UNIVERSITY OF OSLO

FACULTY OF MEDICINE

ABNORMAL GLUCOSE REGULATION IN PATIENTS WITH ACUTE ST-ELEVATION MYOCARDIAL INFARCTION

A prospective observational cohort study

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Contents

1. Acknowledgements

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2. Abbreviations

ADA	American Diabetes Association
AGR	abnormal glucose regulation
BMI	body mass index
CAD	coronary artery disease
CRP	high-sensitivity C- reactive protein
CVD	cardiovascular disease
F_{1+2}	prothrombin fragment 1+2
GAMI	Glucose Tolerance in Patients with Acute Myocardial Infarction
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IL-6	Interleukin-6
IL-18	Interleukin-18
LDL	low density lipoprotein
MCP-1	monocyte chemoattractant protein-1
MI	myocardial infarction
NGT	normal glucose tolerance
NSTEMI	non-ST-elevation myocardial infarction
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitor-1
PCI	percutaneous coronary intervention
SPECT	Single Photon Emission Computed Tomography
STEMI	ST-elevation myocardial infarction
T2DM	type 2 diabetes
TnT	Troponin T
t-PA	tissue plasminogen activator
WHO	World Health Organization
ECG	electrocardiogram

3. List of papers

Paper I: Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Arnesen H, Andersen GØ. Abnormal glucose regulation in patients with acute ST-elevation myocardial infarction - a cohort study on 224 patients Cardiovasc Diabetol 2009;8:6.

Paper II: Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Müller C, Arnesen H, Andersen GØ. Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST-elevation myocardial infarction. Submitted.

Paper III: Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Müller C, Arnesen H, Andersen GØ. Increased levels of CRP and MCP-1 are associated with previously unknown abnormal glucose regulation in patients with acute STEMI: a cohort study. Cardiovasc Diabetol 2010, 9:47

Paper IV: Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Müller C, Arnesen H, Andersen GØ. Elevated levels of PAI-1 activity and t-PA antigen are associated with newly diagnosed abnormal glucose regulation in patients with acute STEMI. J Thromb Haemost. 2011 May 27. doi: 10.1111/j.1538-7836.2011.04377.x.

4. Introduction

4.1 Type 2 diabetes and coronary artery disease.

There is a close relationship between type 2 diabetes and coronary artery disease (CAD) [1]. Despite the improving survival rate in patients with CAD, the prognosis for individuals with CAD and type 2 diabetes remains poor [2]. The risk of developing CAD is increased by 2-3 fold in individuals with type 2 diabetes and CAD accounts for approximately 70 % of total mortality [3,4]. Moreover, patients with diabetes without previous myocardial infarction (MI) have similar risk for MI as patients without diabetes with a previous MI [5]. It is estimated that 50 % of subjects with newly diagnosed type 2 diabetes already have CAD and about 10-20 % of patients presenting with an acute MI have known type 2 diabetes [6]. Additionally, several prospective studies have reported a high prevalence of newly diagnosed impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes in patients with acute MI without previously known diabetes (Table 2) [7-9]. The primary objective of the present work was to study the association between MI and glucometabolic disturbances in patients with acute ST-elevation myocardial infarction (STEMI) without previously known diabetes.

4.2 Abnormal glucose regulation

Globally, the number of people diagnosed with diabetes was estimated to 285 million in 2010 [10]. Many individuals are undiagnosed and the prevalence will increase exponentially because of the change in lifestyle with increasing obesity and reduced physical activity. Moreover, the prevalence seems to increase more in developing than in developed countries [10]. In Norway, about 90000-120000 people were estimated to have diabetes in 2004, and about the same number were considered to be undiagnosed [11].

Type 2 diabetes is a chronic disease that develops when the pancreas fails to produce enough insulin or the body cannot utilize the insulin produced efficiently [12]. Type 2 diabetes can be insulin dependent according to metabolic control, or insulin independent according to acceptable control by non–pharmacological methods or drugs other than insulin [12]. Impaired glucose regulation (IFG, IGT) is classified as a metabolic state intermediate between normal glucose regulation and diabetes [12]. In the present work the term abnormal glucose regulation defined as the sum of IFG, IGT and type 2 diabetes will be used. Glucometabolic status is usually classified according to the World Health Organization (WHO) or the American Diabetes Association (ADA) criteria [12,13]. In the present work the WHO criteria from 2005 have been followed [14].

4.3 Oral glucose tolerance test.

Post-load hyperglycaemia reflects the acute increase in blood glucose after glucose loading, whereas fasting glucose concentration after an overnight fast reflects mostly hepatic glucose production [15]. Fasting plasma glucose and glucose 2-hour after loading with 75 g glucose are both measures of glucometabolic disturbances and a fasting value of 7.0 mmol/L has been suggested to represent a similar degree of hyperglycaemia as a 2-h value of 11.1 mmol/L, but the tests are not concordant [16]. Thus, a patient could be diagnosed with diabetes using one test but not the other [16]. In epidemiological studies the oral glucose tolerance test (OGTT) has been accepted as a screening tool and retesting is rarely performed. However, in clinical practice when diagnosing asymptomatic individuals, retesting to confirm the diagnosis is required [14]. WHO recommend, whereas ADA do not recommend, the use of an OGTT in routine clinical practice [12,13].

European guidelines on diabetes, prediabetes, and cardiovascular disease (CVD) from 2007 recommend that patients without previously known diabetes, but with established CVD

should be investigated with an OGTT [17]. However, there exists no consensus about the timing of an OGTT after acute MI [17]. The European guidelines rely mainly on the Swedish GAMI (Glucose Tolerance in Patients with Acute Myocardial Infarction) study, which was the first study to perform an OGTT in patients with acute MI without previously known diabetes and admission glucose <11.1 mmol/l [7]. The OGTT was performed the fourth or fifth day after hospital admission (before discharge) and the test was repeated at three-month follow-up. The investigators concluded that the OGTT performed before discharge provided reliable information on long-term glucometabolic state [18]. The GAMI results, were however, not confirmed by similar studies before incorporated into the guidelines.

4.4 Acute myocardial infarction

The survival rates are improving for patients with CVD, however, CVD remains to be the leading cause of death worldwide both in men and women. In 2004, about 17 million people died of CVD globally. Sedentary lifestyle, unhealthy diet, smoking, hypertension, hypercholesterolemia and a family history of CVD seem to be the main causes of CVD [19]. CAD is a chronic disease with stable or unstable periods [20]. Acute coronary syndromes are clinically defined as unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI) or STEMI and are characterized by myocardial ischemia and / or cell death due to perfusion imbalance between supply and demand [20,21]. Acute STEMI is defined according to the universal definition of MI as typical rise and fall of the cardiac biomarker troponin T (TnT) with at least one value above the 99th percentile of the upper reference limit in patients presenting with symptoms of ischemia together with electrocardiogram (ECG) changes indicative of new ST elevation at the J-point in two contiguous leads with the cut-off points: 0.2 mV in men or 0.15 mV in women in leads V2–V3 and/or 0.1 mV in other leads *or* new left bundle-branch block [20].

4.5 Prognostic aspects

It is well established that patients with acute MI and diabetes have a worse short- and long-term prognosis compared to patients without diabetes, and that this association seems to be independent of traditional cardiovascular risk factors [5,22,23]. Moreover, in multiple large prospective studies both admission and fasting blood glucose, regardless of diabetic status, have been shown to be independent predictors of both in-hospital and long-term outcome in patients with acute MI [24-29]. The association between newly diagnosed impaired glucose tolerance and clinical outcome after an acute MI is less clear. In a mixed population with both acute and stable CAD, no association between impaired glucose regulation (IFG, IGT) and mortality was found after one-year follow-up [30]. However, in the follow-up of the GAMI trial, newly diagnosed abnormal glucose tolerance (IGT, T2DM) was associated with poor prognosis after three-year follow-up [31]. In spite of diverging results, patients with CAD and impaired glucose regulation as well as type 2 diabetes have been categorized as high-risk patients important to identify as early as possible.

4.6 Pathophysiological aspects

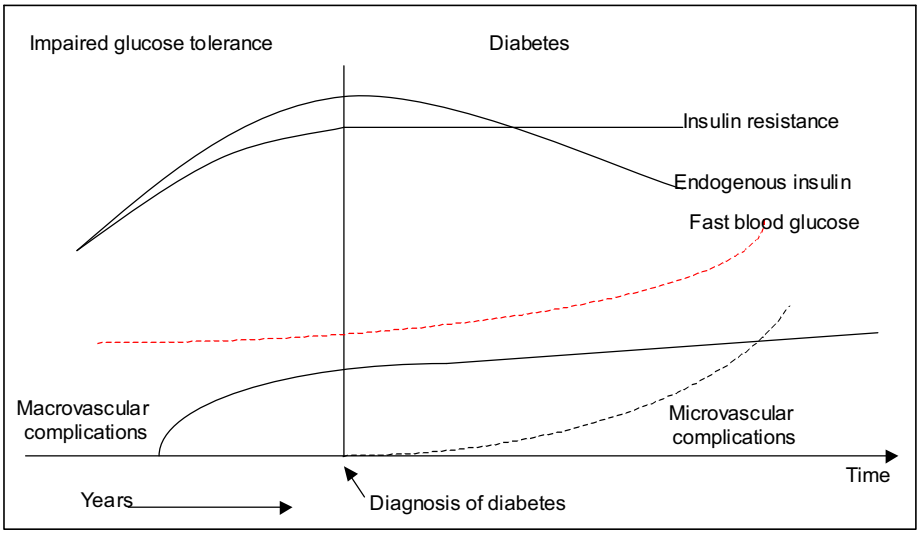
4.6.1 Abnormal glucose regulation

Type 2 diabetes is a metabolic disorder characterized by hyperglycaemia, which arises from insufficient pancreatic insulin secretion and insulin resistance in peripheral tissue [32]. Insulin is a hormone that controls the glucose homeostasis in humans. It promotes glucose uptake and glycogen synthesis in fat and muscles tissue and prevents glucose production by inhibition of glycogenolysis and gluconeogenesis in the liver [33]. Skeletal muscle is responsible for more than 80 % of insulin stimulated glucose utilization [34]. The glucose uptake in muscle tissue is a complex process. Insulin stimulates the phosphorylation of the insulin receptor substrate

that activate a series of intracellular signal molecules resulting in translocation and activation of GLUT-4 to the cell membrane, resulting in increased glucose uptake [32].

The progression from normal to impaired glucose regulation (IFG, IGT) and subsequently type 2 diabetes is associated with decreasing insulin action in peripheral tissue and impaired insulin secretion due to progressive pancreatic beta cell dysfunction (Figure 1) [35]. In a condition with insulin resistance, the capacity of insulin to stimulate glucose uptake and utilization is reduced [32]. Skeletal muscles are the major sites of peripheral insulin resistance and defects in the intracellular insulin signalling sequences results in reduced GLUT-4 translocation, activation, and glucose uptake [32].

Figure 1. Progression from insulin resistance to type 2 diabetes. Modified from Laakso and Kuusisto [36].



4.6.2 Atherosclerosis

Atherosclerosis is a chronic systemic disease that occurs in large and medium-sized arteries and may cause clinical symptoms from the brain, heart and extremities [37]. Coronary atherosclerosis is asymmetrical lesions with focal thickening of the arterial intima consisting of cells, connective-tissue elements, lipids, and debris often described as atherosclerotic plaques [37-39]. An occlusion of the coronary artery occurs either by endothelial erosion or plaque rupture that arise most often in the thinnest part of the fibrous cap exposing prothrombotic material to the circulation, triggering a platelet rich thrombus formation within the atherosclerotic lesion and an acute MI may occur [21,40]. Inflammation has been shown to be involved in the formation, progression, rupture of atherosclerotic plaques, and in the healing of the ischemic myocardium. Monocyte infiltration into the vascular intima is central in the initial phase of the atherosclerotic process [39].

4.6.3 Atherosclerosis and abnormal glucose regulation

Type 2 diabetes and atherosclerosis are multifactorial conditions, which may share cardiovascular risk factors associated with the metabolic syndrome [41]. Although, the association between type 2 diabetes and atherosclerotic disorders are not fully understood, chronic hyperglycaemia, insulin resistance and dyslipidemia have been shown to make arteries susceptible to atherosclerosis [42]. It has also been suggested that atherosclerosis, type 2-diabetes and metabolic syndrome are characterized by chronic inflammation [43,44]. During normal conditions the vascular endothelium does not support adhesion and transmigration of blood cells [45]. However, the endothelium might become dysfunctional and leaky by exposure to different stimuli such as hyperglycaemia, insulin resistance, inflammation, hypertension, elevated levels of free radicals, and accumulation of modified lipids [42].

4.6.4 Inflammation

Inflammation has been suggested to be the bridging link between abnormalities in glucose metabolism and atherosclerotic disorders [38]. On the cell surface of activated endothelium, different adhesion molecules are expressed [43]. Circulating blood cells like monocytes and lymfocytes roll along the vascular surface and adhere at the site of endothelial activation. Different pro-inflammatory cytokines stimulate endothelial cells, smooth muscle cells and macrophages to release chemokines responsible for the recruitment of monocytes and lymfocytes to sites of inflammation [42]. Chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 promotes the transmigration of monocytes and lymfocytes to the intima through activation of the interendothelial junctions. In the intima, monocytes are differentiated in to macrophages. Scavenger and toll-like receptors on macrophages regulate this process. The scavenger receptors mediate the uptake of oxidized low density lipoprotein (LDL) particles leading to the formation of foam cells, while toll-like receptors promote signalling cascades that lead to inflammatory activation and initiation of atherosclerosis [46].

In endothelial cells the glucose uptake is mediated by facilitative diffusion independent of insulin action, if overfed they cannot downregulate the influx of nutrients [47]. During hyperglycaemic periods intracellular glucose overload causes uncontrolled overproduction of superoxide within the mithochondrial electron transport chain. This may have multiple functional and pathogenetic consequences such as initiating endothelial dysfunction, and vascular inflammation [47,48].

The hyperglycaemia-induced inflammatory process in the atherosclerotic wall may lead to elevated levels of circulating inflammatory cytokines and chemokines that can be measured [38,39]. C-reactive protein (CRP), which is produced in the liver by interleukin-6 stimulation, is well known as an acute-phase reactant, and circulating levels of CRP have been identified

to be a non-specific biomarker of low-grade inflammation [49-53]. Other circulating inflammatory variables such as the chemokine MCP-1 have been shown to be elevated after an acute MI, suggesting that mononuclear cells may play an important role in the early phase of the pathogenesis of an acute MI [54].

4.6.5 Haemostasis

As well as being a pro-inflammatory state, type 2 diabetes has also been shown to be a prothrombotic condition due to platelet dysfunction, suppressed fibrinolysis and enhanced coagulation [55]. The normal vascular endothelium release substances like prostacyclin and nitric oxide that promote a vasodilatory and antithrombotic condition [56]. Additionally, insulin has been shown to antagonise platelet activation/aggregation by cell surface receptors [57,58]. However, in patients with insulin-resistance the platelet response to insulin, nitric oxide and prostacyclin seems inadequate [57,58]. Moreover, in type 2 diabetic patients, platelets seem to adhere to the endothelium and aggregate more rapidly than in healthy subjects [57,59-61].

In patients with insulin resistance and CAD the fibrinolytic activity is suppressed mostly due to elevated levels of plasminogen activator inhibitor-1 (PAI-1) [33,62]. During weight loss the levels of PAI-1 have been reported to decrease [63,64]. Furthermore, PAI-1 is an acute phase protein known to increase rapidly in response to acute illness [65].

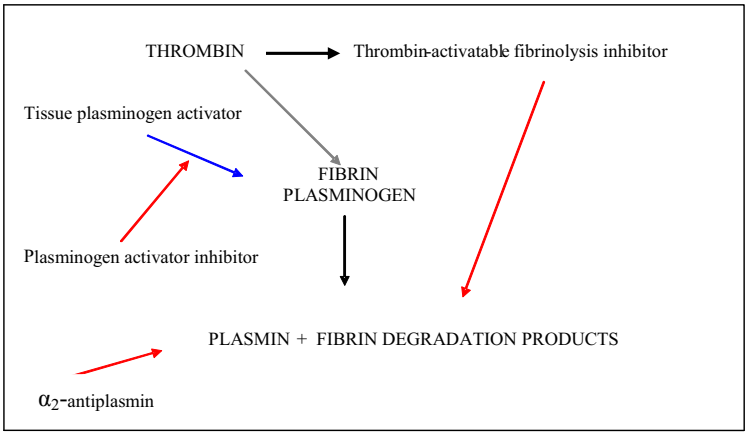
PAI-1 is the main inhibitor of the fibrinolytic system acting by inhibiting tissue plasminogen activator (t-PA), leading to reduced activation of plasminogen to plasmin and as a consequence, less available plasmin, which is required for lysis of fibrin [66]. Circulating levels of PAI-1 reflect secretion and release from several sources, including the liver, adipose tissue, endothelium and the α-storage granules of platelets [65]. PAI-1 circulates in plasma, in an active form and in an inactive complex with t-PA [65]. In patients with insulin resistance,

type 2 diabetes and CAD, circulating PAI-1 levels have been shown to correlate with levels of insulin, triglycerides, body mass index, and blood pressure, indicating that PAI-1 seems to be an important part of the cluster of risk factors leading to CAD [55].

Tissue plasminogen activator is the main activator of the fibrinolytic system acting by converting plasminogen to plasmin (Figure 2) [55]. t-PA is produced and secreted mainly by endothelial cells and has a half-life of about 2 min in the circulation [66]. In the absence of fibrin, t-PA activates plasminogen at a slow rate, but when t-PA and plasminogen both bind to fibrin the catalytic effect of t-PA enhances about 1000-fold [55]. Most of the secreted t-PA will be inactivated by PAI-1 before it binds fibrin due to the high affinity to PAI-1. The most common method used for t-PA measurements is t-PA antigen including both free t-PA and t-PA in complex with PAI-1 [66]. Elevated levels of t-PA antigen appear to be beneficial due to an increased potential to generate plasmin resulting in increased fibrinolysis. However, elevated levels of t-PA antigen mainly reflect the level of PAI-1 and appear rather to be harmful than beneficial and are claimed to be a marker of endothelial dysfunction and atherosclerosis [55,67].

Furthermore, patients with diabetes mellitus are known to have a prothrombotic phenotype based on both measured biochemical abnormalities and a high frequency of vascular clinical events [68]. Hyperglycaemia has been reported to correlate with increase in coagulation factors both in patients with diabetes and in normal subjects in whom a hyperglycaemic state has been initiated [69-71]. Experimentally induced hyperglycaemia in healthy subjects has been shown to increase FVII clotting activity [72] and soluble tissue factor [73]. Additionally, a direct glycation of coagulation factors during hyperglycaemia have been reported to alter their activity [74].

Figure 2. Fibrinolysis (simplified), blue arrows denote stimulation, and red arrows inhibition.



4.7 Rationale for the study.

When the present project was initiated, very little was known about the prevalence of abnormal glucose regulation in Norwegian patients with CAD and especially in patients with STEMI. In addition, according to institutional guidelines, routine use of OGTT to screen for glucometabolic perturbations was not a part of common routine in patients with CAD. However, in one clinical trial in Norway in which an OGTT was performed in patients hospitalized with CAD, cerebrovascular disease or peripheral artery disease, glucometabolic disturbance was found in 49 %, 55% and 57% of the patients, respectively [75]. Our research group performed a pilot study on 100 non-diabetic patients with acute MI hospitalized at Oslo University Hospital, Ullevål and found that about half of the patients had abnormal glucose regulation classified by an OGTT performed early after primary percutaneous coronary intervention (PCI) [76]. Furthermore, European guidelines recommended OGTT as a screening tool for all patients with CAD, but did not specify the timing of OGTT after an acute MI [17]. As the recent European Guidelines were mainly based on a single clinical study regarding the timing of an OGTT in MI patients, we also wanted to evaluate the reproducibility of an OGTT in patients with STEMI by repeating the test during stable

conditions. In addition, type 2 diabetes has been shown to be a prothrombotic and a pro-inflammatory condition [41,74] and we wanted to investigate whether newly detected abnormal glucose regulation was associated with inflammatory and haemostatic variables in patients with acute STEMI without previously known diabetes, in order to obtain new insights into mechanisms involved in these closely related diseases. Based on these considerations the present work was initiated and carried out.

5. Aims of the study

- to study the prevalence of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes early in-hospital and at three-month follow-up, in a primary PCI treated STEMI population without known diabetes. Furthermore, to evaluate the reliability of an OGTT-based glucometabolic classification early in-hospital in order to predict glucometabolic disturbance defined by a repeated OGTT at three-month follow-up (Paper I).
- to elucidate a possible association between HbA1c, admission glucose and fasting glucose identified during the initial hospitalization and abnormal glucose regulation classified by an OGTT at three-month follow-up (Paper I).

- to investigate clinical outcome in patients with acute STEMI after exclusion of patients with known diabetes (Paper II).
- to evaluate whether abnormal glucose regulation classified by an OGTT in-hospital or at three-month follow-up was associated with poor long-term prognosis after acute STEMI (Paper II).

- to study potential associations between circulating levels of selected inflammatory markers and plasma glucose levels measured during an acute STEMI (Paper III).
- to identify any associations between circulating levels of inflammatory markers measured during an acute STEMI and abnormal glucose regulation classified by an OGTT at three month follow-up in the same cohort (Paper III).

