	50 (73.5)	109 (67.7)
Aspirin	507 (73.8)	194 (77.3)	49 (72.1)	109 (67.7)
Ca antagonist	57 (8.3)	18 (7.2)	7 (10.3)	22 (13.7)
Diuretics	214 (25.7)	35 (33.7)	19 (27.9)	78 (28.8)
Digitalis	16 (2.3)	7 (2.8)	3 (4.4)	9 (5.6)
ACE inhibitors	78 (11.4)	18 (7.2)	8 (11.8)	22 (13.7)

BMI, body mass index; HDL, high density lipoprotein; hsCRP, high sensitivity C-reactive protein; PAI-1, plasminogen activator inhibitor 1; tPA, tissue plasminogen activator; HOMA, homeostatis model assessment, insulin resistance = fasting glucose × fasting insulin/22.5.

Table 2 Adverse outcomes during the follow-up amongst SHEEP patients according to their fasting glucose values and diabetic status

Glucose	≤5.6 mmol L^{-1}	5.6–7 mmol L^{-1}	>7 mmol L^{-1}	History of diabetes
n	687	251	68	161
All-cause death	99 (14.4)	49 (19.5)	22 (32.4)	49 (30.4)
Cardiac death	52 (7.6)	27 (10.8)	10 (14.7)	32 (19.9)
At least one nonfatal reinfarction	128 (18.6)	54 (21.5)	18 (26.5)	61 (37.9)
Hospitalization for heart failure	159 (21.8)	62 (24.7)	25 (36.8)	69 (42.9)
Hospitalization for stroke	53 (7.7)	31 (12.4)	10 (14.7)	21 (13.0)
Combination of cardiovascular events	256 (37.3)	114 (45.4)	35 (51.5)	99 (61.5)

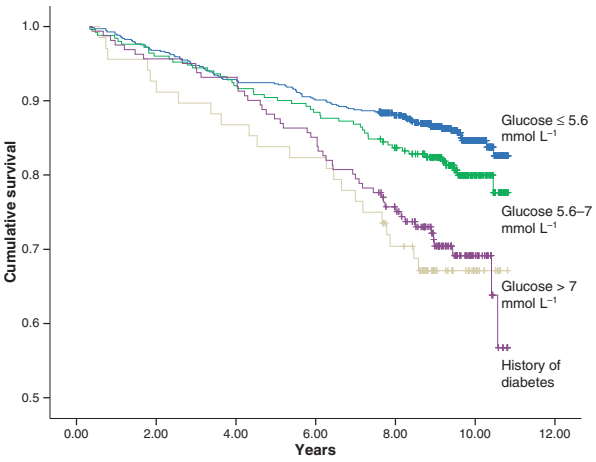

Fig. 1 Cumulative survival according to fasting glucose values and diabetic status ($P < 0.001$, log rank test).

showed a similar trend as well as hospitalization for heart failure. Figure 1 shows the cumulative survival according to fasting glucose values and diabetic status.

In Table 3, we present un-, gender/age- and multivariable-adjusted hazard ratios associated with IFG, newly detected and old diabetes with NG as the reference group. Patients with IFG showed a moderate trend towards higher total and cardiac mortality. As a secondary analyses, we divided the IFG group for those having fasting glucose between 5.6–6.1 mmol L^{-1} and those with 6.1–7 mmol L^{-1}. We found that the point estimates of risk for adverse events were not materially different between these groups. For example, hazard ratios in the multiadjusted models were 1.27 (0.79–2.05) and 1.47 (0.90–2.42) for total mortality and 1.55 (0.84–2.85) and 1.14 (0.55–2.39) for cardiac mortality in these two groups of IFG when compared with NG respectively.

Both newly detected and old diabetes was characterized with an increased risk for total and cardiac mortality, new AMI and heart failure. Associations with cardiac mortality, new AMI and hospitalization for heart failure were somewhat stronger for patients with a history of diabetes when compared to those with newly detected diabetes.

