Elevated levels of PAI-1 activity and t-PA antigen are associated with newly diagnosed abnormal glucose regulation in patients with ST-elevation myocardial infarction

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Summary. Background: Both Type 2 diabetes and cardiovascular disease have been associated with enhanced coagulation and suppressed fibrinolysis. Objectives: To investigate a possible relationship between selected hemostatic variables and abnormal glucose regulation (AGR) in patients with acute ST-elevation myocardial infarction (STEMI) without known diabetes and to study changes in selected hemostatic variables from baseline to follow-up in STEMI patients with or without AGR. Methods: Plasminogen activator inhibitor-1 (PAI-1) activity, tissue plasminogen activator (t-PA) antigen, prothrombin fragment 1 + 2 (F1+2) and von Willebrand factor (vWF) were measured in fasting blood samples from 199 STEMI patients 16.5 h (median time) after admission and 3 months later. All patients were classified into normal glucose regulation (NGR) or AGR based on an oral glucose tolerance test at follow-up, according to the WHO criteria. Results: High PAI-1 activity (≥75th percentile) measured in-hospital was associated with AGR (n = 49) with an adjusted odds ratio of 2.2 (95% confidence interval, 1.1, 4.4). In addition, high levels of t-PA antigen (≥75th percentile) were associated with AGR (adjusted odds ratio, 3.5; 95% confidence interval, 1.5, 8.2), but only in men. Changes in the levels of F1+2 were significantly more pronounced in patients with AGR compared with NGR. The data suggest an enhanced prothrombotic state after an acute STEMI in patients with AGR without known diabetes.

Keywords: abnormal glucose regulation, fibrinolytic disorders, ST-elevation myocardial infarction, fibrinolysis.

Introduction

There is a close relationship between Type 2 diabetes and cardiovascular disease (CVD) [1]. Several prospective studies have reported a high incidence of impaired glucose tolerance and Type 2 diabetes in patients with acute myocardial infarction (MI) without previously known diabetes [2–5]. The risk of MI is 2-fold higher in diabetic compared with non-diabetic patients [6], and about 70–80% of individuals with Type 2 diabetes die of atherothrombosis and its complications [7]. Clustering of cardiovascular risk factors, including underlying insulin resistance, low-grade inflammation and endothelial dysfunction, has been suggested to explain the enhanced incidence of CVD in patients with Type 2 diabetes [8,9].

Furthermore, growing evidence suggests that both Type 2 diabetes and CVD involve enhanced coagulation, suppressed fibrinolysis and increased platelet activity [10,11].

Plasminogen activator inhibitor-1 (PAI-1), a marker of suppressed fibrinolysis, is elevated in patients with coronary artery disease and Type 2 diabetes [12,13] and has been shown to be an independent risk factor for the development of Type 2 diabetes in healthy subjects [14]. Prothrombin levels have been shown to be higher in patients with diabetes compared with healthy controls [15] and increased levels of von Willebrand factor (VWF) are suggested to indicate vascular damage [16]. The extent of endothelial damage post-MI is shown to be more pronounced in patients with impaired glucose regulation compared with patients with normal glucose regulation [17]. Based on these considerations we hypothesized that STEMI...
patients having abnormal glucose regulation would present with a more pronounced prothrombotic profile. The aims of the present study were, in STEMI patients without previously known diabetes: (i) to investigate a possible association between circulating levels of PAI-1 activity, tissue plasminogen activator (t-PA) antigen, VWF and prothrombin fragment 1 + 2 (F1+2) measured in-hospital and the presence of abnormal glucose regulation classified at 3-month follow-up; and (ii) to compare changes in these hemostatic variables from baseline to 3-month follow-up in patients with or without abnormal glucose regulation.