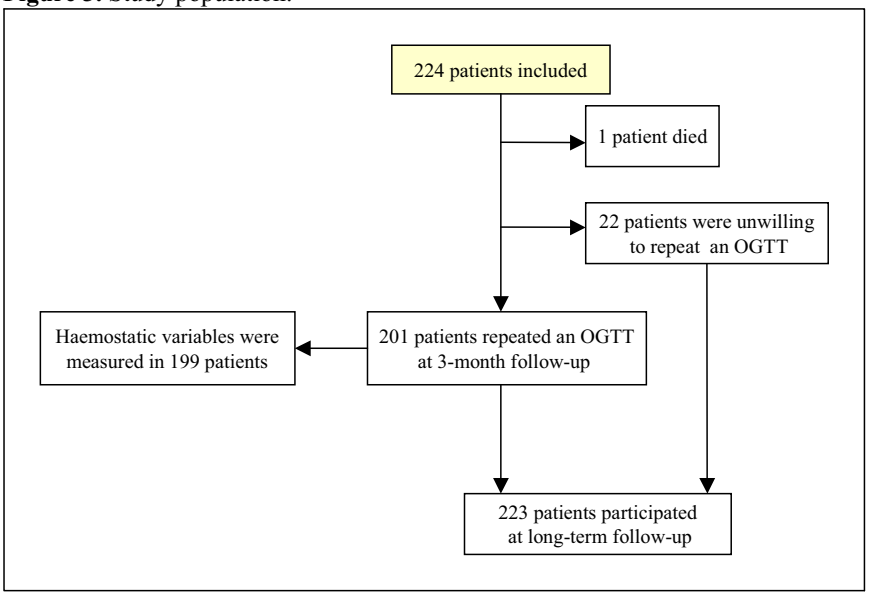
- to investigate any associations between circulating levels of selected haemostatic variables measured in-hospital and the presence of abnormal glucose regulation classified at three-month follow-up (Paper IV).
- to explore changes in measured haemostatic variables from baseline to follow-up in patients with or without abnormal glucose regulation classified at follow-up (Paper IV).

6. Material and methods

6.1 Study subjects and design

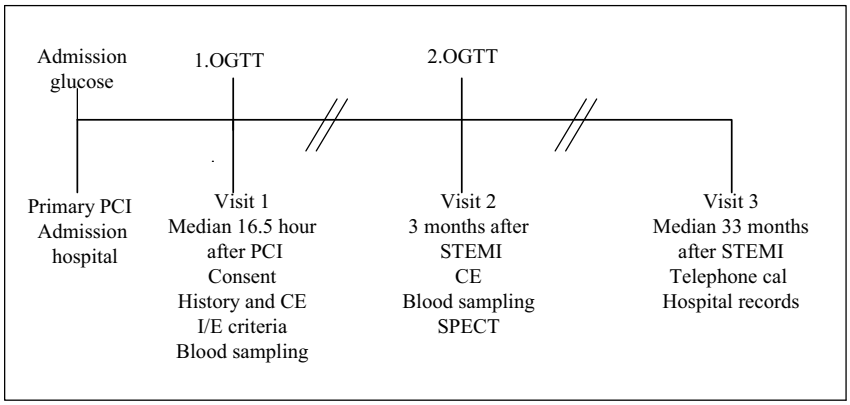
All papers report results from the same cohort of 224 patients with a primary PCI treated STEMI admitted to the coronary care unit at Oslo University Hospital, Ullevål, Oslo, Norway, between November 2005 and May 2007 (Figure 3).

Figure 3. Study population.



At enrolment, patients were clinical and hemodynamically stable, without persistent glyseroltrinitrat infusion, chest pain, nausea or symptoms of heart failure. Patients with previously known diabetes, persistent hyperglycaemia, serum creatinine concentration ≥ 200 umol/L, or age > 85 years were excluded.

Figure 4. Study design



CE; clinical examination, I/E; inclusion/exclusion, SPECT; Single Photon Emission Computed Tomography.

The study design is shown in Figure 4. The first OGTT was performed after an overnight fast, before transfer from the coronary care unit back to the referring hospitals.

The second OGTT was performed after an overnight fast in a stable condition at three-month follow-up. The Regional Ethics Committee approved the study and all patients gave written informed consent. The study is registered at www.clinicaltrials.gov, NCTC00926133.

Paper II was a follow-up study. The date of inclusion was set to the date when the primary PCI was performed. In June 2009, at a median follow up time of 33 months, the patients were contacted and interviewed by telephone, regarding their health status, and any hospital admissions. Final closing date was set to August 1st 2009. The primary endpoint of the study was defined as the composite of the first event of non-fatal myocardial re-infarction, recurrent ischemia causing hospital admission, stroke, and all cause mortality. An end-point committee classified the end-points according to the hospital records, and death certificates were obtained from the Norwegian Death certificate Registry.

In paper III fasting blood samples drawn in-hospital mainly in the first morning (between 8:00-10:00 am) after the acute MI were used for determination of a panel of inflammatory variables known to be of importance in the atherosclerotic process.

In paper IV fasting blood samples drawn mainly the first morning after the acute MI and in a stable condition at three-month follow-up (between 8:00-10:00 am) were used for determination of the selected haemostatic variables.

6.2 Classification of glucometabolic state

A standardised OGTT (75g glucose in 200 ml water with plasma glucose measurements at 0 and 120 min) was performed in-hospital (median 16.5 hours after acute PCI) and at an outpatient visit three months later. The classification of glucometabolic state was based on the result of the OGTT and the patients were divided into one of the following four categories according to the WHO criteria (Table 1) [14].

Table 1 Criteria used for glucometabolic classification according to WHO 2005 [14].

Glucometabolic category	Classification criteria (plasma glucose in mmol/l)
Normal glucose tolerance (NGT)	
Fasting glucose	<6.1
2-hour glucose	<7.8
Impaired fasting glucose (IFG)	
Fasting glucose	≥6.1 and <7.0
2-hour glucose	<7.8
Impaired glucose tolerance (IGT)	
Fasting glucose	<7.0
2-hour glucose	≥7.8 and <11.1
Diabetes mellitus (T2DM)	
Fasting glucose	≥7.0
2-hour glucose	≥11.1

The term abnormal glucose regulation was defined as the sum of IFG, IGT and T2DM.

6.3 Classification of acute STEMI.

STEMI was defined according to the universal definition of MI as typical rise and fall of the cardiac biomarker troponin T (TnT) with at least one value above the 99th percentile of the upper reference limit in patients presenting with symptoms of ischemia together with ECG changes indicative of new ST elevation at the J-point in two contiguous leads with the cut-off points: 0.2 mV in men or 0.15 mV in women in leads V2–V3 and/or 0.1 mV in other leads *or* new left bundle-branch block [20].

6.4 Laboratory methods

Admission plasma glucose was analysed from blood samples drawn in the catheterisation laboratory as soon as possible after PCI. Further blood samples were drawn at inclusion and at three-month follow-up in a fasting condition between 8-10 a.m. Plasma glucose, HbA1c, and other routine analyses were determined by use of conventional methods. Serum cardiac specific Troponin T (TnT) was measured by electrochemiluminescence technology for quantitative measurement as described in paper I. Circulating levels of serum insulin, serum proinsulin, and inflammatory and haemostatic variables, were measured by commercially available enzyme immunoassay, as described in detail in paper II, III and IV. All blood samples except routine samples were stored at -80°C until analysis.

Left ventricular ejection fraction and infarct size expressed as percent of left ventricular mass, were assessed at rest at three-month follow-up by Single Photon Emission Computed Tomography imaging with technetium 99 m-tetrofosmin. The method is described in detail in paper II.

6.6 Statistics

The study design was a prospective observational cohort study. Due to skewness in most of the measured variables, non-parametric statistics were used throughout. Continuous variables are presented as median values with 25th, 75th percentiles and categorical variables as proportions. Differences among groups were analysed by Mann-Whitney test for continuous variables and the chi-squared test for categorical data. The null hypothesis was rejected if the p-value was below 0.05. The STROBE guidelines were followed [77]. Statistical analyses were performed using Epi-info software (2005, version 3.3.2) except for Spearman correlation coefficient and multiple linear regressions analyses that were made using SPSS version 6.0 for windows (SPSS Inc., Chicago, Illinois, USA).

In **paper I, III and IV** an explanatory strategy was followed. A potential independent association between different exposition variables and outcome (disease) were studied. Outcome was defined as abnormal glucose regulation. All exposition variables were dichotomized in the model. Continuous exposition variables were dichotomised into high and low levels based on a linear trend analysis across quartiles with identification of the cut off point. Other traditional risk factors that were not a part of the causal chain (exposition to outcome) were analyzed as potential confounders or effect modifiers on this association. The Mantel-Haenszel method (a stratification model) was used to quantify potential confounders based on the assumption that the true exposition – outcome odds ratio is the same in each stratum, and that the reason for differences in the observed odds ratios between strata is only sampling variations. However, if the effect of exposition on outcome varies in the two strata according to a risk factor, heterogeneity between strata is present and the risk factor is identified as an effect modifier and not a confounder. The Breslow and Day test of heterogeneity was used to highlight potential effect modification before quantifying potential

confounders by the Mantel-Haenszel model [78]. Potential confounders that were associated with the exposition and / or outcome with a p-value <0.2, were included in the model. Finally, logistic regression models, including backward elimination procedures were performed to adjust for potential confounders on the association between exposition and outcome.

Paper II was a follow-up study. Both univariate and multivariate analyses of this cohort with censored data were performed (Kaplan–Meier survival, Log-Rank test and Cox proportional hazard models).

7. Summary of results

7.1 Paper I

We investigated the prevalence of abnormal glucose regulation in a primary PCI treated STEMI population without known diabetes by performing an OGTT early in-hospital and at three-month follow-up. The prevalence of abnormal glucose regulation in-hospital and at three month was 47% and 25%, respectively. The observed reproducibility of the OGTT performed in-hospital and when repeated after three-month follow-up was poor. Only 54% of the patients were classified into the same glucometabolic state at both occasions. Additionally, we studied a potential association between HbA1c, admission glucose and fasting glucose measured during the acute STEMI and abnormal glucose regulation classified by an OGTT at three-month follow-up. High levels of HbA1c, as well as admission glucose were associated with abnormal glucose regulation classified three months later with an adjusted odds ratio of 3.8 (95% CI 1.8, 7.8) and 2.2 (1.0, 4.3), respectively. High levels of fasting glucose were associated with abnormal glucose regulation with an adjusted odds ratio of 5.5 (2.0, 15.1), but only in patients with small or medium-sized MI (TnT<8.80 ug/L).

7.2 Paper II

We prospectively followed the cohort for a median time of 33 months ((25, 75 % percentiles) 27, 39). In the total population the long-term clinical outcome was excellent with a low event-rate. Subsequently, clinical outcome were correlated to the glucometabolic condition found. The results from the OGTT performed early in-hospital and at three months follow-up were both correlated to clinical events. The composite endpoint was defined as all cause mortality, non-fatal re-infarction, stroke and recurrent ischemia causing hospital admission. No significant difference in survival free of composite end-point was found between the groups

when classified either by an OGTT in-hospital or at three-month follow-up (Log-Rank p=0.38 and p=0.26, respectively).

7.3 Paper III

We investigated a potential association between the circulating inflammatory markers and hyperglycaemia measured during the acute STEMI. No significant associations were observed. Subsequently, we studied a potential association between the levels of inflammatory markers measured during the acute STEMI and abnormal glucose regulation classified by an OGTT at three-month follow-up. We found that high levels of CRP and MCP-1 measured acutely were associated with abnormal glucose regulation at three-month follow-up (adjusted odds ratio 3.2 (95 % CI 1.5, 6.8) and 7.6 (1.7, 34.2)). The association between high levels of MCP-1 and abnormal glucose regulation were, however, present only in the 150 patients with normal levels of triglycerides (<1.8 mmol/l).

7.4 Paper IV

A potential association between four selected haemostatic variables measured during the acute STEMI and abnormal glucose regulation classified by an OGTT at three-month follow-up was investigated. High levels of circulating PAI-1 activity and t-PA antigen measured acutely were associated with abnormal glucose regulation classified three months later (adjusted odds ratio 2.2 (95 % CI 1.1, 4.4) and 3.5 (1.5, 8.2)). The association between high levels of t-PA antigen and abnormal glucose regulation was, however, present only in men. Finally, we investigated changes in the levels of haemostatic variables when measured acutely and again at three-month follow-up according to glucometabolic state. The levels of all the haemostatic variables were lower when measured in a stable condition. There were no significant differences in changes in the measured variables from baseline to three-month follow-up

between patients with or without abnormal glucose regulation. However, after adjustments for infarct size, age and gender the reduction in the levels of prothrombin fragment 1+2 (F_{1+2}) was significantly more pronounced in patients with abnormal compared to normal glucose regulation ($p=0.04$).

8. Discussion

8.1 Prevalence of abnormal glucose regulation.

In paper I, the main approach was to evaluate the reliability of an OGTT-based glucometabolic classification performed in-hospital and at three-month follow-up in a STEMI population in order to elucidate the prevalence of abnormal glucose regulation and the reproducibility of an OGTT.

The first report on a high incidence of glucosuria in patients with myocardial infarction was published in 1922 [79]. Later on it became evident that transient hyperglycaemia was common during acute MI [80]. However, the mechanisms for this phenomenon are still unclear. Hyperglycaemia may result from a transient stress-induced response or a latent impairment in β-cell function [81-83]. Furthermore, hyperglycaemia during acute MI has been shown to be a risk factor for future cardiovascular events and according to guidelines, this potential disturbance should be diagnosed before discharge or early after [31,84]. In the Swedish GAMI trial, the prevalence of abnormal glucose regulation at discharge and at three-month follow-up was 66% (IGT 35% and T2DM 31%) and 65 % (IGT 40% and T2DM 25%), respectively [7]. In the present study the prevalence in-hospital and at follow-up was 47% (IGR 36 % and T2DM 11%) and 25% (IGR 20% and T2DM 5%), respectively. The prevalence in-hospital was in accordance with previous studies [7-9], however, at follow-up the prevalence was unexpectedly low and not in line with the above mentioned GAMI trial [7]. Very recently a Polish study group reported new prevalence results from a MI population comparable to our results [85]. They included patients with acute STEMI without previously known diabetes and performed an OGTT before discharge and at three-month follow-up. The prevalence of abnormal glucose regulation at discharge and at three-month follow-up was 48% (IGR 34 % and T2DM 14%) and 29% (IGR 24 % and T2DM 5%), respectively [85] (Table 2).

In the present study the OGTT was used as a screening tool and the test was performed very early after the acute MI, mainly during the first day after admission. The OGTT has been criticized regarding the poor reproducibility and the poor validity of a single test. Additionally, an OGTT are well known to be time-consuming and burdensome to perform [16]. However, a single blood glucose measurement 60 minutes after ingestion of 75 g glucose or a standardized OGTT performed the fourth day after acute MI have been shown to associate with abnormal glucose regulation three months later [83].

The reproducibility of the OGTT is frequently assessed by kappa statistics [86]. In the present study the criteria for use of kappa statistics were not met due to two different test situations, during acute illness and in a stable condition. As a replacement for kappa statistics the observed reproducibility of the OGTT was used [87]. The observed reproducibility was poor, only 54 % of the patients were classified into the same glucometabolic state at both occasions. This result is in line with similar studies, (Table 2) [18,85,88,89]. Poor reproducibility is partly due to the considerable day-to-day within person variability of up to 40 % in blood glucose concentrations measured during OGTTs [88].

Table 2 The prevalence of abnormal glucose regulation (AGR) in hospital and at three-month, and the observed reproducibility, in three different studies on patients with acute MI.

	AGR Prevalence (%) In-hospital	AGR Prevalence (%) At three-month	Observed reproducibility
Norhammar A et al. [7]	66	65	49
Knudsen EC et al. (Paper I)	47	25	54
Bronisz A et al.[85]	48	29	60

The guidelines from 2008 on management of acute MI in patients with persistent ST-segment elevation recommend an OGTT to be performed before or early after discharge in patients without previously known diabetes [84]. Based on our results, which was confirmed by the

polish study, such recommendations might not be advisable in patients with MI. In a relatively young patient population with uncomplicated MI it seems reasonable to postpone an OGTT screening to clinical follow-up, after the patients have been stabilized.

An alternative test in diagnosing glucometabolic disturbances is HbA1c. In the present study, HbA1c measured early after an acute STEMI was significantly associated with abnormal glucose regulation classified at follow-up. HbA1c measured at admission in patients with acute MI without known diabetes has in some studies been shown to associate with newly diagnosed diabetes at three-month follow-up [7,90], however, conflicting results exist [85,91]. Previously, HbA1c has not been recommended as a diagnostic test for several reasons. A standardized method for measuring HbA1c has been lacking. The test is unreliable in patients with anaemia or hemoglobinopathies and the existing assays are relatively expensive [16]. When the present study was almost finished, an international expert committee with members appointed by the ADA, the European Association for the study of Diabetes, and the International Diabetes Federation have recommended the use of HbA1c in the diagnosis of diabetes [16]. In January 2011, WHO adapted this recommendation [92].

8.2 Prognostic aspects.

In paper II our main findings were that patients with uncomplicated acute STEMI, without previously known diabetes, have an excellent long-term prognosis independent of abnormal glucose regulation classified either in-hospital or in a stable condition at three-month follow-up. However, it should be pointed out that five out of six patients, who died during follow-up, were classified with abnormal glucose regulation in-hospital. The present results are not in line with the similar sized follow-up study of the GAMI trial that found a worse prognosis in patients with acute MI and newly diagnosed abnormal glucose tolerance (IGT, T2DM) [31].

However, the GAMI trial is not fully comparable with our study, as demonstrated in Table 3. The Swedish patients were older, included a mixed group of patients with NSTEMI and STEMI, and only 5 % and 38 % of the patients underwent primary PCI or thrombolysis, respectively. Coronary revascularization has been shown to have a positive impact on one-year prognosis in patients with CAD and diabetes [93]. In the present study 100 % of the patients underwent primary PCI and received double anti-platelet treatment.

Table 3 Differences in baseline characteristics between the GAMI trial and the present study.

	Norhammar et al [7] (n=181)	Knudsen et al (Paper I) (n=224)
Age (years) (mean,SD)	63.5 (9.4)	59 (11.3)
Male	123 (68%)	185 (83%)
Previous disorder:		
Myocardial infarction	36 (20%)	16 (7%)
Angina pectoris	60 (33%)	7 (3%)
Heart failure	14 (8%)	0
Hypertension (treated)	57 (31%)	58 (26%)
Hyperlipidaemia (treated)	27 (15%)	20 (9%)
BMI (kg/m2) (mean,SD)	26.6 (4.1)	26.6 (3.4)
Current smoker	61 (34%)	109 (49%)
HbA1c at admission (%) (mean,SD)	5.0 (0.6)	5.6 (0.3)
Blood glucose at admission (mmol/L) (mean,SD)	6.5 (1.4)	7.1 (1.5)
Treatment during hospital stay and at discharge		
Primary PCI	9 (5%)	224 (100%)
Thrombolysis	68 (38%)	0
Aspirin	93 %	100%
Clopidogrel	---	99%
β-blockers	92%	81%
Lipid lowering agents	66%	99%
Angiotensin converting enzyme-inhibitors	14%	16%
Angiotensin II-receptor blockers	---	8%

The follow-up study of the Euro Heart Survey on diabetes and the heart that included a mixed population with acute and stable CAD showed that patients with CAD and previously known

diabetes had poor prognosis, while patients with newly diagnosed type 2 diabetes were at an intermediate risk. Impaired glucose regulation (IFG, IGT) was, however, not identified as an independent predictor of poor outcome during one-year follow-up [30]. The follow-up time in the Euro Heart Survey on diabetes and the heart might have been too short to demonstrate a difference in clinical outcome between patients with normal and impaired glucose regulation. In a Japanese study on patients with acute MI, newly detected abnormal glucose tolerance (IGT, T2DM) was shown to be a risk factor for future cardiovascular events after five years follow-up [94].

In our patient population only 24 and 10 patients were diagnosed with newly detected diabetes in-hospital and at follow-up, respectively. Few patients with newly diagnosed diabetes, a relatively young patients population, a majority of first episode of MI and a high frequency of patients with one-vessel disease, may explain the excellent prognosis found in the present study compared to the results from the follow-up of the GAMI trial and the Euro Heart Survey on diabetes and the heart [30,31]. Finally, with a relatively small sample size and a limited number of endpoints, we should be cautious with the interpretation of the present results. An increased risk of type II errors might have been present.

8.3 Inflammation and abnormal glucose regulation.

In paper III we showed that elevated levels of MCP-1 and CRP measured in-hospital in our patient population were associated with abnormal glucose regulation classified at three-month follow-up. Growing evidence support that inflammation plays an important role in atherosclerosis and CVD [95]. The levels of CRP have been shown to be elevated in patients with STEMI [96,97]. However, there are controversies concerning the stimuli of CRP production following revascularized MI. Increased circulating levels have been suggested to reflect either the inflammatory response to vascular damage or the systemic inflammatory

response to myocardial damage [98]. CRP is produced by the liver as a response to stimulation by interleukin-6 (IL-6) that has been suggested to partly be released from the ischemic myocardium after MI [99].

MCP-1 is a chemokine suggested to recruit a proinflammatory subgroup of monocytes to sites of atherosclerosis [95]. Patients with an acute MI seem to have a biphasic monocyte response with a peak in pro-inflammatory monocytes after 3 days, and a reparative monocytes reaction dominating at 5 days [100]. In diabetic patients, circulating MCP-1 levels were shown to correlate with HbA1c, BMI, and triglycerides and the serum levels of MCP-1 were significantly higher in diabetic than in non-diabetic patients [101].