Table 4 and 5 present the risk for adverse outcomes associated with insulin and HOMA quartiles respectively. Both insulin and HOMA were associated to adverse outcomes, especially for heart failure and cardiac mortality. However, when we repeated these analyses excluding patients with old or newly detected diabetes, we found that the effect of insulin and HOMA had substantially decreased. For example, hazard ratios for cardiac mortality for the second, third and fourth insulin quartiles when compared with the first one were 1.45 (0.67–3.16), 1.62 (0.70–3.73) and 1.35 (0.52–3.52) respectively (P for trend = 0.44). The corresponding numbers for the HOMA quartiles were 1.78 (0.83–3.83), 1.26 (0.53–2.99) and 1.43 (0.50–4.12) respectively (P for trend = 0.63).

Table 3 Hazard ratios for adverse outcomes with 95% confidence intervals to fasting glucose values and diabetic status

	Unadjusted HR (95% CI)	*P* for trend	Age and gender adjusted HR (95% CI)	*P* for trend	Multiadjusted HR (95% CI)[a]	*P* for trend
Total mortality (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.34 (0.95–1.89)		1.30 (0.92–1.83)		1.36 (0.93–1.99)	
fasting glucose >7	2.55 (1.61–4.05)		2.83 (1.77–4.50)		2.27 (1.26–4.09)	
History of diabetes	2.27 (1.61–3.20)	<0.001	2.20 (1.56–3.10)	<0.001	2.15 (1.43–3.21)	<0.001
Cardiac mortality (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.41 (0.88–2.24)		1.36 (0.85–2.16)		1.36 (0.82–2.28)	
fasting glucose >7	2.19 (1.11–4.31)		2.37 (1.20–4.69)		1.77 (0.76–4.15)	
History of diabetes	2.81 (1.81–4.37)	<0.001	2.76 (1.77–4.29)	<0.001	2.90 (1.76–4.78)	<0.001
New AMI (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.17 (0.85–1.61)		1.14 (0.83–1.57)		1.12 (0.80–1.58)	
fasting glucose >7	1.54 (0.94–2.52)		1.58 (0.96–2.60)		1.27 (0.71–2.27)	
History of diabetes	2.27 (1.67–3.08)	<0.001	2.25 (1.66–3.06)	<0.001	2.01 (1.43–2.82)	<0.001
Stroke (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.62 (1.04–2.53)		1.57 (1.01–2.44)		1.31 (0.79–2.16)	
fasting glucose >7	2.30 (1.17–4.52)		2.64 (1.33–5.22)		1.77 (0.73–4.30)	
History of diabetes	1.88 (1.14–3.12)	0.004	1.81 (1.09–3.01)	0.004	1.50 (0.83–2.71)	0.15
Heart failure (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.14 (0.85–1.53)		1.12 (0.83–1.51)		1.13 (0.82–1.55)	
fasting glucose >7	1.99 (1.30–3.04)		2.25 (1.47–3.45)		1.59 (0.96–2.65)	
History of diabetes	2.27 (1.71–3.02)	<0.001	2.17 (1.63–2.89)	<0.001	1.98 (1.43–2.74)	<0.001
Combination of cardiovascular events[b] (mmol L^{-1})						
fasting glucose ≤5.6	1.00		1.00		1.00	
fasting glucose 5.6–7	1.25 (1.00–1.56)		1.22 (0.98–1.52)		1.11 (0.87–1.42)	
fasting glucose >7	1.65 (1.16–2.34)		1.75 (1.23–2.50)		1.30 (0.85–1.98)	
History of diabetes	2.05 (1.62–2.58)	<0.001	2.01 (1.60–2.54)	<0.001	1.82 (1.40–2.36)	<0.001

[a]Multiadjustment includes age, gender, obesity, hypertension, physical activity total cholesterol, hypertension, triglycerides, apo B/apo A ratio, Q wave infarction and education. [b]Combination of cardiovascular events included cardiac mortality, new AMI, stroke and heart failure.

Discussion

We found that history of diabetes and newly detected diabetes was associated with a markedly increased long-term mortality amongst survivors of a first AMI. We also observed a trend towards increased mortality amongst IFG patients when compared to patients with normal glucose levels. Similar patterns were seen for other outcomes than death, especially for new AMI and hospitalization for heart failure.