Methods

Study population

A total of 199 patients with a primary percutaneous coronary intervention (PCI) treated STEMI, originally included in a prospective observational cohort study on the incidence of abnormal glucose regulation classified by an oral glucose tolerance test (OGTT), were investigated [5]. Patients with acute STEMI, without previously known diabetes, admitted to the coronary care unit, Oslo University Hospital, Ullevål, Oslo, Norway, were prospectively enrolled from November 2005 to May 2007. The study population has been described in detail elsewhere [5]. In brief, patients with a primary PCI treated STEMI were enrolled if they were stable, without chest pain or nausea, age < 85 years and had serum creatinine < 200 μmol L⁻¹. Patients with a diagnosis of diabetes or persistent hyperglycemia were excluded. Patients with persistent hyperglycemia were defined as patients with both admission plasma glucose > 11 mmol L⁻¹ and a fasting capillary glucose level > 8 mmol L⁻¹ the following morning. STEMI was defined according to the universal definition of MI as typical rise and fall of the cardiac specific 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 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 [18].

The median time from onset of chest pain to balloon (PCI) was 3 h and 45 min. The regional ethics committee approved the study and all patients provided written and oral informed consent. The study is registered at http://www.clinicaltrials.gov, NCT00926133.

Glucometabolic classification by OGTT

A standardized OGTT (75 g glucose in 200 mL water with plasma glucose measurements at 0 and 120 min) was performed at 3-month follow-up [19]. 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 Organization criteria [20] (glucose levels given in mmol L⁻¹):

- 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; and
- 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.

Laboratory methods

Admission plasma glucose was analysed from blood samples taken in the catheterization laboratory immediately after primary PCI. Further blood samples were drawn in the morning when patients were stable (median time 16.5 h after the PCI) and repeated after 3 months. At both occasions the blood samples were drawn after an overnight fast between 08.00 and 10.00 in order to avoid differences due to circadian variations in the hemostatic variables [21]. For determination of glucose and HbA1c conventional routine methods were used. 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 μg L⁻¹ with a recommended diagnostic threshold of 0.03 μg L⁻¹. The inter-assay coefficient of variation was 7%. High sensitivity C-reactive protein (CRP) was determined by enzyme-linked immunosorbent assays (DRG Instruments, Marburg/Lahn, Germany) (detection limit 0.1 μg L⁻¹). The inter-assay coefficient of variation was < 5%. Citrated plasma was used for measurements of VWF, F1+2, t-PA antigen and PAI-1 activity. Blood samples were 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 analyzed. VWF, t-PA antigen and F1+2 were determined by enzyme-linked immunosorbent assays (ELISA) (Asserachrom Stago Diagnostica, Asnieres, France, TintElize tPA, Biopool AB, Trinity Biotech plo, Bray, Ireland [measuring both free t-PA and that in complex with PAI-1] and Enzygnost F1+2, Siemens, Marburg, Germany, respectively). PAI-1 activity was measured by Spectrolyse PL (Biopool AB). In our laboratory, the inter-assay coefficients of variation were as follows: VWF 8.0%, F1+2 4.9%, t-PA antigen 3.5%, and PAI-1 activity 4.4%.

Left ventricular ejection fraction and infarct size expressed as percentage of left ventricular mass were assessed at rest after 3 months by single photon emission computed tomography imaging with technetium 99m-tetrofosmin [22].

Statistics

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

The Mantel-Haenszel method was used to highlight potential effect modification by the Breslow and Day test of heterogeneity and to quantify potential confounders [23]. Continuous variables were categorized into quartiles and chi-squared for trend across the quartiles of a hemostatic variable identified the cut-off point used. A logistic regression model, including a backward elimination procedure, was performed to adjust for potential confounders. Potential effect modifiers or confounders that were associated with the measured variables or abnormal glucose regulation with a \( P \)-value < 0.2 were included in the model (gender, age, current smoking, treated hypertension, TnT peak value, triglycerides, CRP and body mass index [BMI]). Gender was an effect modifier for the association between elevated levels of t-PA antigen and abnormal glucose regulation. The latter association was therefore analyzed for women and men separately.

For changes in the variables over time according to the glucometabolic groups, adjustments for gender, age and infarct size were performed in a covariance analysis by use of logarithmically transformed data.