In the present study, the association between levels of CRP and MCP-1 measured in-hospital and abnormal glucose regulation classified at follow-up may indicate that impaired beta-cell function or transient hyperglycaemia during acute illness may activate the immune system during acute STEMI. Experimental hyperglycaemia has been shown to acutely increase the concentration of various cytokines (IL-6, tumor necrosis factor-alpha, and interleukin-18 (IL-18)) in subjects with both normal and impaired glucose tolerance, and the effect was more pronounced in the latter [102]. Furthermore, incubation of endothelial cells with CRP increased the endothelin-1 production, decreased endothelial nitric oxide release and upregulated adhesion molecules and MCP-1 expression [103]. These proatherogenic effects of CRP were further potentiated in the presence of hyperglycaemia [103]. In line with this, in patients with acute MI, hyperglycaemia was associated with increased levels of inflammatory markers such as CRP and IL-18 [104]. In a substudy from the present cohort of STEMI patients, we demonstrated that activin A, a member of the transforming growth factor (TGF)-β superfamily, was significantly associated with abnormal glucose regulation in patients with acute MI. Additionally, in vitro findings indicated that this association may represent a counteracting mechanism to protect against inflammation, hyperglycaemia, and oxidative

stress [105]. All studies taken together, stress-induced hyperglycaemia or hyperglycaemia related to impaired β-cell function during acute MI, seem to be markers of multiple metabolic disorders that may influence the outcome of an acute MI.

8.4 Haemostasis and abnormal glucose regulation.

In paper IV we demonstrated that elevated levels of PAI-1 activity and t-PA antigen measured in-hospital in our study population were significantly associated with abnormal glucose regulation classified at three-month follow-up. Additionally, the reduction (from baseline to follow-up) in the levels of F_{1+2} was significantly more pronounced in patients with abnormal compared to normal glucose regulation. These results indicate that patients with abnormal glucose regulation have a more prothrombotic response during acute STEMI. These results are in line with previous studies, which have shown that type 2 diabetes and CAD are known prothrombotic conditions due to suppressed fibrinolysis, enhanced coagulation and alterations in platelet reactivity [44,55,106,107].

Suppressed fibrinolysis seems to be associated with type 2 diabetes and CAD mainly due to elevated levels of the fibrinolytic inhibitor, PAI-1 [62,108]. The mechanisms that link this suppressed fibrinolysis to glucometabolic abnormalities and CAD are, however, unknown although in vitro studies have reported that excess insulin may induce PAI-1 expression in liver cells [62,109]. Additionally, hyperglycaemia seems to increase PAI-1 expression and secretion in endothelial cells and PAI-1 is expressed in adipose tissue [55,110-113]. However, these results have not been reproduced in vivo. Hyperinsulinaemia generated during an OGTT in patients with CAD, were shown to decrease PAI-1 activity and hyperinsulinaemia during glucose clamp showed the same pattern [114-116]. Another study indicates that PAI-1 secretion probably is dependent on a combination of several metabolic factors [116].

Tissue plasminogen activator, the activator of the fibrinolytic system is mainly assessed as t-PA antigen, reflecting both free t-PA and t-PA in complex with PAI-1 [66]. Elevated levels of t-PA antigen have been found in patients with both acute MI and in patients with abnormal glucose regulation [106,117]. t-PA antigen are associated with endothelial cell dysfunction and is thought to be a robust biomarker of widespread atherosclerosis [118,119]. In our study, however, elevated levels of t-PA antigen were probably a measure of elevated PAI-1 activity. Furthermore, in the present work the level of F_{1+2} declined more (from baseline to follow-up) in patients with abnormal compared to normal glucose regulation, indicating an elevated prothrombotic profile in these patients during acute illness. Markers of thrombin generation such as F_{1+2} and thrombin-anti-thrombin complexes have previously been found to be elevated in diabetes [68]. In addition, improved glycemic control in type 2 diabetes has been shown to decrease thrombogenecity irrespective of treatment allocation [120].

As pointed out in paper III and IV patients classified with abnormal compared to normal glucose regulation in a stable condition after STEMI appeared to have an enhanced inflammatory and prothrombotic condition during hospitalization. Inflammation in combination with transient hyperglycaemia and or hyperinsulinemia in vivo has been shown to induce excess coagulation and reduced fibrinolytic activity [73]. Acute stress-induced hyperglycaemia, a latent pre-existing disturbance in glucose metabolism accompanied by hyperinsulinemia during the acute STEMI or both, may explain the enhanced inflammatory and prothrombotic condition found in this patient population. Our findings of a prothrombotic condition in patients with abnormal glucose regulation reinforce previous data showing a prothrombotic phenotype in patients with diabetes mellitus and insulin resistance.

8.5 Limitations

The recruiting hospital, Oslo University Hospital, Ullevål serves patients from the east regions of Norway and stable patients are regularly returned back to the referring hospitals within 24-hours after PCI treatment. The short duration of hospitalization limited the ability to do a more thorough investigation of glucose regulation during the acute STEMI, including repeated OGTTs before hospital discharge.

Furthermore, according to the described exclusion criteria a selection bias towards more glucometabolically normal patients with a low proportion of incident type 2 diabetes, may be present. Additionally, at inclusion, all patients were hemodynamically stable without clinical signs of heart failure or cardiogenic shock, which may explain the low incidence of new events during follow-up.

9. Conclusions

The main conclusions from the present work are summarized as follows:

- The prevalence of abnormal glucose regulation found in our cohort was lower than previously reported in patients with acute MI. The prevalence in-hospital was relatively high, but half of these patients were classified as having normal glucose regulation when re-tested at three-month follow-up. Based on our findings, an early OGTT should probably not be recommended, whereas an OGTT performed in a stable condition during follow-up in order to identify patients with persistent glucometabolic disturbances, seems advisable (Paper I).
- High levels of HbA1c, admission plasma glucose and fasting plasma glucose (except in patients with large MI) measured in-hospital were associated with abnormal glucose regulation classified by an OGTT at three-month follow-up, indicating that these variables can be used as early markers of a long standing glucometabolic disturbance in patients with acute STEMI (Paper I).

- Hemodynamically stable patients with a primary PCI treated STEMI without previously known diabetes seem to have an excellent long-term prognosis. Additionally, clinical outcome seems to be independent of the presence of newly diagnosed abnormal glucose regulation (whether classified in-hospital or at three-month follow-up) within a three years follow-up period. Any effect of abnormal glucose regulation on long-term prognosis (> three years) cannot be interpreted from the present work (Paper II).

- Elevated levels of CRP and MCP-1 measured in-hospital in our study population were associated with abnormal glucose regulation classified by an OGTT at three-month

follow-up, indicating a proinflammatory state during acute STEMI in patients with stress induced hyperglycaemia or impaired pancreatic β-cell function (Paper III).

- Elevated levels of PAI-1 activity and t-PA antigen measured in-hospital in the same study population were associated with abnormal glucose regulation classified at three-month follow-up. Furthermore, the decline (from baseline to follow-up) in the levels of $F_{1+2,}$ a measure of thrombin generation, was significantly more pronounced in patients with abnormal compared to normal glucose regulation. The data indicate an enhanced prothrombotic condition during acute STEMI in patients with newly detected abnormal glucose regulation (Paper IV).

Reference List

1 **Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes* 1995; 44: 369-74.**

2 **Abbud ZA, Shindler DM, Wilson AC, Kostis JB. Effect of diabetes mellitus on short- and long-term mortality rates of patients with acute myocardial infarction: a statewide study. Myocardial Infarction Data Acquisition System Study Group. *Am Heart J* 1995; 130: 51-8.**

3 **Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 1999; 48: 937-42.**

4 **Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979; 241: 2035-8.**

5 **Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; 339: 229-34.**

6 **Demir I, Yilmaz H, Basarici I, Sancaktar O, Deger N. Primary percutaneous coronary interventions in acute myocardial infarction in diabetic versus non-diabetic patients. In-hospital and long-term results. *Kardiol Pol* 2003; 58: 182-9.**

7 **Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; 359: 2140-4.**

8 **Hu DY, Pan CY, Yu JM. The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey. *Eur Heart J* 2006; 27: 2573-9.**

9 **Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, Standl E, Soler-Soler J, Ohrvik J. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880-90.**

10 **Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 4-14.**

11 **Stene LC, Midthjell K, Jenum AK, Skeie S, Birkeland KI, Lund E, Joner G, Tell GS, Schirmer H. [Prevalence of diabetes mellitus in Norway]. *Tidsskr Nor Laegeforen* 2004; 124: 1511-4.**

12 **World Health Organization Department of Noncommunicable Disease Surveillance G. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complication Report of a WHO Consultation 1999, 1-59 1999:1-59. Available from: URL:** http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf

13 **Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; 20: 1183-97.**

14 **World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia Report of a WHO/IDF Consultation 2005, 1-46 2005:1-46. Available from: URL: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf**

15 **Defronzo RA, Ferrannini E, Simonson DC. Fasting hyperglycemia in non-insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. *Metabolism* 1989; 38: 387-95.**

16 **Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes: Diabetes Care 2009; 32(7): 1327-1334. *Clin Biochem Rev* 2009; 30: 197-200.**

17 **Ryden L, Standl E, Bartnik M, Van den BG, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; 28: 88-136.**

18 **Wallander M, Malmberg K, Norhammar A, Ryden L, Tenerz A. Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study. *Diabetes Care* 2008; 31: 36-8.**

19 **World Health Organization Cardiovascular diseases (CVDs). Fact sheet N°317Updated September 2009 2010Available from: URL: http://www.who.int/mediacentre/factsheets/fs317/en/index.html**

20 **Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007; 28: 2525-38.**

21 **Shah PK, Forrester JS. Pathophysiology of acute coronary syndromes. *Am J Cardiol* 1991; 68: 16C-23C.**

22 **Norhammar A, Malmberg K, Ryden L, Tornvall P, Stenestrand U, Wallentin L. Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. *Eur Heart J* 2003; 24: 838-44.**

23 **De BD, De BG, Ostor E, Simon J, Pyorala K. Predictive value of classical risk factors and their control in coronary patients: a follow-up of the EUROASPIRE I cohort. *Eur J Cardiovasc Prev Rehabil* 2003; 10: 289-95.**

24 **Norhammar AM, Ryden L, Malmberg K. Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients. *Diabetes Care* 1999; 22: 1827-31.**

25 Lavi S, Kapeliovich M, Gruberg L, Roguin A, Boulos M, Grenadier E, Amikam S, Markiewicz W, Beyar R, Hammerman H. Hyperglycemia during acute myocardial infarction in patients who are treated by primary percutaneous coronary intervention: impact on long-term prognosis. *Int J Cardiol* 2008; 123: 117-22.

26 Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 2000; 355: 773-8.

27 Gasior M, Pres D, Stasik-Pres G, Lech P, Gierlotka M, Hawranek M, Wilczek K, Szygula-Jurkiewicz B, Lekston A, Kalarus Z, Strojek K, Gumprecht J, Polonski L. Effect of blood glucose levels on prognosis in acute myocardial infarction in patients with and without diabetes, undergoing percutaneous coronary intervention. *Cardiol J* 2008; 15: 422-30.

28 Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008; 117: 1610-9.

29 Suleiman M, Hammerman H, Boulos M, Kapeliovich MR, Suleiman A, Agmon Y, Markiewicz W, Aronson D. Fasting glucose is an important independent risk factor for 30-day mortality in patients with acute myocardial infarction: a prospective study. *Circulation* 2005; 111: 754-60.

30 Lenzen M, Ryden L, Ohrvik J, Bartnik M, Malmberg K, Scholte Op RW, Simoons ML. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2006; 27: 2969-74.

31 Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. *Eur Heart J* 2004; 25: 1990-7.

32 Petersen KF, Shulman GI. Etiology of insulin resistance. *Am J Med* 2006; 119: S10-S16.

33 Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. *Clin Biochem* 2009; 42: 1331-46.

34 Dyck DJ, Heigenhauser GJ, Bruce CR. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. *Acta Physiol (Oxf)* 2006; 186: 5-16.

35 Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104: 787-94.

36 Laakso M, Kuusisto J. Diabetology for cardiologists. *European Heart Journal Supplements* 2003; 5: B5-B13.

37 Ross R. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999; 340: 115-26.

38 Libby P. Inflammation and cardiovascular disease mechanisms. *Am J Clin Nutr* 2006; 83: 456S-60S.

39 Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685-95.

40 Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation* 1995; 92: 657-71.

41 Pradhan AD, Ridker PM. Do atherosclerosis and type 2 diabetes share a common inflammatory basis? *Eur Heart J* 2002; 23: 831-4.

42 Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002; 287: 2570-81.

43 Ziegler D. Type 2 diabetes as an inflammatory cardiovascular disorder. *Curr Mol Med* 2005; 5: 309-22.

44 Grant PJ. Inflammatory, atherothrombotic aspects of type 2 diabetes. *Curr Med Res Opin* 2005; 21 Suppl 1: S5-12.

45 Felmeden DC, Lip GY. Endothelial function and its assessment. *Expert Opin Investig Drugs* 2005; 14: 1319-36.

46 Young JL, Libby P, Schonbeck U. Cytokines in the pathogenesis of atherosclerosis. *Thromb Haemost* 2002; 88: 554-67.

47 Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004; 24: 816-23.

48 Dragomir E, Simionescu M. Monocyte chemoattractant protein-1--a major contributor to the inflammatory process associated with diabetes. *Arch Physiol Biochem* 2006; 112: 239-44.

49 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973-9.

50 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836-43.

51 Zieske AW, Tracy RP, McMahan CA, Herderick EE, Homma S, Malcom GT, McGill HC, Jr., Strong JP. Elevated serum C-reactive protein levels and advanced atherosclerosis in youth. *Arterioscler Thromb Vasc Biol* 2005; 25: 1237-43.

52 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327-34.

53 Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 2002; 25: 2016-21.

54 Matsumori A, Furukawa Y, Hashimoto T, Yoshida A, Ono K, Shioi T, Okada M, Iwasaki A, Nishio R, Matsushima K, Sasayama S. Plasma levels of the monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 are elevated in patients with acute myocardial infarction. *J Mol Cell Cardiol* 1997; 29: 419-23.

55 Grant PJ. Diabetes mellitus as a prothrombotic condition. *J Intern Med* 2007; 262: 157-72.

56 Gryglewski RJ, Botting RM, Vane JR. Mediators produced by the endothelial cell. *Hypertension* 1988; 12: 530-48.

57 Trovati M, Anfossi G. Influence of insulin and of insulin resistance on platelet and vascular smooth muscle cell function. *J Diabetes Complications* 2002; 16: 35-40.

58 Hajek AS, Joist JH, Baker RK, Jarett L, Daughaday WH. Demonstration and partial characterization of insulin receptors in human platelets. *J Clin Invest* 1979; 63: 1060-5.

59 Betteridge DJ, El Tahir KE, Reckless JP, Williams KI. Platelets from diabetic subjects show diminished sensitivity to prostacyclin. *Eur J Clin Invest* 1982; 12: 395-8.

60 Anfossi G, Mularoni EM, Burzacca S, Ponziani MC, Massucco P, Mattiello L, Cavalot F, Trovati M. Platelet resistance to nitrates in obesity and obese NIDDM, and normal platelet sensitivity to both insulin and nitrates in lean NIDDM. *Diabetes Care* 1998; 21: 121-6.

61 Vinik AI, Erbas T, Park TS, Nolan R, Pittenger GL. Platelet dysfunction in type 2 diabetes. *Diabetes Care* 2001; 24: 1476-85.

62 Juhan-Vague I, Roul C, Alessi MC, Ardissone JP, Heim M, Vague P. Increased plasminogen activator inhibitor activity in non insulin dependent diabetic patients--relationship with plasma insulin. *Thromb Haemost* 1989; 61: 370-3.

63 Andersen P, Seljeflot I, Abdelnoor M, Arnesen H, Dale PO, Lovik A, Birkeland K. Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. *Metabolism* 1995; 44: 611-6.

64 Folsom AR, Qamhieh HT, Wing RR, Jeffery RW, Stinson VL, Kuller LH, Wu KK. Impact of weight loss on plasminogen activator inhibitor (PAI-1), factor VII,

and other hemostatic factors in moderately overweight adults. *Arterioscler Thromb* 1993; 13: 162-9.

65 Vaughan DE. PAI-1 and atherothrombosis. *J Thromb Haemost* 2005; 3: 1879-83.

66 Dobrovolsky AB, Titaeva EV. The fibrinolysis system: regulation of activity and physiologic functions of its main components. *Biochemistry (Mosc)* 2002; 67: 99-108.

67 Jansson JH, Olofsson BO, Nilsson TK. Predictive value of tissue plasminogen activator mass concentration on long-term mortality in patients with coronary artery disease. A 7-year follow-up. *Circulation* 1993; 88: 2030-4.

68 Carr ME. Diabetes mellitus: a hypercoagulable state. *J Diabetes Complications* 2001; 15: 44-54.

69 Jones RL. Fibrinopeptide-A in diabetes mellitus. Relation to levels of blood glucose, fibrinogen disappearance, and hemodynamic changes. *Diabetes* 1985; 34: 836-43.

70 Ceriello A, Giugliano D, Quatraro A, Dello RP, Marchi E, Torella R. Hyperglycemia may determine fibrinopeptide A plasma level increase in humans. *Metabolism* 1989; 38: 1162-3.

71 Boden G, Vaidyula VR, Homko C, Cheung P, Rao AK. Circulating tissue factor procoagulant activity and thrombin generation in patients with type 2 diabetes: effects of insulin and glucose. *J Clin Endocrinol Metab* 2007; 92: 4352-8.

72 Ceriello A, Giugliano D, Quatraro A, Dello RP, Torella R. Blood glucose may condition factor VII levels in diabetic and normal subjects. *Diabetologia* 1988; 31: 889-91.

73 Stegenga ME, van der Crabben SN, Blumer RM, Levi M, Meijers JC, Serlie MJ, Tanck MW, Sauerwein HP, van der PT. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. *Blood* 2008; 112: 82-9.

74 Lemkes BA, Hermanides J, Devries JH, Holleman F, Meijers JC, Hoekstra JB. Hyperglycemia: a prothrombotic factor? *J Thromb Haemost* 2010; 8: 1663-9.

75 Johansen OE, Birkeland KI, Brustad E, Aaser E, Lindahl AK, Midha R, Ueland T, Aukrust P, Gullestad L. Undiagnosed dysglycaemia and inflammation in cardiovascular disease. *Eur J Clin Invest* 2006; 36: 544-51.

76 Andersen GO, Eritsland J, Aasheim A, Neuburger J, Knudsen EC, Mangschau A. Impaired glucose tolerance in patients with acute myocardial infarction. *Tidsskr Nor Laegeforen* 2006; 126: 2264-7.

77 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453-7.

78 Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research. Principles and quantitative methods. New York: Van Nostrand Reinhold Company Inc; 1982.

79 Levine SA. Angina pectoris. Some clinical considerations. *JAMA* 1922; 79: 928-33.

80 Opie LH, Stubbs WA. Carbohydrate metabolism in cardiovascular disease. *Clin Endocrinol Metab* 1976; 5: 703-29.

81 Lukomsky PE, Oganov RG. Blood plasma catecholamines and their urinary excretion in patients with acute myocardial infarction. *Am Heart J* 1972; 83: 182-8.

82 Opie LH. Metabolic management of acute myocardial infarction comes to the fore and extends beyond control of hyperglycemia. *Circulation* 2008; 117: 2172-7.

83 Tenerz A, Norhammar A, Silveira A, Hamsten A, Nilsson G, Ryden L, Malmberg K. Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. *Diabetes Care* 2003; 26: 2770-6.

84 Van de Werf F., Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909-45.

85 Bronisz A, Kozinski M, Magielski P, Fabiszak T, Gierach J, Swiatkiewicz I, Sukiennik A, Kubica A, Bronisz M, Grabczewska Z, Sinkiewicz A, Junik R, Kubica J. Value of oral glucose tolerance test in the acute phase of myocardial infarction. *Cardiovasc Diabetol* 2011; 10: 21.

86 Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther* 2005; 85: 257-68.

87 McDonald GW, Fisher GF, Burnham C. Reproducibility of the oral glucose tolerance test. *Diabetes* 1965; 14: 473-80.

88 Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, Cockram CS. The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. *Ann Clin Biochem* 1998; 35 (Pt 1): 62-7.

89 Lankisch M, Futh R, Gulker H, Lapp H, Bufe A, Haastert B, Martin S, Rathmann W. Screening for undiagnosed diabetes in patients with acute myocardial infarction. *Clin Res Cardiol* 2008; 97: 753-9.

90 Soler NG, Frank S. Value of glycosylated hemoglobin measurements after acute myocardial infarction. *JAMA* 1981; 246: 1690-3.

91 Tenerz A, Lonnberg I, Berne C, Nilsson G, Leppert J. Myocardial infarction and prevalence of diabetes mellitus. Is increased casual blood glucose at admission a reliable criterion for the diagnosis of diabetes? *Eur Heart J* 2001; 22: 1102-10.

92 World Health Organization. Health Experts Accept use of HbA1c for Diagnosing Diabetes . WHO 2011Available from: URL: http://www.who.int/chp/media/news/releases/2011_1_diabetes/en/index.html

93 Anselmino M, Malmberg K, Ohrvik J, Ryden L. Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart. *Eur J Cardiovasc Prev Rehabil* 2008; 15: 216-23.

94 Tamita K, Katayama M, Takagi T, Akasaka T, Yamamuro A, Kaji S, Morioka S, Kihara Y. Impact of newly diagnosed abnormal glucose tolerance on long-term prognosis in patients with acute myocardial infarction. *Circ J* 2007; 71: 834-41.

95 Hohensinner PJ, Niessner A, Huber K, Weyand CM, Wojta J. Inflammation and cardiac outcome. *Curr Opin Infect Dis* 2011; 24: 259-64.