Compelling evidence suggests that diabetes is a strong adverse prognostic factor after an AMI [3–6, 25]. As overviewed by Capes *et al.*[7] and confirmed by more recent studies [8–14], elevated admission and/or fasting glucose levels measured in the early phase of

Table 4 Hazard ratios for adverse outcomes with 95% confidence intervals across the insulin quartiles

Insulin quartiles	Unadjusted HR (95% CI)	*P* for trend	Age and gender adjusted HR (95% CI)	*P* for trend	Multiadjusted HR (95% CI)[a]	*P* for trend
Total mortality (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	1.36 (0.85–2.17)		1.34 (0.83–2.14)		1.23 (0.74–2.05)	
third quartile 10–15	1.50 (0.92–2.43)		1.57 (0.96–2.55)		1.39 (0.81–2.37)	
fourth quartile >15	1.67 (1.06–2.63)	0.03	1.72 (1.09–2.73)	0.02	1.35 (0.76–2.37)	0.28
Cardiac mortality (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	1.68 (0.86–3.27)		1.67 (0.86–3.26)		1.55 (0.75–3.18)	
third quartile 10–15	1.81 (0.91–3.58)		1.90 (0.95–3.77)		1.83 (0.86–3.88)	
fourth quartile >15	1.99 (1.04–3.81)	0.05	2.06 (1.08–3.96)	0.03	2.03 (0.94–4.40)	0.07
New AMI (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	1.46 (0.96–2.20)		1.45 (0.96–2.19)		1.46 (0.95–2.27)	
third quartile 10–15	1.12 (0.71–1.76)		1.13 (0.72–1.79)		0.96 (0.58–1.60)	
fourth quartile >15	1.76 (1.18–2.63)	0.02	1.79 (1.20–2.67)	0.01	1.64 (1.02–2.65)	0.15
Stroke (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	0.81 (0.44–1.49)		0.79 (0.43–1.46)		0.74 (0.38–1.44)	
third quartile 10–15	1.42 (0.80–2.51)		1.47 (0.83–2.61)		1.15 (0.59–2.22)	
fourth quartile >15	1.17 (0.67–2.06)	0.26	1.23 (0.70–2.17)	0.18	1.05 (0.52–2.13)	0.65
Heart failure (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	1.47 (1.00–2.17)		1.42 (0.96–2.09)		1.48 (0.97–2.24)	
third quartile 10–15	1.42 (0.95–2.14)		1.42 (0.94–2.14)		1.18 (0.75–1.85)	
fourth quartile >15	2.12 (1.46–3.07)	<0.001	2.16 (1.49–3.12)	<0.001	1.77 (1.14–2.76)	0.04
Combination of all events[b] (μU mL^{-1})						
first quartile <6	1.00		1.00		1.00	
second quartile 6–10	1.12 (0.84–1.49)		1.09 (0.82–1.46)		1.09 (0.74–1.45)	
third quartile 10–15	1.15 (0.85–1.55)		1.15 (0.85–1.56)		0.95 (0.68–1.32)	
fourth quartile >15	1.54 (1.17–2.03)	0.002	1.58 (1.20–2.07)	<0.001	1.37 (0.98–1.91)	0.13

[a]Multiadjustment includes age, gender, obesity, hypertension, physical activity total cholesterol, hypertension, triglycerides, apo B/apo A ratio, Q wave infarction and education. [b]Combination of events included cardiac mortality, new AMI, stroke and heart failure.

AMI, i.e. within a few days after the admission, also seem to predict poor prognosis even in nondiabetic patients. However, the role of hyperglycemia in the early phase is a complex issue. Acute stress because of the MI may raise blood glucose levels but higher stress is also accompanied with higher cathecolamine levels, which could impair endothelial function, myocardial metabolism or coagulation [12, 26]. Hyperglycemic patients during the acute phase of AMI may have higher free fatty acid concentrations, which together with hyperglycemia itself can have deleterious effects on the myocardium [27, 28]. It is also possible that higher glucose level in the acute phase is simply a marker of the severity of myocardial damage [7]. Therefore, it is not possible to generalize the results on admission glucose or fasting glucose measured a few days after the onset to a metabolically more stable phase. To the best of our knowledge, the

Table 5 Hazard ratios for adverse outcomes with 95% confidence intervals across the HOMA quartiles