A value of \( P < 0.05 \) was considered statistically significant. The STROBE guidelines were followed [24]. All analyses were performed using EPI-INF software, 2005, version 3.3.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

**Results**

**Study population**

Clinical characteristics of the study population according to the glucometabolic status at 3 months are shown in Table 1. Notably, patients with abnormal glucose regulation were older. Patients treated with warfarin (\( n = 13 \)) were excluded from the analysis of F1+2. The prevalence of abnormal glucose regulation classified by an OGTT at 3 months was 25% (\( n = 49 \)). The proportion of patients classified with Type 2 diabetes at 3 months was 5% (\( n = 10 \)).

**Association between the hemostatic variables measured and abnormal glucose regulation**

As shown in Table 2, patients with abnormal glucose regulation at 3-month follow-up, had significantly higher levels of

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**Table 1** Clinical characteristics of patients with acute STEMI according to glucometabolic classifications made by an OGTT at 3-month follow-up

|                      | NGR \((n = 150)\) | AGR \((n = 49)\) | \(P\) |
|----------------------|------------------|-----------------|------|
| Age (years)          | 57 (51, 65)      | 63 (53, 72)     | 0.03 |
| Male                 | 128 (85.3)       | 36 (73.5)       | 0.06 |
| Previous disorder    |                  |                 |      |
| Treated hypertension | 38 (25.3)        | 17 (34.7)       | 0.20 |
| Treated dyslipemia   | 15 (10)          | 4 (8.2)         | 0.70 |
| Previous AMI         | 10 (6.7)         | 4 (8.2)         | 0.72 |
| Previous angina pectoris | 6 (4.0)     | 1 (2.0)         | 0.52 |
| Baseline             |                  |                 |      |
| Current smoker       | 67 (44.7)        | 23 (46.9)       | 0.78 |
| BMI \((\text{kg m}^{-2})\) | 26.1 (24.3, 28.7) | 26.0 (24.6, 28.1) | 0.99 |
| Cholesterol \((\text{mmol L}^{-1})\) | 5.1 (4.4, 5.7) | 5.1 (4.4, 5.7) | 0.77 |
| Triglycerides \((\text{mmolL}^{-1})\) | 1.27 (0.89, 1.78) | 1.24 (0.96, 1.80) | 0.72 |
| HDL-cholesterol \((\text{mmol L}^{-1})\) | 1.19 (0.97, 1.43) | 1.11 (1.00, 1.35) | 0.60 |
| TnT peak value \((\mu \text{g L}^{-1})\) | 4.87 (2.45, 8.31) | 5.09 (2.38, 10.25) | 0.44 |
| CRP                  | 11.29 (5.95, 30.00) | 19.49 (8.40, 41.98) | 0.04 |
| Stents               | 142 (94.7)       | 48 (98)         | 0.34 |
| One-vessel disease   | 92 (61.3)        | 29 (59.2)       | 0.79 |
| Left anterior descending artery disease | 57 (38) | 21 (43) | 0.55 |
| IIb/IIIa inhibitors  | 54 (36)          | 19 (39)         | 0.73 |
| Measured at 3 months |                  |                 |      |
| LVEF \%(\ast)       | 63 (56, 69)      | 63 (51, 69)     | 0.44 |
| Infarct size \%(\ast)\(1\) | 13 (0.0, 27)   | 23 (3.0, 43)    | 0.02 |
| Medication at 3 months |               |                 |      |
| Aspirin              | 149 (99)         | 48 (98)         | 0.40 |
| Clopidogrel          | 142 (95)         | 42 (86)         | 0.04 |
| \(\beta\)-blocker    | 142 (95)         | 45 (92)         | 0.47 |
| Lipid lowering agents | 146 (97)        | 46 (94)         | 0.26 |
| ACEIs               | 54 (36)          | 18 (37)         | 0.93 |
| ARBs                | 22 (15)          | 5 (10)          | 0.43 |
| Warfarin            | 8 (5.3)          | 4 (8.2)         | 0.47 |