96 Gottsauner-Wolf M, Zasmeta G, Hornykewycz S, Nikfardjam M, Stepan E, Wexberg P, Zorn G, Glogar D, Probst P, Maurer G, Huber K. Plasma levels of C-reactive protein after coronary stent implantation. *Eur Heart J* 2000; 21: 1152-8.

97 Solheim S, Grogaard HK, Hoffmann P, Arnesen H, Seljeflot I. Inflammatory responses after percutaneous coronary intervention in patients with acute myocardial infarction or stable angina pectoris. *Scand J Clin Lab Invest* 2008; 68: 555-62.

98 Orn S, Manhenke C, Ueland T, Damas JK, Mollnes TE, Edvardsen T, Aukrust P, Dickstein K. C-reactive protein, infarct size, microvascular obstruction, and left-ventricular remodelling following acute myocardial infarction. *Eur Heart J* 2009; 30: 1180-6.

99 Gwechenberger M, Mendoza LH, Youker KA, Frangogiannis NG, Smith CW, Michael LH, Entman ML. Cardiac myocytes produce interleukin-6 in culture and in viable border zone of reperfused infarctions. *Circulation* 1999; 99: 546-51.

100 Tsujioka H, Imanishi T, Ikejima H, Kuroi A, Takarada S, Tanimoto T, Kitabata H, Okochi K, Arita Y, Ishibashi K, Komukai K, Kataiwa H, Nakamura N, Hirata K, Tanaka A, Akasaka T. Impact of heterogeneity of human peripheral blood monocyte subsets on myocardial salvage in patients with primary acute myocardial infarction. *J Am Coll Cardiol* 2009; 54: 130-8.

101 Mine S, Okada Y, Tanikawa T, Kawahara C, Tabata T, Tanaka Y. Increased expression levels of monocyte CCR2 and monocyte chemoattractant protein-1 in patients with diabetes mellitus. *Biochem Biophys Res Commun* 2006; 344: 780-5.

102 Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are

acutely increased by hyperglycemia in humans: role of oxidative stress. *Circulation* 2002; 106: 2067-72.

103 Verma S, Wang CH, Weisel RD, Badiwala MV, Li SH, Fedak PW, Li RK, Mickle DA. Hyperglycemia potentiates the proatherogenic effects of C-reactive protein: reversal with rosiglitazone. *J Mol Cell Cardiol* 2003; 35: 417-9.

104 Marfella R, Siniscalchi M, Esposito K, Sellitto A, De FU, Romano C, Portoghese M, Siciliano S, Nappo F, Sasso FC, Mininni N, Cacciapuoti F, Lucivero G, Giunta R, Verza M, Giugliano D. Effects of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune process in functional cardiac outcome. *Diabetes Care* 2003; 26: 3129-35.

105 Andersen GO, Ueland T, Knudsen EC, Scholz H, Yndestad A, Sahraoui A, Smith C, Lekva T, Otterdal K, Halvorsen B, Seljeflot I, Aukrust P. Activin a levels are associated with abnormal glucose regulation in patients with myocardial infarction: potential counteracting effects of activin a on inflammation. *Diabetes* 2011; 60: 1544-51.

106 Carter AM, Catto AJ, Grant PJ. Determinants of tPA antigen and associations with coronary artery disease and acute cerebrovascular disease. *Thromb Haemost* 1998; 80: 632-6.

107 Hamsten A, de FU, Walldius G, Dahlen G, Szamosi A, Landou C, Blomback M, Wiman B. Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. *Lancet* 1987; 2: 3-9.

108 Juhan-Vague I, Alessi MC, Vague P. Increased plasma plasminogen activator inhibitor 1 levels. A possible link between insulin resistance and atherothrombosis. *Diabetologia* 1991; 34: 457-62.

109 Alessi MC, Juhan-Vague I, Kooistra T, Declerck PJ, Collen D. Insulin stimulates the synthesis of plasminogen activator inhibitor 1 by the human hepatocellular cell line Hep G2. *Thromb Haemost* 1988; 60: 491-4.

110 Alessi MC, Peiretti F, Morange P, Henry M, Nalbone G, Juhan-Vague I. Production of plasminogen activator inhibitor 1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease. *Diabetes* 1997; 46: 860-7.

111 Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; 414: 813-20.

112 Madonna R, De CR. Cellular and molecular mechanisms of vascular injury in diabetes - Part I: Pathways of vascular disease in diabetes. *Vascul Pharmacol* 2011; 54: 68-74.

113 Cugno M, Castelli R, Mari D, Mozzi E, Zappa MA, Boscolo-Anzoletti M, Roviaro G, Mannucci PM. Inflammatory and prothrombotic parameters in normotensive non-diabetic obese women: effect of weight loss obtained by gastric banding. *Intern Emerg Med* 2011, doi: 10.1007/s11739-011-0522-x.

114 Landin K, Tengborn L, Chmielewska J, von SH, Smith U. The acute effect of insulin on tissue plasminogen activator and plasminogen activator inhibitor in man. *Thromb Haemost* 1991; 65: 130-3.

115 Seljeflot I, Eritsland J, Torjesen P, Arnesen H. Insulin and PAI-1 levels during oral glucose tolerance test in patients with coronary heart disease. *Scand J Clin Lab Invest* 1994; 54: 241-6.

116 Grant PJ, Kruithof EK, Felley CP, Felber JP, Bachmann F. Short-term infusions of insulin, triacylglycerol and glucose do not cause acute increases in plasminogen activator inhibitor-1 concentrations in man. *Clin Sci (Lond)* 1990; 79: 513-6.

117 Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PW. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA* 2000; 283: 221-8.

118 Steins MB, Padro T, Li CX, Mesters RM, Ostermann H, Hammel D, Scheld HH, Berdel WE, Kienast J. Overexpression of tissue-type plasminogen activator in atherosclerotic human coronary arteries. *Atherosclerosis* 1999; 145: 173-80.

119 Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Hennekens CH. Endogenous tissue-type plasminogen activator and risk of myocardial infarction. *Lancet* 1993; 341: 1165-8.

120 Osende JI, Badimon JJ, Fuster V, Herson P, Rabito P, Vidhun R, Zaman A, Rodriguez OJ, Lev EI, Rauch U, Heflt G, Fallon JT, Crandall JP. Blood thrombogenicity in type 2 diabetes mellitus patients is associated with glycemic control. *J Am Coll Cardiol* 2001; 38: 1307-12.

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Abnormal glucose regulation in patients with acute ST- elevation myocardial infarction-a cohort study on 224 patients

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Abstract

Background: A high prevalence of impaired glucose tolerance and unknown type 2-diabetes in patients with coronary heart disease and no previous diagnosis of diabetes have been reported. The aims of the present study were to investigate the prevalence of abnormal glucose regulation (AGR) 3 months after an acute ST-elevation myocardial infarction (STEMI) in patients without known glucometabolic disturbance, to evaluate the reliability of a 75-g oral glucose tolerance test (OGTT) performed very early after an acute STEMI to predict the presence of AGR at 3 months, and to study other potential predictors measured in-hospital for AGR at 3 months.

Methods: This was an observational cohort study prospectively enrolling 224 STEMI patients treated with primary PCI. An OGTT was performed very early after an acute STEMI and was repeated in 200 patients after 3 months. We summarised the exact agreement observed, and assessed the observed reproducibility of the OGTTs performed in-hospital and at follow up. The patients were classified into glucometabolic categories defined according to the World Health Organisation criteria. AGR was defined as the sum of impaired fasting glucose, impaired glucose tolerance and type 2-diabetes.

Results: The prevalence of AGR at three months was 24.9% (95% CI 19.1, 31.4%), reduced from 46.9% (95% CI 40.2, 53.6) when measured in-hospital. Only, 108 of 201 (54%) patients remained in the same glucometabolic category after a repeated OGTT. High levels of HbA1c and admission plasma glucose in-hospital significantly predicted AGR at 3 months ($p < 0.001$, $p = 0.040$, respectively), and fasting plasma glucose was predictive when patients with large myocardial infarction were excluded ($p < 0.001$).

Conclusion: The prevalence of AGR in STEMI patients was lower than expected. HbA1c, admission plasma glucose and fasting plasma glucose measured in-hospital seem to be useful as early markers of longstanding glucometabolic disturbance. An OGTT performed very early after a STEMI did not provide reliable information on long-term glucometabolic state and should probably not be recommended.

Background

Several prospective studies have reported a high prevalence of impaired glucose tolerance (IGT) and unknown type 2-diabetes (DM) in patients with coronary heart disease and no previous diagnosis of DM [1-4] although data on patients with acute ST-elevation myocardial infarction are scarce. IGT and DM have been shown to be strong risk factors for future cardiovascular events after acute myocardial infarction [5]. Recent European guidelines on DM, prediabetes, and cardiovascular disease recommend that patients without known diabetes, but with established cardiovascular disease should be investigated with an oral glucose tolerance test (OGTT) [6]. However a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism do not encourage routine use of such screening [7]. In the European guidelines there is no consensus about the timing of an OGTT performed after an acute myocardial infarction [6]. Early testing may be confounded by stress reactions accompanying an acute myocardial infarction, but could be important in order to identify patients with cardiovascular events in the first weeks after an acute myocardial infarction [8]. The Glucose tolerance in Acute Myocardial Infarction (GAMI) study indicated that an OGTT performed early (day 4–5) after an acute myocardial infarction [1] provided reliable information on long-term glucometabolic state [9].

Routine use of OGTT, as stated by the European guidelines, in the follow-up of patients with myocardial infarction has so far not been implemented in Norway. Rapid transfer of stable patients after primary PCI from tertiary centers to community hospitals makes it difficult to implement the new guidelines into daily-life practice. This study was undertaken to investigate the prevalence of unknown DM, IGT and impaired fasting glucose (IFG) in patients with STEMI during stable conditions after 3 months of follow-up and to evaluate the reliability of performing an OGTT-based glucometabolic classification in-hospital in order to predict glucometabolic disturbance defined by a repeated OGTT at 3 months. The study had a practical approach: Performing a very early OGTT at the PCI center in stable patients, before transfer (usually within 24 hours) back to community hospitals, in order to establish screening for unknown DM and IGT in STEMI patients in our community. Finally, in an explanatory strategy, to study various biomarkers and risk factors identified during the initial hospitalisation as possible predictors of DM and IGT defined at 3 months.

Methods

Study population

The study was designed as an observational cohort study prospectively including STEMI patients treated with primary PCI admitted to the coronary care unit at Ullevål University Hospital, Oslo, Norway, between November 2005 and May 2007. The OGTT was performed after overnight fasting, before transfer from the coronary care unit back to the referring hospitals. At Ullevål University Hospital, stable patients are regularly returned within 24-hours after treatment. At enrolment, patients were clinically stable, without persistent glyseroltrinitrat infusion, chest pain, nausea or symptoms of heart failure. Patients with known DM, serum creatinine concentration ≥ 200 umol/L, and age > 85 years were excluded. The OGTT was not performed in patients with persistent hyperglycaemia in order to avoid further glucose overloading.

The Regional ethics committee approved the study and all patients provided written informed consent. STEMI was defined as ST-segment elevation of > 2 mm in two or more contiguous chest leads *or* > 1 mm in two or more limb leads *or* new left bundle-branch block, together with typical symptoms (chest pain or discomfort > 20 min).

Laboratory methods

Admission plasma glucose concentration was analysed from a blood sample taken in the catheterisation laboratory as soon as possible after PCI. After overnight fasting, blood samples for routine analysis by use of conventional methods including plasma glucose, were drawn. A standardised OGTT (2 h) with 75 g of glucose dissolved in 200 mL water was performed [10]. The median time from balloon to OGTT was 16 hr and 35 min. The OGTT was repeated after three months.

Serum-cTroponin T was measured by electrochemiluminescence technology for quantitative measurement (3rd generation cTroponinT, Elecsys 2010, Roche, Mannheim, Germany). The lower detection limit of the assay is 0.01 ug/l with a recommended diagnostic threshold of 0.03 ug/l. The inter-assay coefficient of variation was 7%.

Urinary albumin excretion was assessed in a morning spot urine sample and expressed as albumin/creatinine ratio. Microalbuminuria was defined as 30–300 mg albumin secreted per 24 hours [11].

Clinical follow-up

At 3 months, the patients underwent an OGTT, clinical examination, and answered a questionnaire about lifestyle changes after discharge from hospital, including weight, smoking habits, and physical activity. Physical activity was reported as 30 min of activity, 0–1 days/week, 2–3 days/week, or > 3 days/week.

Single Photon Emission Computed Tomography imaging

Left ventricular ejection fraction, end-diastolic and end-systolic volume and infarct size expressed as percent of left ventricular mass, were assessed at rest after 3 months by

Single Photon Emission Computed Tomography imaging with technetium 99 m-tetrofosmin [12].

Classification of glucometabolic state

The different glucometabolic categories were defined according to the World Organisation criteria [13]. Classification of glucometabolic state was primarily based on the result of an OGTT and the patients were divided into one of the following four categories, (glucose levels given in mmol/l):

Normal Glucose Regulation (NGR) = OGTT (0 min) < 6.1 and OGTT (2 h) < 7.8

Impaired Fasting Glucose (IFG) = OGTT (0 min) ≥ 6.1 < 7.0 and OGTT (2 h) < 7.8

Impaired Glucose Tolerance (IGT) = OGTT (0 min) < 7.0 and OGTT (2 h) ≥ 7.8 < 11.1

Type 2-diabetes (DM) = OGTT (0 min) ≥ 7.0 and/or OGTT (2 h) ≥ 11.1

Because of limited number in each category, the patients were also divided into:

Abnormal Glucose Regulation (AGR) = IFG+IGT+DM or NGR.

The patients were also categorised based on the results of fasting plasma glucose (FPG) only:

Normal Glucose Regulation (NGR) = FPG < 6.1

Impaired Fasting Glucose (IFG) = FPG ≥ 6.1 < 7.0

Type 2-diabetes (DM) = FPG ≥ 7.0

Statistics

In the prevalence study an apriori power analysis was performed. With a hypothesised prevalence of AGR of 60% [1-3] with a precision of 5% and a chosen probability of 90% a sample size of 222 patients was needed to determine the prevalence of unknown AGR. Furthermore, a post hoc power analysis was done for potential in-hospital predictors for the outcome AGR at 3 months showing that 116 patients were required considering a type 1-error of 5%, a power of 80%, a prevalence of AGR in patients with low HbA1c of 17%, and an OR (crude) = 4.15 for the association HbA1c on AGR. Similar analyses were also performed with the associations of fasting plasma glucose and admission plasma glucose on AGR.

Values are presented as median (25, 75% quartiles) or proportions. Mann-Whitney's test was used for comparing groups. In order to identify possible in-hospital predictors of AGR defined at 3 months, we hypothesised an association between the 3 exposition variables HbA1c, fasting plasma glucose, and admission plasma glucose and the outcome AGR. The other variables were potential confounders or effect modifiers of this association. The odds ratio (OR) and its 95% confidence interval (CI) were used to quantify this association. We performed a stratification analysis and dichotomised continuous exposition variables into high and low values using the cut-off point 6.1 mmol/l for fasting plasma glucose according to the literature and the 75% percentile in the present material for the other variables. The Mantel-Haenszel method was used to highlight potential effect modification by the Breslow-Day test of heterogeneity and to quantify potential confounders [14]. Additional information is available online (see additional file 1).

A logistic regression model, including a backward elimination procedure and finally taking in consideration the concept of validity and precisions, performed adjustment for multi-confounders. The STROBE guidelines were followed [15].

Analyses were performed using Epi-info software, 2005, version 3.3.2.

A value of $p < 0.05$ was considered statistically significant.

Results

Baseline and follow up characteristics

Two hundred and twenty five patients without previously known DM or IGT were enrolled in the study. The OGTT was well tolerated, 224 completed an in-hospital OGTT while one patient interrupted the test because of acute nausea. None of the patients complained of chest-pain or underwent a new coronary angiography. No in-hospital deaths occurred. The median time from onset of chest pain to balloon (PCI) was 3 hr and 39 min and 16 hr and 35 min from balloon to OGTT. The OGTT was repeated in 200 patients after 3 months. The reasons for not repeating the test were: death (n = 1), fasting plasma glucose > 7.0 mmol/L (n = 1) and unwillingness (n = 22). Table 1 summarises the baseline characteristics of the study population. Notably, the majority of the patients presented with their first myocardial infarction, 62% had single vessel disease and 92% of the patients were in Killip class 1 (data not shown). Single photon emission computed tomography imaging at 3 months showed that 85% of the patients had an left ventricular ejection fraction > 50%.

At 3 months 25% of the patients had stopped smoking, 41% had increased the number of days per week of physical activity, 36% had lost weight and 30% had gained weight. The proportion of AGR in patients who had lost

Table 1: Baseline characteristics of the total population (n = 224)

	Patients
Age (years)	58 (51, 67)
Male	185 (82.6%)
Previous disorder:	
Myocardial infarction	16 (7.1%)
Angina pectoris	7 (3.1%)
Hypertension (treated)	58 (25.9%)
Hyperlipidaemia (treated)	20 (8.9%)
Status at baseline	
Current smoker	109 (48.7%)
BMI (kg/m2)	26 (24.4, 28.7)
Waist circumference (cm)	100 (94, 107)
Stent in culprit lesion	215 (96.0%)
Gp IIb/IIIa antagonist treated	79 (35.3%)
Single -coronary vessel disease	139 (62.1%)
Double-coronary vessel disease	64 (28.6%)
Triple-coronary vessel disease	21 (9.4%)
Time from symptoms to balloon (min)	219 (140, 378)
Time from PCI to OGTT (min)	995 (689, 1277)
Medication at discharge from CCU	
Aspirin	224 (100%)
Clopidogrel	222 (99.1%)
β-blockers	181 (80.8%)
Lipid lowering agents	221 (98.7%)
Angiotensin converting enzyme-inhibitors	36 (16.1%)
Angiotensin II-receptor blockers	18 (8.0%)
LVEF[a]	64 (56, 70)

Data are presented as median with inter-quartile range or proportions.
BMI: body mass index, LVEF: left ventricular ejection fraction. [a]LVEF diagnosed 3 months after discharge.

weight and in patients who had gained weight was 28% and 25%, respectively (data not shown).

Prevalence of AGR

The median plasma glucose concentration at admission was 6.9 mmol/L ((25, 75% percentiles) 6.0, 7.8), the median fasting plasma glucose was 5.3 mmol/L (4.9, 5.9) and the median HbA1c value was 5.5% (5.3, 5.8) (n = 207). Figure 1 shows the prevalence of NGR, IFG, IGT and DM in-hospital and at 3 months, based on a glucometabolic classification by OGTT and alternatively, by fasting plasma glucose alone. Based on the given categories we defined, abnormal glucose regulation (AGR) as the sum of IFG, IGT and DM, in spite of different risk profiles between IFG, IGT and DM. The prevalence of AGR after an OGTT- based classification was 46.9% (95% CI 40.4, 53.9) (n = 224) in-hospital and 24.9% (19.1, 31.4) (n = 201) at 3 months, respectively.

Table 2 compares the results of an OGTT- based glucometabolic classification of the patients in-hospital and at 3 months. Fifty-four % of the patients remained in the same glucometabolic category after a repeated OGTT. Only 5 out of 22 patients defined as diabetic in-hospital remained in the diabetic category after 3 months.

Predictors of AGR

In Table 3, patient characteristics assessed at hospitalisation are compared between the NGR group and the AGR group, as defined by an OGTT three months later. Patients with AGR were older, there were significantly more women, and they had significantly higher levels of HbA1c, admission plasma glucose, and fasting plasma glucose.

In univariate analyses HbA1c, admission plasma glucose and fasting plasma glucose significantly predicted the presence of AGR at 3 months ($p < 0.001$, $p = 0.006$ and $p = 0.011$, respectively) (Table 4). HbA1c ($p < 0.001$) and admission plasma glucose ($p = 0.040$), analysed separately, remained significantly predictive after adjustment for confounders (Table 4). When analysing on fasting plasma glucose concentration as an independent biomarker, serum-cTroponinT modified the effect of fasting plasma glucose on AGR, thus the results were stratified into two subgroups, and as shown in Table 4, fasting plasma glucose was independently predicting AGR at 3 months only in patients with serum-cTroponin T below the highest quartile (< 8.80 ug/l), with an adjusted OR 5.50 (95% CI 2.00, 15.10).

Discussion

Prevalence of AGR

The main findings in the present study were that only 25% of the patients were classified by OGTT as having AGR in a clinically steady situation 3 months after an acute STEMI and only about 5% had previously unknown DM. About 50% of the patients with STEMI were classified as having undetected AGR based on an OGTT classification in-hospital, but only half of these patients remained in the AGR group after a repeated OGTT 3 months later. Using fasting plasma glucose classification only, about 50% of the patients with AGR would have been misclassified, both in-hospital and after 3 months. To disclose the actual glucometabolic state in these patients it seems necessary to perform an OGTT. The latter result is in line with a previous study, showing that two-thirds of the patients with undiagnosed diabetes would have been missed using fasting plasma glucose classification alone [2].