HOMA quartiles	Unadjusted HR (95% CI)	*P* for trend	Age and gender adjusted HR (95% CI)	*P* for trend	Multiadjusted HR (95% CI)[a]	*P* for trend
Total mortality						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.34 (0.81–2.22)		1.29 (0.78–2.13)		1.28 (0.74–2.21)	
third quartile (2.40–4.31)	1.30 (0.79–2.14)		1.25 (0.76–2.07)		1.18 (0.67–2.09)	
fourth quartile (>4.31)	2.16 (1.36–3.42)	0.001	2.17 (1.37–3.45)	0.001	1.99 (1.11–3.58)	0.04
Cardiac mortality						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.68 (0.84–3.34)		1.62 (0.81–3.23)		1.73 (0.81–3.71)	
third quartile (2.40–4.31)	1.38 (0.67–2.80)		1.35 (0.66–2.75)		1.44 (0.64–3.24)	
fourth quartile (>4.31)	2.56 (1.34–4.89)	0.01	2.59 (1.35–4.95)	0.01	3.01 (1.36–6.70)	0.01
New AMI						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.15 (0.75–1.75)		1.12 (0.73–1.70)		1.21 (0.77–1.91)	
third quartile (2.40–4.31)	0.79 (0.50–1.25)		0.77 (1.49–1.22)		0.73 (0.44–1.22)	
fourth quartile (>4.31)	1.76 (1.19–2.60)	0.02	1.76 (1.19–2.60)	0.02	1.65 (1.02–2.67)	0.18
Stroke						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.45 (0.76–2.76)		1.40 (0.73–2.65)		1.20 (0.60–2.38)	
third quartile (2.40–4.31)	1.40 (0.74–2.66)		1.37 (0.72–2.60)		1.17 (0.57–2.42)	
fourth quartile (>4.31)	1.75 (0.93–3.27)	0.11	1.75 (0.94–3.28)	0.10	1.29 (0.58–2.88)	0.56
Heart failure						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.34 (0.89–1.99)		1.26 (0.84–1.87)		1.31 (0.85–2.03)	
third quartile (2.40–4.31)	1.09 (0.72–1.65)		1.04 (0.68–1.57)		1.01 (0.63–1.61)	
fourth quartile (>4.31)	2.26 (1.56–3.27)	<0.001	2.25 (1.55–3.25)	<0.001	1.93 (1.22–3.05)	0.02
Combination of all events[b]						
first quartile (<1.46)	1.00		1.00		1.00	
second quartile (1.46–2.40)	1.15 (0.86–1.55)		1.09 (0.81–1.47)		1.08 (0.79–1.49)	
third quartile (2.40–4.31)	0.93 (0.68–1.25)		0.89 (0.65–1.20)		0.82 (0.58–1.16)	
fourth quartile (>4.31)	1.77 (1.34–2.33)	0.001	1.77 (1.34–2.33)	0.001	1.56 (1.10–2.20)	0.07

[a]Multiadjustment includes age, gender, obesity, hypertension, physical activity total cholesterol, hypertension, triglycerides, apo B/apo A ratio, Q wave infarction and education. [b]Combination of events included cardiac mortality, new AMI, stroke and heart failure.

present study is the first to investigate directly the prognostic role of IFG evaluated in a stable phase, i.e. 3 months after an AMI.

The role of impaired glucose metabolism was evaluated in other stable nondiabetic CHD populations. Lenzen *et al.*[29] could not identify impaired fasting glucose or impaired glucose tolerance without diabetes as an adverse prognostic factor in patients admitted to cardiology outpatient clinics with coronary artery disease. In contrast, Fisman *et al.*[30] demonstrated that fasting glucose is a strong predictor of mortality amongst nondiabetic patients with a history of myocardial infarction or with a documented coronary heart disease. Arcavi *et al.*[31] also concluded that IFG predicts adverse outcomes in patients with an established coronary artery disease. Similarly, Port *et al.*[32] investigated nondiabetic participants from

the Framingham Heart Study who reported CHD, stroke, congestive heart failure or intermittent claudication and found a steep increase in risk associated with glucose level through the whole range with no indication of a threshold. Moreover, IFG seems to be a predictor of outcome in CHD patients undergoing revascularization procedures [33, 34].