Median values (25th, 75th percentiles) and proportions are given. ACEIs, angiotensin-converting enzyme inhibitors; AGR, abnormal glucose regulation; ARBs, angiotensin II-receptor blockers; BMI, body mass index; NGR, normal glucose regulation; CRP, high sensitivity C-reactive protein; TnT peak value, cardiac specific biomarker Troponin T peak value. \( \ast \)Measured at 3 months by SPECT analysis. \( \ast \)LVEF, left ventricular ejection fraction. \( \ast \)Infarct size in % of left ventricular mass.
PAI-1 activity and t-PA antigen measured in-hospital. Measured at 3 months, t-PA antigen was still higher in patients with abnormal glucose regulation \((P = 0.001)\). The higher levels of F\(_{1+2}\) measured in-hospital were of borderline significance \((P = 0.06)\). High levels of PAI-1 activity \((\geq 24.2 [75\text{th percentile}] \text{ U mL}^{-1})\), t-PA antigen \((\geq 16.2 [75\text{th percentile}] \text{ ng mL}^{-1})\) and \(F_{1+2} \geq 238 [50\text{th percentile}] \text{ pmol L}^{-1}\) measured in-hospital were associated with a 2–3-fold increase in the odds of having abnormal glucose regulation at 3-month follow-up (crude odds ratio, OR, 2.4 [95% confidence interval, CI, 1.2, 4.9], 2.8 [95% CI 1.4, 5.5] and 2.1 [95% CI 1.1, 4.1], respectively) (Table 3). Adjustment for identified confounders (CRP, TnT and gender) had only a minor attenuating effect on the association between PAI-1 activity and abnormal glucose regulation. The association between t-PA antigen and abnormal glucose regulation was only present in men, as gender was identified as an effect modifier. This association was not weakened by adjustment for identified confounders (age, TnT and CRP) (Table 3). As shown in Table 1, patients with abnormal glucose regulation classified at follow-up had significantly larger infarct size measured by SPECT. However, when infarct size was included in the multivariate analysis (replacing TnT) the associations between PAI-1 activity, t-PA antigen and abnormal glucose regulation were not attenuated (OR 2.1 [95% CI 1.0, 4.4] and OR 3.7 [95% CI 1.6, 8.4], respectively). The association between high levels of \(F_{1+2}\) and abnormal glucose regulation disappeared after adjustments for potential confounders (Table 3).

### Discussion

Our main finding was that elevated levels of PAI-1 activity, t-PA antigen and \(F_{1+2}\) measured after the acute STEMI were associated with abnormal glucose regulation classified at 3-
month follow-up in patients without known diabetes. Additionally, the adjusted changes from baseline to 3-month follow-up in the levels of F$_{1+2}$ were significantly more pronounced in patients with abnormal glucose regulation classified at follow-up.

Our results indicate that patients with acute STEMI and abnormal glucose regulation have a more pronounced prothrombotic condition during the acute MI compared with patients with normal glucose regulation. The mechanisms that link this enhanced hypercoagulable state to glucometabolic abnormalities are, however, unknown although acute hyperglycemia has been shown to induce oxidative stress associated with both a proinflammatory and a prothrombotic condition, each influencing the other [25,26]. Previously, we have shown that high levels of the inflammatory markers MCP-1 and CRP measured in-hospital were associated with abnormal glucose regulation at follow-up in the same cohort, indicating an association between inflammation and abnormal glucose regulation in STEMI patients [27]. In addition to more severe inflammation at admission, patients with abnormal glucose regulation had significantly larger infarct size measured at follow-up. As PAI-1 is an acute-phase reactant protein [28] the observed elevated levels of PAI-1 activity and t-PA antigen in patients with abnormal glucose regulation could be explained by the elevated levels of CRP and larger infarct size in these patients. However, the association between elevated levels of PAI-1 activity and t-PA antigen and abnormal glucose regulation remained significant when adjustments for CRP and infarct size were performed.