In the present study the OGTT was performed very early after a PCI treated STEMI and an initially higher prevalence of AGR could be expected as an acute STEMI is accompanied by a substantial release of stress hormones. However, we found a somewhat lower prevalence of AGR than reported in previous studies, both in-hospital and at 3 months. Three prospective studies on mixed populations of patients with acute and stable coronary artery dis-

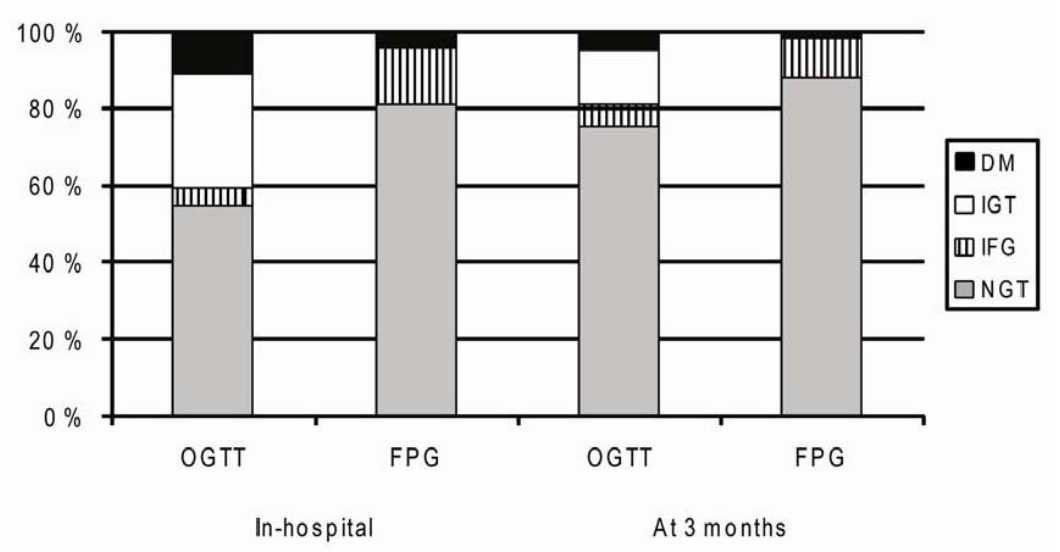

Figure 1
Glucometabolic classification of 201 STEMI patients based on the results of an OGTT or fasting plasma glucose only, in-hospital and at 3 months. FPG: fasting plasma glucose, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, NGR: normal glucose regulation, OGTT: oral glucose tolerance test, DM: type 2-diabetes.

ease have shown that about 60% of the patients had undiagnosed AGR [1-3]. A repeated OGTT was performed only in one of these studies showing that 66% of the patients had AGR before hospital discharge [1] and the prevalence was reported to be similar after 3 and 12 months [9]. In the present study the prevalence of AGR at 3 months was much lower, which the selected population of STEMI patients may partly explain. The patients were mainly Caucasians, relatively young, included a low number of women, a high proportion of first acute myocardial infarction, and a preponderance of single vessel disease. Additionally, patients with persistent hyperglycaemia were excluded. It is possible that the prevalence of AGR after 3 months would have been higher if these patients had been included in the 3 months follow-up.

The prevalence of AGR was reduced by about 50% after 3 months indicating poor reliability of the early classifica-

Table 2: Glucometabolic classification by OGTT in patients with ST-elevation infarction in-hospital (OGTT1, row), and at 3 months (OGTT2, column)

	NGR (OGTT2)	IFG (OGTT2)	IGT (OGTT2)	DM (OGTT2)	Total (OGTT1)
NGR (OGTT1)	91	6	11	1	109
IFG (OGTT1)	8	1	1	0	10
IGT (OGTT1)	41	4	11	4	60
DM (OGTT1)	11	0	6	5	22
Total (OGTT2)	151	11	29	10	201

Data are number of patients.
Observed concordance: 53.7%
One patient was categorized based on the results of fasting plasma glucose only, because of persistent hyperglycaemia.

Table 3: Clinical and laboratory characteristics of patients in-hospital according to glucometabolic category defined by OGTT at 3 months

	NGR (n = 151)	AGR (n = 50)	P
Age (years)	57 (51, 65)	61 (52, 72)	0.037
Male	129 (85.4%)	36 (72.0%)	0.032
Current smoker	67 (44.4%)	24 (48.0%)	0.656
Treated hypertension	38 (25.2%)	17 (34.0%)	0.226
BMI (kg/m^2)	26.2 (24.3, 28.7)	26.1 (24.6, 28.7)	0.741
Cholesterol (mmol/l)	5.1 (4.4, 5.7)	5.1 (4.4, 5.7)	0.839
Triglycerides (mmol/l)	1.27(0.89, 1.79)	1.25 (0.96, 1.83)	0.623
HDL-cholesterol (mmol/l)	1.19 (0.97, 1.43)	1.12 (1.00, 1.35)	0.659
Serum uric acid (mmol/l)	334 (289, 382)	347 (282, 409)	0.288
Microalbuminuria	26 (18.2%)	10 (22.2%)	0.549
scTnT (ug/l)	4.85 (2.45, 8.31)	4.97 (2.38, 10.25)	0.469
HbA1c (%)	5.5 (5.3, 5.7)	5.8 (5.5, 6.0)	< 0.001
Admission plasma glucose (mmol/l)	6.6 (5.8, 7.5)	7.4 (6.6, 8.7)	<0.001
FPG (mmol/l)	5.2 (4.9, 5.7)	5.6 (5.1, 6.3)	0.003

Data are presented as median with inter-quartile range or proportions.
AGR: abnormal glucose regulation, BMI: body-mass index, FPG: fasting plasma glucose, NGR: normal glucose regulation, scTnT: serum-cTroponinT.

tion. The measured in-hospital prevalence of AGR reflects not only long-standing glucometabolic disturbance, but also an acute stress epiphenomenon as discussed.

OGTT in patients with STEMI

Patients with acute myocardial infarction and diabetes have a higher short and long-term mortality rate than non-diabetic patients [16]. The 2-hour blood glucose has been shown to be superior to fasting blood glucose to predict the risk of future cardiovascular disease and death from all causes in individuals with hyperglycaemia [17]. The present study revealed that a very early OGTT in STEMI-patients was well tolerated, except in one patient. None of the patients died in-hospital, reflecting the intention to exclude unstable patients.

To examine the reproducibility of an OGTT, two independent tests should be performed within a short period of time in stable patients without persistent acute illness[10]. Even under these circumstances previous studies have suggested poor reproducibility of an OGTT [18]. In the present study we compared the OGTT performed after initial stabilisation of acute illness, and stable disease, thus we did not test the reproducibility of the OGTT, but evaluated the reliability of an early glucometabolic classification by OGTT by repeating the test after 3 months. Generally, the variation in the repeated OGTT results has to a great extent been explained by the random variation of plasma glucose concentration [19]. In our study the variation in the OGTT results after 3 months of follow up to a great extent may have been influenced by the different test situation mentioned. This is in line with another

Table 4: Logistic regression analysis of HbA1c, admission plasma glucose and fasting plasma glucose as independent predictors in-hospital for AGR defined by an OGTT at 3 months

	AGR		AGR		AGR scTnT > 8.80 ug/l (n = 51)		AGR scTnT < 8.80 ug/l (n = 150)	
	OR (crude) (95% CI)	P	OR (adjusted) (95% CI)	P	OR (adjusted) (95% CI)	P	OR (adjusted) (95% CI)	P
HbA1c[a] > 5.7%	4.15 (2.03, 8.48)	<0.001	3.76 (1.82, 7.79)	<0.001				
Admission plasma glucose[b] > 7.7 mmol/l	2.59 (1.31, 5.12)	0.006	2.12 (1.03, 4.33)	0.040				
FPG [c] ≥ 6.1 mmol/L	2.62 (1.25, 5.50)	0.011			0.69 (0.15, 3.14)	0.636	5.50 (2.00, 15.10)	<0.001

AGR: abnormal glucose regulation, FPG: fasting plasma glucose, scTnT: serum-cTroponinT.
[a]Adjusted for gender and age.
[b]Adjusted for age.
[c]scTnT > 8.80 ug/l (highest quartile) was an effect modifier on the association FPG on AGR, thus data are presented in 2 subgroups, both adjusted for age, uric acid and gender.

study showing that acute myocardial infarction induces hyperglycaemia and give rice to insulin resistance [20]. These investigators demonstrated that blood glucose levels and HOMA-IR decreased significantly during hospital stay with no further decrease between discharge (day 4–5) and 3 months of follow up reflecting that acute illness influence the very early rise and fall in glucose levels in-hospital [20].

Only 54% of the patients in our study were classified into the same glucometabolic state on both occasions which is in accordance with results from other studies performing repeated OGTTs [20,21]. The intra-individual tracking of oral glucose tolerance in our study was poor, but comparable to what was found in the GAMI study (49 and 54%, respectively) [20]. In the present study, 11 out of 22 patients classified as having diabetes in-hospital converted to NGR at 3 months. These results underline the World Health Organisation recommendation for a repeated OGTT under stable conditions to confirm or exclude an abnormality of glucose regulation in asymptomatic individuals [10]. Nevertheless, individuals with one abnormal OGTT have been shown to have a higher cardiovascular risk profile compared to individuals who had two normal OGTTs [18] and a single positive OGTT in patients with acute myocardial infarction seems to identify patients at higher risk of future cardiovascular event [5]. The present study do not address whether an early OGTT after a myocardial infarction can identify patients with worse prognosis.

Predictors of AGR

In order to identify patients with AGR after 3 months without performing an in-hospital OGTT, analysis of risk markers was undertaken. We could not demonstrate any differences in baseline values of conventional cardiovascular disease risk factors between the AGR and NGR groups, classified after 3 months. However, a high HbA1c value and a high admission plasma glucose value in-hospital were independently predicting AGR at 3 months with an adjusted OR of 3.76 and 2.12, respectively. Furthermore, a high fasting plasma glucose value in-hospital, strongly predicted AGR at 3 months (adjusted OR 5.50), when patients with large myocardial infarction were excluded indicating that an acute stress reaction may dominate in patients with a large acute myocardial infarction.

This is in accordance with other studies showing HbA1c values at admission and fasting plasma glucose at discharge from hospital (day 4 after acute myocardial infarction) to be independent predictors of AGR at 3 months [1].

Clinical implication

The European guidelines recommend that patients without known diabetes, but with established cardiovascular disease should be investigated with an OGTT [6]. In order to try to implement the new guidelines in our region we performed an OGTT before transfer to referring hospitals. The present results demonstrate that it is safe to perform a very early OGTT in stable patients with acute STEMI, but a very early classification did not provide reliable information on long-term glucometabolic state, and the present results do not encourage routine use of an OGTT at this early time point in acute STEMI patients However, a substantial proportion of the patients had undetected AGR after 3 months and it is important to diagnose these patients and offer them a close follow- up on lifestyle interventions and optimal medical treatment in order to reduce events in this high-risk population.

Limitations

Unstable patients and patients with persistent hyperglycaemia in-hospital were excluded from the study to avoid further glucose loading, possibly making a selection bias towards more glucometabolically normal patients. This may have contributed to the somewhat unexpected low prevalence of undetected AGR in STEMI patients.

Conclusion

The prevalence of AGR in a STEMI-population was lower than previously reported in patients with acute myocardial infarction. The prevalence was relatively high when measured in-hospital by a very early OGTT, but half of these patients were categorised as having normal glucose regulation when re-tested at 3 months. Based on these results an OGTT should probably not be recommended very early after an acute STEMI whereas an OGTT should be performed during follow-up in order to identify patients with persistent glucometabolic disturbances. High levels of HbA1c, admission plasma glucose and fasting plasma glucose (except in patients with large myocardial infarction) measured in-hospital predicted an increased risk of AGR defined at 3 months, indicating that these biomarkers can be used as early markers of a long standing glucometabolic disturbance in patients with acute myocardial infarction.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ECK performed the statistical analysis of the data presented and drafted the manuscript. MA made substantial contribution with statistical analysis. GØA contributed with the conception and design of the study. ECK, IS, MA, JE, AM, HA and GØA participated in the study design and interpretation and revised the manuscript critically for

important intellectual content. All authors have read and approved the final manuscript.

Additional material

Additional file 1

Table A. *Stratified analysis on the association between the 3 exposition variables HbA1c, fasting plasma glucose, and admission plasma glucose and the outcome abnormal glucose regulation on major potential confounders using the Mantel-Haenzel method.*
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2840-8-6-S1.doc]

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References

1. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, *et al.*: **Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study.** *Lancet* 2002, **359:**2140-2144.
2. Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, *et al.*: **The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart.** *Eur Heart J* 2004, **25:**1880-1890.
3. Hu DY, Pan CY, Yu JM: **The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey.** *Eur Heart J* 2006, **27:**2573-2579.
4. Andersen GO, Eritsland J, Aasheim A, Neuburger J, Knudsen EC, Mangschau A: **Impaired glucose tolerance in patients with acute myocardial infarction.** *Tidsskr Nor Laegeforen* 2006, **126:**2264-2267.
5. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L: **Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction.** *Eur Heart J* 2004, **25:**1990-1997.
6. Ryden L, Standl E, Bartnik M, Van den BG, Betteridge J, de Boer MJ, *et al.*: **Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).** *Eur Heart J* 2007, **28:**88-136.
7. Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, *et al.*: **Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism.** *Circulation* 2008, **117:**1610-1619.
8. Bartnik M, Norhammar A, Ryden L: **Hyperglycaemia and cardiovascular disease.** *J Intern Med* 2007, **262:**145-156.
9. Wallander M, Malmberg K, Norhammar A, Ryden L, Tenerz A: **Oral glucose tolerance test: a reliable tool for early detection of glucose abnormalities in patients with acute myocardial infarction in clinical practice: a report on repeated oral glucose tolerance tests from the GAMI study.** *Diabetes Care* 2008, **31:**36-38.
10. World Health Organization Department of Noncommunicable Disease Surveillance, Geneva: **Definition, Diagnosis and Classification of Diabetes Mellitus and its Complication. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus.** 2008 [http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf].
11. Hartmann A, Jenssen T, Midtvedt K, Reisaeter AV, Fauchald P, Henriksen T, *et al.*: **Protein-creatinine ratio–a simple method for proteinuria assessment in clinical practice.** *Tidsskr Nor Laegeforen* 2002, **122:**2180-2183.
12. Gibbons RJ, Miller TD, Christian TF: **Infarct size measured by single photon emission computed tomographic imaging with (99 m)Tc-sestamibi: A measure of the efficacy of therapy in acute myocardial infarction.** *Circulation* 2000, **101:**101-108.
13. World Health Organization and International Diabetes Federation: **Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia.** *Report of a WHO/IDF Consultation* 2005:1-46 [http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf].
14. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic research. Principles and quantitative methods* New York: Van Nostrand Reinhold Company Inc; 1982.
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Lancet* 2007, **370:**1453-1457.
16. Abbud ZA, Shindler DM, Wilson AC, Kostis JB: **Effect of diabetes mellitus on short- and long-term mortality rates of patients with acute myocardial infarction: a statewide study. Myocardial Infarction Data Acquisition System Study Group.** *Am Heart J* 1995, **130:**51-58.
17. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group: **Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria.** *Arch Intern Med* 2001, **161:**397-405.
18. Ko GT, Chan JC, Woo J, Lau E, Yeung VT, Chow CC, *et al.*: **The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors.** *Ann Clin Biochem* 1998, **35(Pt 1):**62-67.
19. Kobberling J, Kerlin A, Creutzfeldt W: **The reproducibility of the oral glucose tolerance test over long (5 years) and short periods (1 week).** *Klin Wochenschr* 1980, **58:**527-530.
20. Tenerz A, Norhammar A, Silveira A, Hamsten A, Nilsson G, Ryden L, *et al.*: **Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes.** *Diabetes Care* 2003, **26:**2770-2776.
21. Lankisch M, Futh R, Gulker H, Lapp H, Bufe A, Haastert B, *et al.*: **Screening for undiagnosed diabetes in patients with acute myocardial infarction.** *Clin Res Cardiol* 2008, **97:**753-759.

Table A. Stratified analysis on the association between the 3 exposition variables HbA1c, fasting plasma glucose, and admission plasma glucose and the outcome abnormal glucose regulation on major potential confounders using the Mantel-Haenzel (MH) method.

	AGR-		AGR+		odds ratio (95%CI)	odds ratio MH (95%CI)	Breslow &Day Heterogeneity test
	HbA1c (< 5.8 % ≤)		HbA1c				p-value
	no	yes	no	yes			
Age							
67 year	93	19	15	13	4.24 (1.74-10.35)	3.72 (1.80-7.70)	0.6476
>67	19	8	8	10	2.97 (0.86-10.30)		
Gender							
Male	98	21	17	17	4.67 (2.05-10.61)	3.91 (1.90-8.02)	0.4225
Female	14	6	6	6	2.33 (0.53-10.27)		
Crude effect	112	27	23	23	4.15 (2.03-8.48)		
	Fasting plasma glucose. (< 6.1 mmol/L ≤)						
	no	yes	no	yes			
Age							
67 year	104	16	18	12	4.33 (1.76-10.66)	2.48 (1.18-5.20)	0.0541
>67	24	7	16	4	0.86 (0.22-3.41)		
Gender							
Male	111	18	25	11	2.71 (1.14-6.45)	2.45 (1.16-5.20)	0.6789
Female	17	5	9	5	1.89 (0.43-8.30)		
scTnT							
<8.80 ug/l	105	12	22	11	4.38 (1.71, 11.18)	*	0.0448
>8.80	23	11	12	5	0.87 (0.25, 3.09)		
High uric acid							
<387 umol/l	97	20	21	12	2.77 (1.18-6.53)	2.86 (1.34-6.10)	0.8838
>387	31	3	13	4	3.18 (0.62-16.24)		
Crude effect	128	23	34	16	2.62 (1.25-5.50)		
	Admission plasma glucose. (< 7.8 mmol/L ≤)						
	no	yes	no	yes			
Gender							
Male	105	24	21	15	3.13 (1.41-6.94)	2.32 (1.17-4.60)	0.1872
Female	13	9	8	6	1.08 (0.28-4.21)		
Age							
67 year	101	19	20	10	2.66 (1.08-6.56)	2.08 (1.02-4.23)	0.4298
>67	17	14	9	11	1.48 (0.48-4.59)		
Current smoker							
No	61	23	13	13	2.65 (1.07-6.56)	2.73 (1.36-5.47)	0.9204
Yes	57	10	16	8	2.85 (0.97-8.41)		
High LDL-cholesterol							
<4.12 mmol/l	90	20	25	15	2.70 (1.21-6.03)		
>4.12	28	13	4	6	3.23(0.78-13.45)	2.82 (1.40-5.68)	0.8298
Crude effect	118	33	29	21	2.59 (1.31-5.12)		

*Cannot be calculated because serum-cTroponinT (scTnT) is an effect modifier of fasting plasma glucose on abnormal glucose regulation (AGR).
The confounding effect is quantified using the formula;
$\text{odds ratio}_{MH} - \text{odds ratio}_{crude} / \text{odds ratio}_{crude}$

II

Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST-elevation myocardial infarction: a follow-up study.

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Abstract

Background: Patients with acute myocardial infarction and newly detected abnormal glucose regulation have been shown to have a less favourable prognosis compared to patients with normal glucose regulation. The importance and timing of oral glucose tolerance testing (OGTT) in patients with acute myocardial infarction without known diabetes is uncertain. The aim of the present study was to evaluate the impact of abnormal glucose regulation classified by an OGTT in-hospital and at three-month follow-up on clinical outcome in patients with acute ST elevation myocardial infarction (STEMI) without known diabetes.

Methods: Patients (n=224, age 58 years) with a primary percutanous coronary intervention (PCI) treated STEMI were followed for clinical events (all-cause mortality, non-fatal myocardial re-infarction, recurrent ischemia causing hospital admission, and stroke). The patients were classified by a standardised 75 g OGTT at two time points, first, at a median time of 16.5 hours after hospital admission, then at three-month follow-up. Based on the OGTT results, the patients were categorised according to the WHO criteria and the term abnormal glucose regulation was defined as the sum of impaired fasting glucose, impaired glucose tolerance and type 2-diabetes.

Results: The number of patients diagnosed with abnormal glucose regulation in-hospital and at three-month was 105 (47 %) and 50 (25 %), respectively. During the follow up time of (median) 33 (27, 39) months, 58 (25.9%) patients experienced a new clinical event. There were six deaths, 15 non-fatal re-infarction, 33 recurrent ischemia, and four strokes. Kaplan-Meier analysis of survival free of composite end-points showed similar results in patients with abnormal and normal glucose regulation, both when classified in-hospital (p=0.4) and re-classified three months later (p=0.3).

Conclusions: Patients with a primary PCI treated STEMI, without previously known diabetes, appear to have an excellent long-term prognosis, independent of the glucometabolic state classified by an OGTT in-hospital or at three-month follow-up.

Trial registration: The trial is registered at www.clinicaltrials.gov, NCT00926133.

Background

Patients hospitalised with acute myocardial infarction (MI) have a reported incidence of known type 2 diabetes between 10 and 20 % [1]. Patients with type 2 diabetes and acute MI have a higher incidence of new cardiovascular events and higher in-hospital and long-term mortality rate compared to non-diabetic patients [2-4]. In diabetic patients with ST elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) with adjunctive glycoprotein IIb/IIIa inhibition has been shown to be associated with improved prognosis compared to fibrinolytic treatment [5].

Several studies have reported that a substantial proportion of patients with acute MI, without known type 2 diabetes, have disturbed glucometabolic regulation [6,7]. In addition, an increased risk of cardiovascular morbidity and mortality has been demonstrated in patients with acute MI and newly detected abnormal glucose regulation [8], emphasizing the importance of diagnosing these patients at an early stage. Accordingly, the European guidelines on diabetes, pre-diabetes and cardiovascular diseases from 2007 recommend that these patients should be investigated with an oral glucose tolerance test (OGTT) [9]. The timing and importance of broad OGTT screening after an acute MI are, however uncertain, especially in patients subjected to modern treatment with primary PCI resulting in smaller infarct size and improved prognosis.