Generally, we found a weaker adverse effect of IFG than the earlier studies. However, direct comparison of the results of the present and that of the earlier studies is difficult. We investigated uniquely a stable metabolic phase of an AMI, and we also used a lower cut off value of fasting glucose concentration to define IFG than the majority of earlier studies. In our alternative analyses, we found no indication that the level of glucose between 6.1 and 7 mmol L^{-1} would be a stronger predictor of adverse outcomes than that of between 5.6 and 6.1 mmol L^{-1}. Therefore, our findings provided some further support for the current ADA definition of using the lower threshold [19]. This is in contrast to the findings of Verges *et al.*[11] who similarly to us divided the IFG category to fasting glucose levels between 5.6–6.1 mmol L^{-1} and 6.1–7 mmol L^{-1}. The authors concluded that only the latter one was associated with increased risk for short-term mortality after AMI.

Previous results are conflicting whether patients with newly detected or those with known diabetes are at a greater risk. According to some studies [8, 12], admission plasma glucose above 11 mmol L^{-1} is more dangerous if newly detected compared to old diabetes. On the other hand, Lenzen *et al.*[29] found that CHD patients with newly diagnosed diabetes had lower mortality than patients with known diabetes. In the present study, history of diabetes mellitus and newly detected diabetes had a similar association to total mortality. Associations with cardiac mortality, new AMI and hospitalization for heart failure were stronger amongst patients with a history of diabetes.

We found that both fasting insulin and HOMA were associated to adverse outcomes. This was especially true for heart failure and cardiac mortality. However, when we restricted our analyses to patients without old or newly detected diabetes these associations weakened substantially. Few studies reported on the association between insulin or insulin resistance and AMI prognosis. Kragelund *et al.*[35] concluded that fasting insulin predicts mortality in nondiabetic AMI patients. Stubbs *et al.* [36] found that the insulin resistance is an important predictive measure of poor outcome in AMI patients without diabetes and is superior to admission glucose. It should be mentioned that these studies were performed a few days after the event and insulin levels are also known to be affected by the metabolic disturbances in the acute phase [28].

There are several potential routes by which hyperglycemia, increased insulin and insulin resistance may impact upon the cardiovascular system. These include glucosylation of LDL and clotting factors [2], increased oxidative stress and mimicking the proinflammatory effects of citokines[1, 37–39], decreased fibrinolysis[40] or elevation in inflammatory markers [41]. It is not clear from our results whether hyperglycemia below the diabetic threshold has adverse effects itself or it is merely a predictor of future diabetes [2].

Limitations

Potential limitations of our study need to be considered. We relied on fasting glucose levels and did not perform an oral glucose tolerance test. Although this is in accordance with the current ADA recommendations [19], Bartnik *et al.*[9] found that oral glucose tolerance test is a superior predictor of adverse events after AMI than fasting glucose.

The point estimates associated with IFG in our analyses suggest a 30–40% excess risk for both cardiac and total mortality. This would imply a biologically and clinically relevant effect. We included more patients than most previous studies, still our statistical power to detect an association between outcome and IFG was limited. This is reflected in the wide confidence intervals. Further studies are warranted to determine the prognostic importance of IFG evaluated in a stable phase after an AMI.

The low sample size for patients with newly detected diabetes is also a limitation of the present study.

Observational studies inherently limit causal inference. Although we adjusted for several potential confounders in our multivariable analyses, we were not able to assure that all potential confounding is controlled for. However, any remaining confounder potentially able to influence our results considerably would need to be strongly associated with glucometabolic status and prognosis of AMI and generally unrelated to the factors included in our models.

To document adverse outcomes during the follow up, we relied on national Swedish registries that have been validated, but are nonetheless prone to misclassification. This – supposedly random – misclassification may partly explain the weak associations with stroke. It should also be emphasized that there were only few cases of stroke amongst subjects with a history of diabetes resulting in wide confidence intervals for hazard ratios. Because of the relatively small number of cases, it was not meaningful to distinguish between ischaemic and haemorrhagic stroke.

Conclusion

We confirmed that both known and newly detected diabetes are strong prognostic factors in AMI. In addition, our findings suggest that glucose levels below the diabetes cut off value might predict poor long-term prognosis when assessed in a metabolically stable phase.

Conflict of interest statement

No conflict of interest was declared.

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