Plasminogen activator inhibitor-1 is an important physiological inhibitor of plasminogen activation [28]. PAI-1 binds to the active site of t-PA, forming a stable complex that neutralizes t-PA, reducing the risk of bleeding and promoting thrombosis [29]. Type 2 diabetes and coronary heart disease are known prothrombotic conditions due to suppressed fibrinolysis, enhanced coagulation and platelet activity [10,30]. Circulating PAI-1 levels are known to correlate with levels of insulin, triglycerides, body mass index and blood pressure in healthy individuals with insulin resistance, in patients with Type 2 diabetes and in patients with coronary heart disease, indicating that PAI-1 is an important part of the clustering of risk factors leading to CVD [30]. The main sources of PAI-1 are the vascular endothelium, adipose tissue and the liver [28]. Detailed mechanisms that link increased PAI-1 levels to the development of coronary heart disease and Type 2 diabetes are, however, unknown. PAI-1 is classified as an acute phase protein and inflammatory cytokines have been shown to induce PAI-1 production in endothelial cells [28] and in the liver [31]. The same cytokines have been shown to promote vascular inflammation and atherosclerosis [28]. In addition, there is evidence for PAI-1 production in ectopic fat tissue and circulating PAI-1 levels have been shown to be increased in obesity and to decrease during weight loss [32,33]. Moreover, hyperglycemia-induced oxidative stress has been suggested to increase PAI-1 production in liver cells in vitro [25], whereas acute hyperinsulinemia irrespective of glucose levels seems to increase circulating PAI-1 levels in healthy volunteers [34]. In our study high levels of PAI-1 activity measured in-hospital were associated with abnormal glucose regulation classified at 3-month follow-up, indicating that PAI-1 is an important player in the prothrombotic profile associated with abnormal glucose regulation.
Tissue plasminogen activator is synthesized and secreted by endothelial cells and the majority of t-PA circulates in plasma in complex with PAI-1 and is measured as t-PA antigen [35]. Elevated levels of t-PA antigen in patients with glucose intolerance and insulin resistance are related to underlying endothelial damage and have been shown to predict future cardiac events. This may basically reflect elevated levels of PAI-1 that occur in these conditions [30]. In our study high levels of t-PA antigen measured in-hospital were associated with abnormal glucose regulation only in men. This is in line with previous reports showing levels of t-PA antigen to be higher in diabetic men compared with women while levels of PAI-1 activity were higher in the diabetic women [36].

\( F_{1+2} \) is a sensitive marker of thrombin generation, reflecting procoagulant activity [37]. In our study, there was a crude association between elevated levels of \( F_{1+2} \) measured in-hospital and abnormal glucose regulation classified at 3-month follow-up. The association, however, disappeared after adjustment for age, confirming previous reports of a correlation between plasma levels of \( F_{1+2} \) and age [37]. We also observed that the adjusted change in the levels of \( F_{1+2} \) from baseline to follow-up was of a greater magnitude in patients with abnormal glucose regulation, probably indicating an even more pronounced thrombin generation in patients with acute MI and abnormal glucose regulation. In a previous study glucose was infused to maintain plasma glucose at approximately 11 mmol L\(^{-1}\) for 24 h in diabetic and non-diabetic controls. Elevated levels of serum insulin and plasma glucose were followed by increased levels of \( F_{1+2} \) in both groups, indicating a positive association between the levels of insulin and glucose and thrombin generation [38].

von Willebrand factor has been shown to be an important marker of endothelial damage [30] and previous investigators have suggested that endothelial damage in patients with acute MI and impaired glucose tolerance or incident diabetes seems to be of a greater magnitude than in patients with normal glucose tolerance [17]. In the present study, however, we did not find any association between VWF and abnormal glucose regulation.

**Limitations**

Unstable patients and patients with persistent hyperglycemia in-hospital were excluded from the study, possibly making a selection bias towards more glucosmetabolically normal patients with a low proportion of incident Type 2 diabetes.

Few women were included in the study and the results regarding t-PA antigen and abnormal glucose regulation in particular, are difficult to interpret with regard to gender difference.

**Conclusion**

Our data show that elevated levels of PAI-1 activity and t-PA antigen measured in the acute phase of STEMI were significantly associated with abnormal glucose regulation classified at 3-month follow-up. However, the association between high levels of t-PA antigen and abnormal glucose regulation was present only in men. Additionally, the adjusted changes in the levels of \( F_{1+2} \) were significantly more pronounced in patients with abnormal glucose regulation. The data suggest an enhanced prothrombotic state during an acute STEMI in patients with abnormal glucose regulation without previously known diabetes.

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**Disclosure of Conflict of Interests**

The authors state that they have no conflict of interest.

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