We have previously reported that patients with a primary PCI treated STEMI without known diabetes, have a high prevalence of undetected abnormal glucose regulation classified by an OGTT either in-hospital or three months later [10]. However, when repeating an OGTT in a stable condition at three-month follow-up the observed reproducibility of the early test was poor, only 54 % of the patients remained in the same glucometabolic category after a repeated OGTT. The OGTT performed early after a STEMI did not provide reliable information on long-term glucometabolic state [10].

An additional rationale for an early OGTT in patients without known diabetes with a recent acute MI is to identify high-risk patients with poor prognosis. The aim of the present study was to investigate clinical outcome in patients with a primary PCI treated STEMI after exclusion of patients with known diabetes. Secondly, to evaluate whether abnormal glucose regulation classified by OGTT acutely in-hospital or in a stable condition at three-month follow-up was associated with poorer long-term prognosis after acute STEMI.

Methods

Study population

Patients with an acute STEMI without known diabetes admitted to the coronary care unit, Oslo University Hospital, Ullevål, Oslo, Norway were prospectively enrolled from November 2005 to May 2007. The cohort is described in detail elsewhere [10]. In brief, patients with a primary PCI treated STEMI were included if they were hemodynamically stable, without chest pain or nausea, age < 85 years and with serum creatinine < 200 umol/L. Patients with previously known type 2 diabetes, persistent hyperglycaemia or clinical signs of heart failure were excluded. Heart failure complicating acute MI was defined according to the ESC Guidelines from 2008 [11]. Patients with persistent hyperglycaemia were defined as patients with both admission plasma glucose >11 mmol/L and a fasting capillary glucose level > 8 mmol/L. A standardized 75 g OGTT (plasma glucose measurements at 0 and 120 min) was performed after an overnight fast [12]. Altogether 224 patients were included. The inclusion date was defined as the date when the primary PCI was performed.

Based on the result of the OGTT, the patients were glucometabolically classified according to the WHO guidelines from 2005 into one of the following categories [13] (glucose levels given in mmol/L):

Normal Glucose Tolerance (NGT) = OGTT (0 min) < 6.1 and OGTT (2 h) < 7.8
Impaired Fasting Glucose (IFG) = OGTT (0 min) ≥ 6.1 < 7.0 and OGTT (2 h) < 7.8
Impaired Glucose Tolerance (IGT) = OGTT (0 min) < 7.0 and OGTT (2 h) ≥7.8 < 11.1
Type 2 diabetes (T2DM) = OGTT (0 min) ≥7.0 and / or OGTT (2 h) ≥11.1.

The term abnormal glucose regulation was defined as the sum of IFG, IGT and T2DM.
This was an observational study. The results of analyses of blood glucose, either fasting or during OGTT were available for the treating physician at all time. Hyperglycaemia, if present, was treated at the physician's decision according to local, hospital practice. Patients were returned back to the referring hospital with a hospital record, which included information about the OGTT results. The responsible physician was asked to perform plasma glucose analyses repeatedly and start treatment if indicated. A diagnosis of diabetes was not based on the early OGTT performed during acute illness. The results of the OGTT and fasting glucose value were communicated to the general practitioners (GP) responsible for the patient. If an asymptomatic patient were diagnosed with type 2 diabetes at both occasions (in-hospital and at follow-up) the GP was contacted by phone and asked to confirm the diagnosis and initiate lifestyle changes and medical treatment according to national guidelines.
STEMI was defined according to the universal definition of myocardial infarction as typical rise and fall of the cardiac biomarker troponin T with at least one value above the 99th percentile of the upper reference limit in patients presenting with symptoms of ischemia together with new ST elevation at the J-point in two contiguous leads with the cut-off points: 0.2 mV in men or 0.15 mV in women in leads V2–V3 and/or 0.1 mV in other leads *or* new left bundle-branch block [14]. The median time from onset of chest pain to balloon (PCI) was 219 minutes (140, 378).
The Regional ethics committee approved the study and all patients provided written and oral informed consent.

Laboratory methods

After overnight fasting, blood samples for routine analysis including glucose and HbA1c were drawn and analysed by use of conventional methods. Serum cardiac specific Troponin T (TnT) was measured by electrochemiluminescence technology for quantitative measurement (3rd generation TnT, Elecsys 2010, Roche, Mannheim, Germany). The lower detection limit of the assay is 0.01 ug/L with a recommended diagnostic threshold of 0.03 ug/L. The inter-assay coefficient of variation was 7 %.

Insulin was measured by a competitive radioimmunoassay (RIA) kit (Linco Research, Inc, ST. Charles, MO, US) and C-peptide was determined by Immulite 2000 (Diagnostic Product Corporation, Los Angeles, CA, US). Proinsulin was measured by an enzyme immunoassay (kit) from DRG instruments (Gmbtt, Marburg. Germany). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum insulin (in pmol/L) multiplied with fasting plasma glucose (in mmol/L) and divided by 135 [15].

Follow up

At three-month follow-up, clinical examination and a repeated OGTT were performed.

In addition, left-ventricular (LV) function and infarct size were assessed at rest at follow-up. Perfusion imaging was performed according to ECG-gated SPECT after injection of ^{99}m-tetrofosmin (Myoview™, Amersham Health, UK). An Exeleris processing station (GE Medical Systems) with 4D-MSPECT™ software (University of Michigan), was used for processing of all recordings and assessment LV volumes, LV ejection fraction (LVEF) and infarct size (proportion perfusion defect) expressed as percent of LV mass [16].

In June 2009, at a median follow up time of 33 months, the patients were contacted and interviewed by telephone, regarding their health status, and any hospital admissions. Closing

date was set to August 1st 2009. None of the patients were lost to long-term follow-up, but only 201 patients attended the three-month follow-up examination. In case of re-hospitalisation, hospital records were collected from the patients' community hospitals.

The primary endpoint of the study was defined as the composite of the first event of non-fatal myocardial re-infarction, recurrent ischemia causing hospital admission, stroke, and all cause mortality. An end-point committee classified the end-points according to the hospital records, and death certificates were obtained from the Norwegian Death Certificate Registry.

Statistics

Continuous variables are presented as median and 25, 75 percentiles and categorical variables as proportions. Due to skewness in most of the measured variables, non-parametric statistics was used throughout. Differences among groups were analysed by Mann-Whitney test for continuous variables and the Chi square test for categorical data.

Univariate and multivariate analyses of this dynamic cohort with censored data (Kaplan–Meier survival, Log-Rank test and Cox proportional hazard models) were performed. Potential confounders that were associated with clinical outcome or abnormal glucose regulation with a p-value <0.2, were included in the model. The following risk factors were included in a stratification model; age, gender, treated hypertension at admission, previous myocardial infarction, smoking, body mass index, elevated triglycerides and cholesterol, TnTmax, and infarct size expressed as percent of ventricular mass. Adjustment for the potential confounders identified by the model was performed [17] and the follow-up time in patients years was included. The STROBE guidelines were followed [18].

A two-sided p value <0.05 was considered statistically significant. All analyses were performed using Epi-info software, 2005, version 3.3.2.

Results

In-hospital OGTT was successfully performed in all patients (n=224) and categorised as described. As previously reported [10], the prevalence of abnormal glucose regulation in-hospital was 47 % (n=105), of whom 24 patients (23 %) (or 11 % of the total population, n=224) were classified with newly detected type 2 diabetes.

The OGTT was repeated in 201 patients three months after the acute STEMI. Twenty-three patients did not perform the repeated OGTT due to death (n=1) or unwillingness (n=22). The 22 patients who were unwilling to participate at three-month follow-up did, however, take part in the interview by telephone in June 2009. Five out of 22 patients reported a new clinical event during follow-up, one patient within the first three months, and four patients between three-months and (median time) 33 months follow-up. The number of patients with normal and abnormal glucose regulation classified in-hospital was 9 and 13, respectively, and two out of five with a new clinical event had abnormal glucose regulation. The prevalence of abnormal glucose regulation in the total population at three-month follow-up was reduced to 25 % (n=50), of whom 10 patients (20 %) (or 5 % of the total population, n=201) were classified as having type 2 diabetes [10].

Clinical and biochemical characteristics

Clinical characteristics of the study population according to the glucometabolic classification in-hospital and at three-month follow-up are shown in Table 1. Notably, patients with abnormal compared to normal glucose regulation were older, a higher proportion were women, and they had larger myocardial infarct size measured as % of left ventricular mass three months later. Significantly higher levels of HbA1c, insulin, proinsulin, and HOMA-IR

(measured in-hospital and at three-month follow-up) were found in patients with newly detected abnormal glucose regulation independently of the classification time point (Table 2). When comparing patients with and without new clinical events, there were no significant differences in clinical or biochemical characteristics (data not shown).
Glucose lowering medication was not introduced in-hospital or during the three-month follow-up period in any of the patients.

Follow-up

The median follow-up time for clinical events was 33 months (27, 39). The long-term clinical outcome was excellent with low event-rate. Of the total population (n=224), 58 (26%) patients experienced a new clinical event including 33 patients with recurrent ischemia. Six patients died, two of myocardial re-infarction, one of cancer, one of an infectious disease with multiorgan failure, and two died without known reason. Fifteen patients experienced a non-fatal re-infarction. Table 3 summarises all first events in relation to the glucometabolic status classified in-hospital.

The Kaplan-Meier curves for patients with normal (n=119) or abnormal glucose regulation (n=105) classified by an OGTT in-hospital are shown in Figure 1. The probability of remaining free from a new clinical event did not differ between the two groups (Log-Rank, p=0.4). In a multivariate analysis adjusting for potential confounders the association remained non-significant between the groups (adjusted HR 0.81 (95 % CI 0.48-1.38), p=0.44).

Long-term prognosis was also compared between groups of patients classified into normal (n=151) and abnormal glucose regulation (n=50) based on an OGTT performed in a stable

condition at three-month follow-up. No significant difference in survival free of composite end-point was found between the groups (Figure 2, Log-Rank, p=0.3). Adjusting for potential confounders did not change the results significantly (adjusted HR 0.68 (95 % CI 0.34-1.36), p= 0.27). Nine patients experienced a new clinical event before the OGTT classification was performed at three months. Among these nine patients, seven and two patients were classified into the abnormal and normal glucose regulation group, respectively, based on the in-hospital OGTT.

Discussion

Our main result was that stable STEMI patients without previously known diabetes have an excellent long-term prognosis independent of newly detected abnormal glucose regulation made by an OGTT screening either in-hospital or at three-month follow-up.

Large prospective studies have demonstrated both admission and fasting blood glucose levels to be independent predictors of long-term mortality in non-diabetic acute MI patients whether treated by primary PCI or not [19-24]. However, data evaluating the prognostic importance of an OGTT performed during or early after an acute MI in patients without previously known diabetes are scarce. The timing of testing patients for abnormal glucose regulation after an acute MI is also uncertain. Recommendation of early screening of acute MI patients with an OGTT in order to detect high-risk patients in the recent European guidelines is mainly based on the follow-up study of the GAMI trial [8,9]. In this follow-up study, abnormal glucose regulation classified by an OGTT day four or five post-MI was associated with worse clinical outcome during a median follow-up time of about three years [8].

Our study is the second study (after the GAMI study) to evaluate early OGTT during an acute STEMI as a prognostic tool, in patients without previously known diabetes, and the first study who compared the prognostic value of an OGTT based classification in-hospital and after

three months. The low event rate in the present study prevents firm conclusions about the prognostic value of OGTT screening in patients with acute STEMI. There was a non-significant trend towards increased hazard in patients with abnormal vs. normal glucose regulation and a real difference between groups may have been detected if the sample size was larger. However, our results are not in line with the similar sized GAMI study and may challenge the present guidelines, which emphasize the importance of early testing of all patients with acute MI, especially in the modern era of acute revascularization of STEMI patients.

The excellent prognosis found in our study, regardless of the glucometabolic status, may partly be explained by the low proportion of patients classified with type 2 diabetes in-hospital and at three months (11 % and 5 %, respectively). Nevertheless, patients classified with abnormal compared to normal glucose regulation in-hospital and at three-month follow-up had significantly higher fasting values of HbA1c, circulating levels of insulin and proinsulin, and higher HOMA-IR score when measured both acutely and in a stable condition. These results correspond to another trial with acute MI patients showing that HbA1c and proinsulin were in the lowest range in patients with normal glucose regulation, intermediate in patients with impaired glucose tolerance, and highest in patients with type 2 diabetes [25]. The present results suggest that the abnormal glucose regulation found in these STEMI patients not only seem to be a transient stress-induced response, but also may be a result of underlying insulin resistance.

The overall mortality rate in the present study was 2.7 %. None died in-hospital and only one patient died during the first 30 days. Nine patients (7 with abnormal glucose regulation) experienced a new clinical event before the OGTT classification was performed at three-month follow-up. However, a low overall incidence of clinical events was found during the

first three months of follow-up, suggesting that a early OGTT based classification of the glucometabolic status in order to identify high risk patients with worse prognosis is possibly of limited importance in low risk patients with a primary PCI treated STEMI.

The low overall incidence of clinical events reported in our study may partly be explained by the inclusion criteria. Unstable patients with cardiogenic shock, renal failure, ongoing chest pain, nausea and persistent hyperglycaemia were excluded from the study, probably making a selection bias towards more glucometabolically normal patients with better prognosis. Furthermore, the patients included were relatively young and previous studies have shown a close relationship between newly diagnosed abnormal glucose regulation and age [8,26-28]. Additionally, a high proportion of our patients were diagnosed with single-vessel disease during coronary angiography [10], which may have contributed to the low event-rate observed in both groups.

Systematic use of recommended treatment (evidenced based medications and revascularisation) has been shown to have a favourable impact on one-year prognosis in patients with diabetes and coronary artery disease [29]. Patients in the present study were all treated by primary PCI in addition to a high proportion of patients on evidence based secondary prevention. All patients were treated according to guidelines regardless of glucometabolic status and this may explain the excellent prognosis observed in this STEMI population. Transient hyperglycaemia in patients with acute MI without known diabetes is common and is associated with worse outcome [19,24]. However, it has been difficult to prove that glucose control by insulin-glucose infusion [30] or insulin-glucose-potassium infusion [31], improve survival in patients with acute MI.

The European guidelines on diabetes, pre-diabetes, and cardiovascular diseases recommend that patients with cardiovascular disease without known diabetes should be investigated with

an OGTT [9], but whether the OGTT should be performed early after a first cardiovascular event or later in a stable condition is not defined. The present results suggest that OGTT screening of patients with acute STEMI without known diabetes should be performed in a stable condition during the post-MI follow-up.

Study limitations

The present study has certain limitations such as a possible selection bias towards more glucometabolically normal patients due to the exclusion of patients who were hemodynamically unstable, severe renal failure and persistent hyperglycaemia. Accordingly, patients included, were somewhat younger than expected from a general STEMI population, had relatively few comorbidities and mainly one-vessel disease. It is possible that different results would be obtained in older MI patients since high age has been shown to be associated with ischemia related hyperglycaemia and poor glycemic control [28].

All aspects taken together may explain the overall low incidence of clinical events during the follow-up period, but may also reflect the advances in modern treatment of STEMI with primary PCI in all patients and optimal post-infarction treatment. The association between abnormal glucose regulation classified by an OGTT and clinical outcome should be further investigated in forthcoming studies including primary PCI treated STEMI patients, with a prolonged follow-up period, using major cardiovascular events as a primary end-point.

Conclusion

Patients with a primary PCI treated STEMI, without previously known diabetes, appear to have an excellent long-term prognosis independent of the glucometabolic state classified by an OGTT in-hospital or at three-month follow-up.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ECK performed the statistical analysis and drafted the manuscript.

MA made substantial contribution with statistical analysis. GØA contributed with the conception and design of the study. CM analysed the SPECT data. ECK, IS, MA, JE, AM, HA and GØA participated in the study design and interpretation and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Reference List

1. Demir I, Yilmaz H, Basarici I, Sancaktar O, Deger N: **Primary percutaneous coronary interventions in acute myocardial infarction in diabetic versus non-diabetic patients. In-hospital and long-term results.** *Kardiol Pol* 2003, **58:**182-189.

2. Aguilar D, Solomon SD, Kober L, Rouleau JL, Skali H, McMurray JJ, Francis GS, Henis M, O'Connor CM, Diaz R et al.: **Newly diagnosed and previously known diabetes mellitus and 1-year outcomes of acute myocardial infarction: the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial.** *Circulation* 2004, **110:**1572-1578.

3. Abbud ZA, Shindler DM, Wilson AC, Kostis JB: **Effect of diabetes mellitus on short- and long-term mortality rates of patients with acute myocardial infarction: a statewide study. Myocardial Infarction Data Acquisition System Study Group.** *Am Heart J* 1995, **130:**51-58.

4. De Luca G, Sauro R, Varricchio A, Capasso M, Lanzillo T, Manganelli F, Mariello C, Siano F, Carbone G, Pagliuca MR et al.: **Impact of diabetes on long-term outcome in STEMI patients undergoing primary angioplasty with glycoprotein IIb-IIIa inhibitors and BMS or DES.** *J Thromb Thrombolysis* 2010, **30:**133-141.

5. Hsu LF, Mak KH, Lau KW, Sim LL, Chan C, Koh TH, Chuah SC, Kam R, Ding ZP, Teo WS et al.: **Clinical outcomes of patients with diabetes mellitus and acute myocardial infarction treated with primary angioplasty or fibrinolysis.** *Heart* 2002, **88:**260-265.

6. Bartnik M, Ryden L, Ferrari R, Malmberg K, Pyorala K, Simoons M, Standl E, Soler-Soler J, Ohrvik J: **The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe. The Euro Heart Survey on diabetes and the heart.** *Eur Heart J* 2004, **25:**1880-1890.

7. Hu DY, Pan CY, Yu JM: **The relationship between coronary artery disease and abnormal glucose regulation in China: the China Heart Survey.** *Eur Heart J* 2006, **27:**2573-2579.

8. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L: **Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction.** *Eur Heart J* 2004, **25:**1990-1997.

9. Ryden L, Standl E, Bartnik M, Van den BG, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K et al.: **Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).** *Eur Heart J* 2007, **28:**88-136.

10. Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Arnesen H, Andersen GO: **Abnormal glucose regulation in patients with acute ST- elevation myocardial infarction-a cohort study on 224 patients.** *Cardiovasc Diabetol* 2009, **8:**6.

11. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW et al.: **ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM).** *Eur J Heart Fail* 2008, **10:**933-989.

12. **World Health Organization Department of Noncommunicable Disease Surveillance G. Definition, Diagnosis and Classification of Diabetes Mellitus and its complication.** Report of a WHO Consultation 1999, 1-59. Available from: URL: http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf

13. **World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia.** Report of a WHO/IDF Consultation 2005, 1-46. Available from: URL: http://whqlibdoc.who.int/publications/2006/9241594934_eng.pdf

14. Thygesen K, Alpert JS, White HD: **Universal definition of myocardial infarction.** *Eur Heart J* 2007, **28:**2525-2538.

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: **Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man.** *Diabetologia* 1985, **28:**412-419.

16. Gibbons RJ, Miller TD, Christian TF: **Infarct size measured by single photon emission computed tomographic imaging with (99m)Tc-sestamibi: A measure of the efficacy of therapy in acute myocardial infarction.** *Circulation* 2000, **101:**101-108.

17. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic research. Principles and quantitative methods.* New York: Van Nostrand Reinhold Company Inc; 1982.

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Lancet* 2007, **370:**1453-1457.

19. Lavi S, Kapeliovich M, Gruberg L, Roguin A, Boulos M, Grenadier E, Amikam S, Markiewicz W, Beyar R, Hammerman H: **Hyperglycemia during acute myocardial infarction in patients who are treated by primary percutaneous coronary intervention: impact on long-term prognosis.** *Int J Cardiol* 2008, **123:**117-122.

20. Norhammar AM, Ryden L, Malmberg K: **Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients.** *Diabetes Care* 1999, **22:**1827-1831.

21. Aronson D, Hammerman H, Suleiman M, Markiewicz W: **Usefulness of changes in fasting glucose during hospitalization to predict long-term mortality in patients with acute myocardial infarction.** *Am J Cardiol* 2009, **104:**1013-1017.

22. Straumann E, Kurz DJ, Muntwyler J, Stettler I, Furrer M, Naegeli B, Frielingsdorf J, Schuiki E, Mury R, Bertel O et al.: **Admission glucose concentrations independently predict early and late mortality in patients with acute myocardial infarction treated by primary or rescue percutaneous coronary intervention.** *Am Heart J* 2005, **150:**1000-1006.

23. Gasior M, Pres D, Stasik-Pres G, Lech P, Gierlotka M, Hawranek M, Wilczek K, Szygula-Jurkiewicz B, Lekston A, Kalarus Z et al.: **Effect of blood glucose levels on prognosis in acute myocardial infarction in patients with and without diabetes, undergoing percutaneous coronary intervention.** *Cardiol J* 2008, **15:**422-430.

24. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF: **In-hospital peak glycemia and prognosis in STEMI patients without earlier known diabetes.** *Eur J Cardiovasc Prev Rehabil* 2010, **17:**419-423.

25. Tenerz A, Norhammar A, Silveira A, Hamsten A, Nilsson G, Ryden L, Malmberg K: **Diabetes, insulin resistance, and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes.** *Diabetes Care* 2003, **26:**2770-2776.

26. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K: **Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study.** *Lancet* 2002, **359:**2140-2144.

27. Lenzen M, Ryden L, Ohrvik J, Bartnik M, Malmberg K, Scholte Op RW, Simoons ML: **Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart.** *Eur Heart J* 2006, **27:**2969-2974.

28. Lazzeri C, Valente S, Chiostri M, Picariello C, Gensini GF: **Acute glucose dysmetabolism in the elderly with ST elevation myocardial infarction submitted to mechanical revascularization.** *Int J Cardiol* 2011.

29. Anselmino M, Malmberg K, Ohrvik J, Ryden L: **Evidence-based medication and revascularization: powerful tools in the management of patients with diabetes and coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart.** *Eur J Cardiovasc Prev Rehabil* 2008, **15:**216-223.

30. Malmberg K, Ryden L, Wedel H, Birkeland K, Bootsma A, Dickstein K, Efendic S, Fisher M, Hamsten A, Herlitz J et al.: **Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity.** *Eur Heart J* 2005, **26:**650-661.

31. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, Paolasso E, Ahmed R, Xie C, Kazmi K et al.: **Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial.** *JAMA* 2005, **293:**437-446.

Figure legends:

Figure 1 Kaplan-Meier curves, survival free of composite end-point for patients with normal (NGR) and abnormal glucose regulation (AGR) classified by an OGTT in-hospital (A) and after three months (B).

Table 1 Clinical characteristic of patients with STEMI according to glucometabolic classifications by an OGTT in-hospital and after three months.

	In-hospital			At three-month follow-up		
	NGR (n=119)	AGR (n=105)	P	NGR (n=151)	AGR (n=50)	P
Age (years)	55 (50,63)	60 (54,71)	<0.001	57 (51, 65)	61 (52, 72)	0.04
Men	106 (89.1)	79 (75.2)	<0.01	129 (85.4)	36 (72.0)	0.03
Previous disorders						
Treated dyslipidaemia	11 (9.2)	9 (8.6)	0.86	15 (9.9)	4 (8.0)	0.47
Treated hypertension	25 (21)	33 (31.4)	0.32	38 (25.2)	17 (34.0)	0.23
Previous acute MI	9 (7.6)	7 (6.7)	0.08	10 (6.6)	4 (8.0)	0.48
Previous angina pectoris	5 (4.2)	2 (1.9)	0.33	6 (4.0)	1 (2.0)	0.45
Current smoker	65 (54.6)	44 (41.9)	0.06	67 (44.4)	24 (48.0)	0.66
Body mass index (kg/m^2)	25.9 (24.5, 28.7)	26.1 (24.3, 28.6)	0.82	26.1 (24.4, 28.5)	25.7 (24.1, 28.7)	0.73
Waist circumference	100 (94, 107)	99 (94, 107)	0.86	101 (94, 107)	98 (94, 107)	0.92
Cholesterol (mmo/L)	5.2 (4.5, 5.8)	5.1 (4.4, 5.8)	0.52	4.1 (3.8, 4.6)	4.0 (3.6, 4.8)	0.43
LDL-cholesterol (mmol/ L)	3.4 (2.7, 4.2)	3.3 (2.7, 4.0)	0.54	2.2 (1.8, 2.6)	2.1 (1.7, 2.6)	0.42
Triglycerides (mmo/ L)	1.4 (1.0,1.8)	1.2 (0.9,1.8)	0.11	1.2 (0.9, 1.6)	1.2 (1.1, 1.6)	0.64
Stents	114 (95.8)	101 (96.2)	0.88	143 (94.7)	49 (98.0)	0.30
One-vessel disease	78 (65.5)	61 (58.1)	0.25	92 (60.9)	30 (60.0)	0.91
Left main disease	47 (39.5)	42 (40.0)	0.94	58 (38.4)	21 (42.0)	0.65
IIb / IIIa inhibitors	37 (31.1)	42 (40.0)	0.17	54 (35.8)	19 (38.0)	0.78
TnT peak value (ug/ L)	4.47 (2.39, 7.32)	5.63 (2.78,10.89)	0.03	4.85 (2.45, 8.31)	4.97 (2.38, 10.25)	0.47
Measured at three-month.						
LVEF[1] (%)	64 (57, 70)	62 (52,69)	0.13	63.5 (56, 70)	63.5 (51, 69)	0.47
Infarct size[2] (%)	9 (0, 25)	20 (4.5, 32)	<0.001	13 (0, 27)	21.5 (0, 43)	0.04
Medication at discharge from CCU and after three months.						
Aspirin	119 (100)	105 (100)		150 (99.3)	50 (100)	0.57
Clopidogrel	118 (99.2)	104 (99.0)	0.93	143 (94.7)	46 (92.0)	0.49
β-blockers	96 (80.7)	85 (81.0)	0.96	142 (94.0)	46 (92.0)	0.61
Lipid lowering agents	118 (99.2)	103 (99.1)	0.49	146 (96.7)	48 (96.0)	0.82
ACEIs	19 (16)	17 (16.2)	0.96	52 (34.4)	17 (34.0)	0.96
ARBs	8 (6.7)	10 (9.5)	0.44	21 (13.9)	4 (8.0)	0.27

Data are presented as median values (25, 75 percentiles) or proportions.
ACEIs: angiotensin-converting enzyme inhibitors, AGR: abnormal glucose regulation, acute MI: acute myocardial infarction, ARBs: angiotensin receptor blockers, CCU: coronary care unit, NGR: normal glucose regulation, TnT peak level: serum peak level of cardiac specific Troponin T. [1,2]Measured at three months by SPECT analysis, [1]LVEF: left ventricular ejection fraction, [2]infarct size in % of left ventricular mass.

Table 2 Biochemical variables in patients according to glucometabolic status classified by an OGTT in-hospital and at three-month.

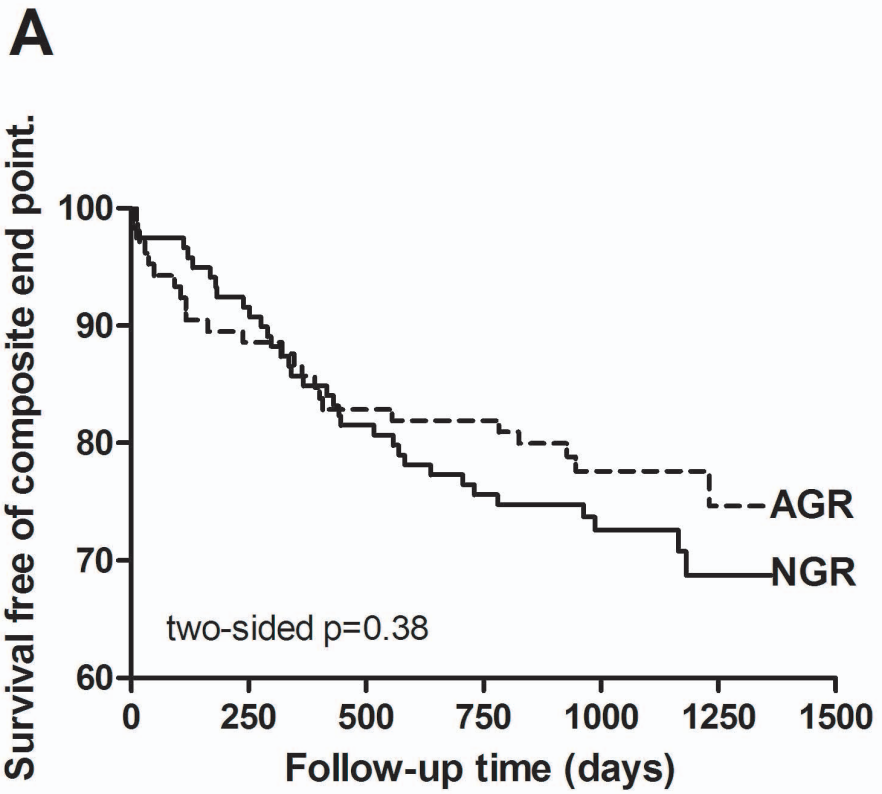
	NGR (in-hospital) (n=119)	AGR (in-hospital) (n=105)	P	NGR (at three-month) (n=151)	AGR (at three-month) (n=50)	P
HbA1c (%)	5.5 (5.3, 5.7)	5.6 (5.4, 5.8)	<0.01	5.5 (5.4, 5.7)	5.8 (5.5, 6.2)	<0.0001
Insulin (pmol/ L)	66 (46, 87)	73 (53,108)	0.03	63 (39, 82)	75 (47, 112)	0.02
C-peptid (pmol/ L)	788 (638, 1026)	1026 (728, 1241)	<0.001	834 (636, 1077)	893 (728, 1129)	0.11
Proinsulin (pmol/ L)	6.8 (4.7, 10.4)	8.6 (5.8, 13.9)	0.02	5.4 (4.3, 8.5)	7.5 (5.4, 10.3)	0.01
HOMA-IR (mU $mmol^{-1}$ L^{-1})	2.45 (1.63, 3.36)	3.00 (2.11, 4.92)	<0.001	2.20 (1.45, 3.23)	3.15 (2.08, 4.99)	<0.01
Proinsulin: insulin ratio	0.12 (0.08, 0.19)	0.13 (0.08, 0.18)	0.87	0.10 (0.07, 0.15)	0.12 (0.07, 0.18)	0.41

Data are presented as median values (25, 75 percentiles)
AGR: abnormal glucose regulation, NGR: normal glucose regulation.

Table 3 Number of first clinical events according to glucometabolic status classified by an OGTT in-hospital in patients (n=224) with STEMI.

	NGR (n=119)	IFG (n=12)	IGT (n=69)	DM (n=24)	
Type of event					Total
Death	1	1	4	0	6
Non-fatal re-infarction	9	0	5	1	15
Recurrent ischemia	20	0	8	5	33
Stroke	4	0	0	0	4
SUM	34	1	17	6	58

NGR: normal glucose regulation, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, DM: type 2 diabetes mellitus.


A
Survival free of composite end point.
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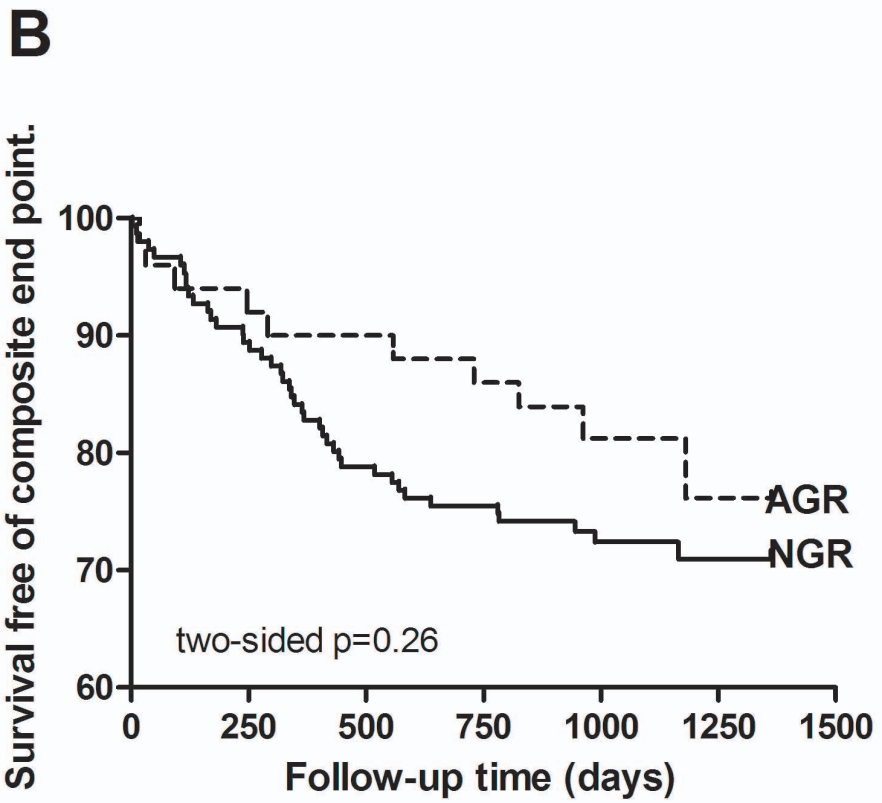
AGR
NGR
two-sided p=0.38
Follow-up time (days)


B
Survival free of composite end point.
100
90
80
70
60
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250
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750
1000
1250
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AGR
NGR
two-sided p=0.26
Follow-up time (days)

III

CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION Open Access

Increased levels of CRP and MCP-1 are associated with previously unknown abnormal glucose regulation in patients with acute STEMI: a cohort study

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Abstract

Background: Inflammation plays an important role in the pathophysiology of both atherosclerosis and type 2 diabetes and some inflammatory markers may also predict the risk of developing type 2 diabetes. The aims of the present study were to assess a potential association between circulating levels of inflammatory markers and hyperglycaemia measured during an acute ST-elevation myocardial infarction (STEMI) in patients without known diabetes, and to determine whether circulating levels of inflammatory markers measured early after an acute STEMI, were associated with the presence of abnormal glucose regulation classified by an oral glucose tolerance test (OGTT) at three-month follow-up in the same cohort.

Methods: Inflammatory markers were measured in fasting blood samples from 201 stable patients at a median time of 16.5 hours after a primary percutanous coronary intervention (PCI). Three months later the patients performed a standardised OGTT. The term abnormal glucose regulation was defined as the sum of the three pathological glucose categories classified according to the WHO criteria (patients with abnormal glucose regulation, n = 50).

Results: No association was found between inflammatory markers and hyperglycaemia measured during the acute STEMI. However, the levels of C-reactive protein (CRP) and monocyte chemoattractant protein-1 (MCP-1) measured in-hospital were higher in patients classified three months later as having abnormal compared to normal glucose regulation (p = 0.031 and p = 0.016, respectively). High levels of CRP (≥ 75 percentiles (33.13 mg/L)) and MCP-1 (≥ 25 percentiles (190 ug/mL)) were associated with abnormal glucose regulation with an adjusted OR of 3.2 (95% CI 1.5, 6.8) and 7.6 (95% CI 1.7, 34.2), respectively.

Conclusion: Elevated levels of CRP and MCP-1 measured in patients early after an acute STEMI were associated with abnormal glucose regulation classified by an OGTT at three-month follow-up. No significant associations were observed between inflammatory markers and hyperglycaemia measured during the acute STEMI.

Background

Increased prevalence of unknown impaired glucose tolerance and type 2 diabetes has been shown in patients suffering an acute myocardial infarction (AMI) [1]. Both the short- and long-term prognoses after an AMI are worse among individuals with abnormal compared to individuals with normal glucose regulation [2]. According to guidelines, it is important to diagnose these high-risk patients with abnormal glucose regulation in order to initiate lifestyle intervention and optimal medical treatment [3].

We have recently shown that high levels of HbA1c, admission glucose, and fasting plasma glucose measured early in-hospital in patients with an acute ST-elevation myocardial infarction (STEMI) were predictive to identify patients with abnormal glucose regulation at three-month

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follow-up [4]. We also demonstrated poor reproducibility of an oral glucose tolerance test (OGTT) performed early after an acute STEMI compared to a new test in a stable condition three months later [4].

There is considerable evidence that inflammation plays an important role in the pathophysiology of both atherosclerosis [5] and type 2 diabetes [6] and some inflammatory markers may also predict the risk of developing type 2 diabetes [7]. Additionally, inflammation has been suggested to be the bridging link between abnormalities in glucose metabolism and atherosclerotic disorders [8] In order to elucidate a possible association between hyperglycaemia, abnormal glucose regulation and inflammation in STEMI patients without known diabetes we chose to investigate a broad panel of pro- and anti-inflammatory markers. The acute phase reactant C-reactive protein (CRP), the pro-inflammatory markers (interleukin 6 (IL-6), interleukin 8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α)), soluble CD40 ligand (sCD40L), the anti-inflammatory marker adiponectin, the matrix metalloproteinase-9 (MMP-9) and its inhibitor (tissue inhibitor of metalloproteinase 1 (TIMP-1)) were investigated. We hypothesized that STEMI patients having abnormal glucose regulation would present with an increased pro-inflammatory profile.

The aims of the study were 1) to assess a potential association between circulating levels of inflammatory markers and hyperglycaemia measured during an acute STEMI in patients without known diabetes and 2) to identify a possible association between circulating levels of inflammatory markers measured acutely and abnormal glucose regulation classified by an OGTT at three-month follow-up in the same cohort.

Methods

Study population

The patient population has been described in detail elsewhere [4]. In brief, patients with a primary percutanous coronary intervention (PCI) treated STEMI were included if they were stable, without chest pain or nausea, age < 85 years and with serum creatinine < 200 umol/L. Patients with previously known type 2 diabetes or persistent hyperglycaemia were excluded. Patients with persistent hyperglycaemia were defined as patients with both admission plasma glucose > 11 mmol/L and a fasting capillary glucose level > 8 mmol/L before an OGTT was performed. STEMI was defined as ST-segment elevation of ≥ 2 mm in two or more contiguous chest leads, ≥ 1 mm in two or more limb leads, or new left bundle-branch block, together with typical symptoms (chest pain or discomfort > 20 min duration).

The Regional ethics committee approved the study and all patients provided written and oral informed consent.

Laboratory methods

Admission plasma glucose concentration was analysed from blood samples taken in the catheterisation laboratory as soon as possible after PCI. Further blood samples were drawn after an overnight fast for determination of glucose, HbA1c, for routine analyses by use of conventional methods and for determination of CRP, MCP-1, TNF-α, IL-6, sCD40L, IL-8, MMP-9, TIMP-1, IL-18, and adiponectin. Serum was prepared by centrifugation within 1 hour at 2500 g for 10 min and used for all analyses, except MCP-1, which was determined in citrated plasma (0.129 mmol/L in dilution 1:10) and sCD40L determined in EDTA plasma, stored on ice and separated within 30 min by centrifugation at 4°C and 3000 g for 20 min to obtain platelet-poor plasma. All blood samples were stored at -80°C until analysis.

CRP and IL-18 were determined by enzyme-linked immunosorbent assays (DRG Instruments, Marburg/Lahn, Germany, and Medical Biological Laboratories, Naku-ku, Nagoya, Japan, respectively). MCP-1, MMP-9, TIMP-1, IL-6, IL-8, TNF-α, adiponectin and sCD40L were all measured by enzyme immunoassays from R&D Systems Europe (Abingdon, Oxon, UK).

In our laboratory, the inter-assay coefficient of variation were as follows, CRP < 5%, MCP-1 9.0%, IL-6 10.5%, IL-8 10.5%, IL-18 6.5%, TNF-α 8.5%, adiponectin 9.5%, MMP-9 7.4%, TIMP-1 4.4%, and sCD40L 9.5%.

Serum cardiac specific Troponin T (TnT) was measured by electrochemiluminescence technology for quantitative measurement (Elecsys 2010, Roche, Mannheim, Germany). The inter-assay coefficient of variation was 7%. TnT maximum was defined as the maximum value measured in each patient during the acute STEMI.

Follow- up

Three months after the initial hospitalisation clinical examination and a standardised oral glucose tolerance test (OGTT) (75 g glucose in 200 ml water with plasma glucose measurements at 0 and 120 min) were performed [9]. The classification of glucometabolic state was based on the result of the OGTT and the patients were divided into one of the following four categories defined according to the World Health Organisation criteria [10] (glucose levels given in mmol/L):

Normal Glucose Tolerance (NGT) = OGTT (0 min) < 6.1 and OGTT (2 h) < 7.8

Impaired Fasting Glucose (IFG) = OGTT (0 min) ≥ 6.1 < 7.0 and OGTT (2 h) < 7.8

Impaired Glucose Tolerance (IGT) = OGTT (0 min) < 7.0 and OGTT (2 h) ≥ 7.8 < 11.1

Type 2 diabetes (T2DM) = OGTT (0 min) ≥ 7.0 and/or OGTT (2 h) ≥ 11.1.

The term abnormal glucose regulation was defined as the sum of IFG, IGT and T2DM.

Left ventricular ejection fraction and infarct size expressed as percent of left ventricular mass were assessed at rest at three-month follow-up by Single Photon Emission Computed Tomography imaging with technetium 99 m-tetrofosmin [11].

Statistics

The study design was a cohort study and the outcome was defined as abnormal glucose regulation. We hypothesised an association between inflammatory variables and the state of glucose regulation. Continuous variables were categorised into quartiles. A linear trend analysis across the quartiles of an inflammatory marker identified the cut off point used. The Mantel-Haenszel method was used to highlight potential effect modification by the Breslow-Day test of heterogeneity and to quantify potential confounders [12]. Additional information is available online [Additional file 1: Supplemental Table S1]. The following risk factors were analysed as potential confounders; gender, age, current smoking, treated hypertension, TnT maximum, body mass index, cholesterol, triglycerides, CRP and MCP-1. A logistic regression model, including a backward elimination procedure was performed to adjust for the confounders.

Continuous variables are presented as median and 25, 75 percentiles and categorical variables as proportions. The correlations between the investigated variables were assessed by use of Spearman's rho and adjustments were performed using a multivariate analysis with logarithmically transformed data. The STROBE guidelines were followed [13]. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using Epi-info software, 2005, version 3.3.2, except Spearman correlation coefficient analyses and multiple regressions, which were made by use of SPSS software, 2006, version 15.0 (SPSS, Chicago, L).

Results

Baseline characteristics

Two hundred and one patients with a primary PCI treated STEMI were enrolled in the study [4]. Baseline characteristics are shown in Table 1. Notably, BMI was 26 kg/m^2, 82% were men and 61% had single vessel disease. Fasting blood samples were drawn at a median time of 20 h and 20 min after the occurrence of symptoms and 16 h and 35 min after the primary PCI.

Table 1 Baseline characteristics of the total population (n = 201)

	Patients
Age (years)	58 (51, 67)
Male	185 (82.6%)
Previous disorder:	
Myocardial infarction	16 (7.1%)
Angina pectoris	7 (3.1%)
Hypertension (treated)	58 (25.9%)
Hyperlipidaemia (treated)	20 (8.9%)
Status at baseline	
Current smoker	109 (48.7%)
TnT maximum (ug/L)	4.70 (2.45, 8.92)
BMI (kg/m2)	26 (24.4, 28.7)
Waist circumference (cm)	100 (94, 107)
Stent in culprit lesion	215 (96.0%)
Gp IIb/IIIa antagonist treated	79 (35.3%)
Single -coronary vessel disease	139 (62.1%)
Double-coronary vessel disease	64 (28.6%)
Triple-coronary vessel disease	21 (9.4%)
Time from symptoms to balloon (min)	219 (140, 378)
Medication at three months (n = 201)	
Aspirin	200 (99.5%)
Clopidogrel	189 (94%)
β-blockers	188 (93.5%)
Lipid lowering agents	194 (96.5%)
Angiotensin converting enzyme-inhibitors	69 (34.3%)
Angiotensin II-receptor blockers	25 (12.4%)
Glucose lowering medication	0
LVEF[a] (%)	64 (56, 70)
Infarct size[a], % of left ventricular mass	14.0 (0.0, 29.0)

Data are presented as median (25, 75 percentiles) values or proportions.
BMI: body mass index, LVEF: left ventricular ejection fraction, TnT maximum: serum cardiac specific Troponin T maximum.[a]LVEF and infarct size were measured at three-month follow-up by SPECT.

The plasma glucose concentration at admission was 6.9 (6.0, 7.8) mmol/L, the fasting plasma glucose 5.3 mmol/L (4.9, 5.9) and HbA1c 5.5% (5.3, 5.8). As previously reported, patients defined with abnormal glucose regulation were older, there were more women, and they had significantly higher levels of HbA1c, admission plasma glucose, and fasting plasma glucose measured in-hospital, compared to patients with normal glucose regulation [4].

Follow-up characteristics

All patients were reached to follow up. However, one patient did not perform the OGTT because the level of fasting glucose measured was above 7 mmol/L. At three-month follow-up the levels of fasting plasma glucose and HbA1c were 5.2 mmol/L (4.8, 5.6) and 5.6% (5.4, 5.8), respectively. The prevalence of abnormal glucose regulation based on the OGTT classification was

25% (n = 50). The prevalence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes were 5.5% (n = 11), 14.4% (n = 29) and 5% (n = 10), respectively. The medications for secondary prevention recorded were according to current guidelines, i.e. 99.5% were on aspirin and 96.5% were on lipid lowering agents (Table 1).

Inflammatory markers and hyperglycaemia

As can be seen from Table 2, there were no associations between admission glucose and the inflammatory markers measured whereas significant correlations were observed between fasting glucose and IL-6 (p = 0.004) and adiponectin (p = 0.038). However, after adjustment for age and TnT maximum measured in-hospital, no significant associations were found (p = 0.14 and p = 0.095, respectively).

Inflammatory markers and abnormal glucose regulation

Elevated levels of CRP (p = 0.031) and MCP-1 (p = 0.016) measured in-hospital were found in patients classified with abnormal glucose regulation at three-month follow-up (Table 3). There was no difference between the two groups according to the other inflammatory markers measured (Table 3). Furthermore, only a weak correlation between MCP-1 and CRP was found (r = -0.14, p = 0.049).

When dividing the MCP-1 and CRP levels into quartiles, there were significant trends for the presence of abnormal glucose regulation with increased levels of both biomarkers (p = 0.005 and p = 0.016, respectively), identifying a threshold for MCP-1 at the 25 percentile (190 ug/mL) and for CRP at the 75 percentile (33.13 mg/L) (Figure 1A and 1B). In univariate analyses, high levels of CRP (≥ 75 percentile) and MCP-1 (≥ 25 percentile) in-hospital were associated with abnormal glucose regulation classified at three-month (p = 0.007 and p = 0.004, respectively) (Table 4). CRP remained associated with abnormal glucose regulation after adjustment for potential confounders with an OR 3.24 (95% CI 1.54, 6.83) (Table 4). Triglycerides were shown to modify the association between MCP-1 and abnormal glucose regulation (Table A online). Consequently, the patients were divided into two strata with high and low triglyceride levels. High levels of MCP-1 were independently associated with abnormal glucose regulation in 150 patients with triglycerides below the 75th percentile (1.8 mmol/L) with an OR 7.56 (95% CI 1.67, 34.18).

Table 2 Correlations between the inflammatory markers and admission plasma glucose (APG) and fasting plasma glucose (FPG), all measured acutely in-hospital

Variables	APG		FPG	
	r_s	p	r_s	p
CRP mg/L	0.04	NS	0.13	NS
MCP-1 pg/mL	0.05	NS	-0.11	NS
TNF-α pg/mL	0.06	NS	-0.02	NS
IL-6 pg/mL	-0.04	NS	0.20	0.004
sCD40L pg/mL	-0.06	NS	-0.05	NS
IL-8 pg/mL	-0.12	NS	-0.12	NS
TIMP-1 ng/mL	0.06	NS	0.03	NS
MMP-9 ng/mL	0.13	NS	0.13	NS
IL-18 pg/mL	-0.03	NS	-0.04	NS
Adiponectin ng/mL	-0.03	NS	0.15	0.04

r_s indicate Spearman correlation coefficient.
Abbreviations: see main text.
NS: non-significant.

Table 3 Levels of inflammatory markers measured in-hospital related to normal (NGR) and abnormal glucose regulation (AGR) categorised by an OGTT after three months

Variables	NGR (n = 151)	AGR (n = 50)	P
CRP mg/L	10.99 (5.95, 30.0)	20.91(8.40, 41.98)	0.031
MCP-1 pg/mL	218 (185, 268)	241 (205, 301)	0.016
TNF-α pg/mL	1.51 (1.25, 2.06)	1.58 (1.26, 2.06)	0.996
IL-6 pg/mL	17.16 (11.22, 28.04)	20.88 (13.76, 31.00)	0.131
CD40L pg/mL	63.3 (44.5, 97.4)	64.6 (43.3, 88.8)	0.599
IL-8 pg/mL	15.1 (13.6, 17.8)	15.4 (13.2, 19.4)	0.432
TIMP-1 ng/mL	190 (162, 217)	199 (163, 220)	0.911
MMP-9 ng/mL	502 (341, 664)	539 (414, 748)	0.254
IL-18 pg/mL	269 (203, 333)	288 (239, 359)	0.096
Adiponectin ng/mL	4794 (3006, 7759)	4385 (2806, 7075)	0.474

Median values (25, 75 percentiles) are given.
Abbreviations: see main text.
P-values refer to difference between groups.

Discussion

The main results of the present study were that elevated levels of CRP and MCP-1 measured in patients early after an acute STEMI were associated with abnormal glucose regulation defined at three-month follow-up. Additionally, during the acute STEMI, there were weak, non-significant associations between fasting glucose and IL-6 and adiponectin, while there was no association between admission glucose and the inflammatory markers measured.

Inflammatory markers and hyperglycaemia

During experimental conditions, induction of hyperglycaemia in humans has been shown to increase circulating levels of cytokines and the effect was more pronounced in subjects with impaired glucose tolerance suggesting a causal role of hyperglycaemia in the activation of the inflammation in diabetes [14]. Furthermore, hyperglycaemia at admission has been reported to be associated with increased risk of in-hospital mortality

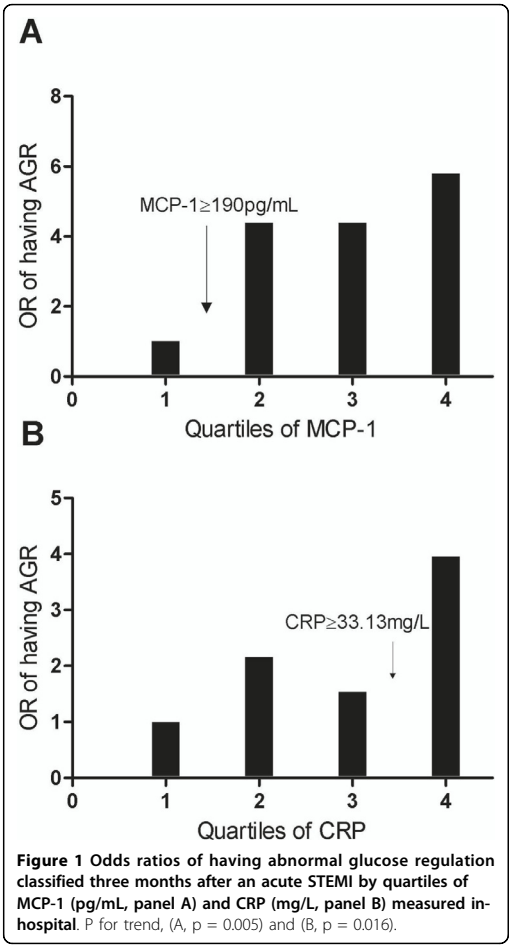

Figure 1 Odds ratios of having abnormal glucose regulation classified three months after an acute STEMI by quartiles of MCP-1 (pg/mL, panel A) and CRP (mg/L, panel B) measured in-hospital. P for trend, (A, p = 0.005) and (B, p = 0.016).

and poor long-term outcome [15-17]. There are, however, no guidelines defining the level of pathological hyperglycaemia at admission with an acute myocardial infarction [17].

It has been shown that patients with a primary PCI treated STEMI generate a marked, short-term increase in circulating levels of inflammatory markers [18] and higher levels of CRP and IL-6 in patients with acute myocardial infarction and diabetes compared to patients without diabetes have also been reported [19]. In the present study we could, however, not reveal any association between the acute hyperglycaemia and the inflammatory responses. The relatively few patients with hyperglycaemia at admission may partly explain these negative results. In addition, we may have missed the peak levels of the measured inflammatory markers by the delayed sampling time point. The association found between fasting glucose and IL-6 and adiponectin probably reflect a relation to infarct size because it was no longer significant after adjustment for TnT maximum.

Associations between inflammatory markers and abnormal glucose regulation

We have recently shown that in patients with a primary PCI treated STEMI, a very early OGTT should probably not be recommended because of lack of reproducibility [4]. However, high levels of admission glucose, fasting glucose, and HbA1c in these patients were shown to be associated with abnormal glucose regulation defined at three-month follow-up [4]. In the present study, searching for novel biomarkers that may associate with abnormal glucose regulation, we found that high levels of CRP and MCP-1 measured early after an acute STEMI were associated with abnormal glucose regulation diagnosed in a stable situation. The associations found between high levels of CRP and MCP-1 measured acutely and abnormal glucose regulation defined three months later might be influenced by the acute STEMI, which are known to release several inflammatory mediators from the necrotic myocardium into the circulation [20].

Our findings may be interpreted along with previous results showing higher levels of CRP in patients with abnormal compared to those with normal glucose regulation [21] thus the high levels of CRP measured acutely may reflect a low-grade systemic inflammation in glucose intolerant patients.

MCP-1 levels have been reported to be elevated in patients with an acute myocardial infarction [22] and poor glycemic control has been suggested to induce high levels of MCP-1 in diabetic patients [23]. Furthermore, increased monocyte recruitment into the subendothelial space has been shown in patients with diabetic angiopathy and MCP-1 seems to play a key role in this process [24]. In our study, the association between high levels of MCP-1 and abnormal glucose regulation may indicate that patients with an abnormal glucometabolic status do present with high levels of MCP-1 before the acute STEMI or it might be suggested that patients with abnormal glucose regulation respond with higher levels of MCP-1 in the acute phase, compared to those with normal glucose regulation.

MCP-1 levels have been shown to correlate with triglyceride levels in post-menopausal women [25] and in patients with diabetes [23]. In our study the association between MCP-1 and abnormal glucose regulation was present in the majority of the patients, but not in patients with triglycerides above 1.8 mmol/L, suggesting that in these patients the high levels of triglycerides may mask the association between MCP-1 and glucose regulation.

Table 4 Crude and adjusted OR of the association between high levels of CRP and MCP-1 measured in-hospital and abnormal glucose regulation defined by an OGTT three months later using logistic regression analyses

	AGR		AGR		AGR TG < 1.8 mmol/l (n = 150)		AGR TG ≥ 1.8 mmol/l (n = 49)	
	OR (crude) (95% CI)	P	OR (adjusted) (95% CI)	P	OR (adjusted) (95% CI)	P	OR (adjusted) (95% CI)	P
CRP[a] (≥ 33.13 mg/L)	2.58 (1.29, 5.14)	0.007	3.24 (1.54, 6.83)	0.002				
MCP-1[b] (≥ 190 pg/mL)	4.82 (1.64, 14.20)	0.004			7.56 (1.67, 34.18)	0.009	1.81 (0.16,19.87)	0.626

TG: triglycerides. AGR: abnormal glucose regulation. Abbreviations: see main text.

[a] Adjusted for identified confounders (gender and MCP-1).

[b] Stratified for triglycerides as an effect modifier and adjusted for identified confounders (age, gender, treated hypertension, TnT maximum and CRP).

CRP and MCP-1 were associated with abnormal glucose regulation independently of each other, indicating that these markers probably are involved in different pathological processes associated with type 2-diabetes.

MCP-1 and IL-8 are functionally related, potent chemoattractants both being shown to be involved in the atherosclerotic process [26]. It has previously been reported that fasting levels of IL-8 correlated with BMI both in subjects with normal and impaired glucose tolerance [27]. In obese subjects without coronary heart disease, the post-load levels of IL-8 increased after an OGTT in subjects with impaired glucose tolerance compared to normoglycaemic weight-matched individuals [27] However, we did not found any association between IL-8 and abnormal glucose regulation.

Elevated levels of IL-18 have been associated with an increased risk of developing type 2-diabetes [28]. Also high levels of MMP-9 and TIMP-2 have been found in patients with an acute coronary syndrome and type 2 diabetes, probably reflecting an abnormal extracellular matrix metabolism in these patients [29]. On the contrary, circulating levels of adiponectin, which is an anti-atherogenic, anti-inflammatory and insulin-sensitizing adipokine, have been shown to be lower in patients with type 2 diabetes and macro vascular disease than those without [30]. We found, however, no associations between abnormal glucose regulation and the levels of IL-18, MMP-9, TIMP-1, and adiponectin. This may be explained by the fact that only a small number of our patients were classified as having type 2-diabetes.

Almost all the patients in the present study were treated according to guidelines for secondary prevention with medication, which included lipid lowering agents and anti-platelet treatment. However, glucose lowering medication, which could have had a confounding effect on the glucometabolic classification, was not introduced.

Study limitations

Unstable patients with cardiogenic shock, renal failure, ongoing chest pain, nausea and persistent hyperglycaemia were excluded from the study, possibly making a selection bias towards more glucometabolically normal patients.

Conclusion

Elevated levels of CRP and MCP-1 measured early after a primary PCI treated STEMI in patients without previously known diabetes were associated with abnormal glucose regulation classified by an OGTT at three-month follow-up indicating an important role of low grade inflammation in glucose regulation. There was however, non-significant association between inflammatory markers and hyperglycaemia during the acute STEMI in the same cohort

Additional material

Additional file 1: Stratified analysis on major potential confounders using the Mantel-Haenszel method. Table S1 shows identified effect modifiers and potential confounders in the associations between CRP and AGR, and MCP-1 and AGR by use of the Mantel-Haenszel method. Abbreviations: see main text.

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Authors' contributions

ECK performed the statistical analysis of the data presented and drafted the manuscript.

MA made substantial contribution with statistical analysis. GØA contributed with the conception and design of the study. ECK, IS, MA, JE, AM, HA and GØA participated in the study design and interpretation and revised the

manuscript critically for important intellectual content. All authors have read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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References

1. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, Malmberg K: **Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study.** *Lancet* 2002, **359**:2140-2144.
2. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L: **Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction.** *Eur Heart J* 2004, **25**:1990-1997.
3. Ryden L, Standl E, Bartnik M, Van den BG, Betteridge J, de Boer MJ, Cosentino F, Jonsson B, Laakso M, Malmberg K, Priori S, Ostergren J, Tuomilehto J, Thrainsdottir I, Vanhorebeek I, Stramba-Badiale M, Lindgren P, Qiao Q, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Deckers JW, Bertrand M, Charbonnel B, Erdmann E, Ferrannini E, Flyvbjerg A, Gohlke H, Juanatey JR, Graham I, Monteiro PF, Parhofer K, Pyorala K, Raz I, Schernthaner G, Volpe M, Wood D: **Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD).** *Eur Heart J* 2007, **28**:88-136.
4. Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Arnesen H, Andersen GO: **Abnormal glucose regulation in patients with acute ST-elevation myocardial infarction-a cohort study on 224 patients.** *Cardiovasc Diabetol* 2009, **8**:6.
5. Libby P: **Inflammation and cardiovascular disease mechanisms.** *Am J Clin Nutr* 2006, **83**:456S-460S.
6. Beckman JA, Creager MA, Libby P: **Diabetes and atherosclerosis: epidemiology, pathophysiology, and management.** *JAMA* 2002, **287**:2570-2581.
7. Freeman DJ, Norrie J, Caslake MJ, Gaw A, Ford I, Lowe GD, O'Reilly DS, Packard CJ, Sattar N: **C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study.** *Diabetes* 2002, **51**:1596-1600.
8. Ziegler D: **Type 2 diabetes as an inflammatory cardiovascular disorder.** *Curr Mol Med* 2005, **5**:309-322.
9. **Definition, Diagnosis and Classification of Diabetes Mellitus and its Complication. Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus.** [http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf].
10. **Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. Report of a WHO/IDF Consultation.** [http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf].
11. Gibbons RJ, Miller TD, Christian TF: **Infarct size measured by single photon emission computed tomographic imaging with (99 m)Tc-sestamibi: A measure of the efficacy of therapy in acute myocardial infarction.** *Circulation* 2000, **101**:101-108.
12. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiologic research. Principles and quantitative methods* New York: Van Nostrand Reinhold Company Inc 1982.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Lancet* 2007, **370**:1453-1457.
14. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D: **Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress.** *Circulation* 2002, **106**:2067-2072.
15. Norhammar AM, Ryden L, Malmberg K: **Admission plasma glucose. Independent risk factor for long-term prognosis after myocardial infarction even in nondiabetic patients.** *Diabetes Care* 1999, **22**:1827-1831.
16. Gasior M, Pres D, Stasik-Pres G, Lech P, Gierlotka M, Hawranek M, Wilczek K, Szygula-Jurkiewicz B, Lekston A, Kalarus Z, Strojek K, Gumprecht J, Polonski L: **Effect of blood glucose levels on prognosis in acute myocardial infarction in patients with and without diabetes, undergoing percutaneous coronary intervention.** *Cardiol J* 2008, **15**:422-430.
17. Capes SE, Hunt D, Malmberg K, Gerstein HC: **Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview.** *Lancet* 2000, **355**:773-778.
18. Solheim S, Grogaard HK, Hoffmann P, Arnesen H, Seljeflot I: **Inflammatory responses after percutaneous coronary intervention in patients with acute myocardial infarction or stable angina pectoris.** *Scand J Clin Lab Invest* 2008, **68**:555-562.
19. Karpinski L, Plaksej R, Derzhko R, Orda A, Witkowska M: **Serum levels of interleukin-6, interleukin-10 and C-reactive protein in patients with myocardial infarction treated with primary angioplasty during a 6-month follow-up.** *Pol Arch Med Wewn* 2009, **119**:115-121.
20. strom-Olsson K, Hedstrom E, Hulten LM, Wiklund O, Arheden H, Ohlin AK, Gottsater A, Ohlin H: **Dissociation of the Inflammatory Reaction following PCI for Acute Myocardial Infarction.** *J Invasive Cardiol* 2007, **19**:452-456.
21. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: **C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.** *JAMA* 2001, **286**:327-334.
22. Matsumori A, Furukawa Y, Hashimoto T, Yoshida A, Ono K, Shioi T, Okada M, Iwasaki A, Nishio R, Matsushima K, Sasayama S: **Plasma levels of the monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 are elevated in patients with acute myocardial infarction.** *J Mol Cell Cardiol* 1997, **29**:419-423.
23. Mine S, Okada Y, Tanikawa T, Kawahara C, Tabata T, Tanaka Y: **Increased expression levels of monocyte CCR2 and monocyte chemoattractant protein-1 in patients with diabetes mellitus.** *Biochem Biophys Res Commun* 2006, **344**:780-785.
24. Dragomir E, Simionescu M: **Monocyte chemoattractant protein-1–a major contributor to the inflammatory process associated with diabetes.** *Arch Physiol Biochem* 2006, **112**:239-244.
25. Park KS, Ahn KJ, Kim BJ, Kim HJ, Yoo SM, Kim JY, Lee KH, Baik HW, Lee SK: **Circulating concentrations of monocyte chemoattractant protein-1 are associated with menopause status in Korean women.** *Clin Chim Acta* 2009, **403**:92-96.
26. Braunersreuther V, Mach F, Steffens S: **The specific role of chemokines in atherosclerosis.** *Thromb Haemost* 2007, **97**:714-721.
27. Straczkowski M, Kowalska I, Nikolajuk A, Dzienis-Straczkowska S, Szelachowska M, Kinalska I: **Plasma interleukin 8 concentrations in obese subjects with impaired glucose tolerance.** *Cardiovasc Diabetol* 2003, **2**:5.
28. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, Illig T, Martin S, Herder C: **Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984-2002.** *Diabetes* 2005, **54**:2932-2938.
29. Derosa G, Cicero AF, Scalise F, Avanzini MA, Tinelli C, Peros E, Fogari E, D'Angelo A: **Metalloproteinases in diabetics and nondiabetics during acute coronary syndromes and after 3 months.** *Endothelium* 2007, **14**:175-183.
30. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: **Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients.** *Arterioscler Thromb Vasc Biol* 2000, **20**:1595-1599.

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