ORIGINAL ARTICLE

The relationship between hemoglobin A1c levels and thrombus load in patients with type 2 diabetes mellitus and non-ST-segment elevation myocardial infarction

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Background: We aimed to investigate the relationship between hemoglobin A1c (HbA1c) and coronary thrombus load in type-2 diabetes mellitus (T2DM) patients with non-ST segment elevation myocardial infarction (NSTEMI). **Materials and Methods:** Ninety diabetic patients with NSTEMI were recruited for the study. They were separated into two groups according to HbA1c levels. Forty-seven patients having HbA1c ≤6.5% formed Group-I (35 male, mean age 58 ± 10.5 years) and the remaining 43 patients with HbA1c >6.5% formed Group-II (23 male, mean age 58 ± 11.1 years). Both the groups were evaluated in terms of thrombolysis in myocardial infarction (TIMI) thrombus score and Syntax score. **Results:** Baseline patient characteristics were comparable in both the groups. TIMI thrombus score and Syntax score were higher in Group II than in Group I (3.2 ± 1.4 vs. 4.7 ± 0.5 and 20.2 ± 3.4 vs. 26.3 ± 3.0 respectively, $P < 0.05$). No significant difference was found in other parameters. In stepwise linear regression analysis, prepercutaneous coronary intervention (PCI) and post-PCI TIMI frame number and HbA1c were significantly related to the coronary thrombus scale. However, no significant relationship has been found between thrombus formation and hypertension, previous PCI history, pre-PCI heart rate, pre-PCI cholesterol status, and high-sensitive troponin T. **Conclusion:** In NSTEMI with T2DM, increased HbA1c (HbA1c >6.5%) is related with coronary thrombus in the target vessel. In those patient population, strict anticoagulation should be considered to prevent potential adverse events.

Key words: Coronary artery disease, coronary thrombus, diabetes mellitus, hemoglobin A1c, non-ST elevation myocardial infarction

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INTRODUCTION

Type-2 diabetes mellitus (T2DM) is an independent predictor of clinical outcome and cardiovascular mortality in patients with coronary artery disease (CAD). DM is associated with a 19% incidence of acute coronary syndrome (ACS) with nonobstructive CAD presentations.[1] Non-ST segment elevation myocardial infarction (NSTEMI) is a clinical presentation of nonobstructive CAD and is associated with a high

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ratio of mortality and morbidity.[2-4] Among patients with T2DM, nonobstructive and obstructive stable CADs are related to increased mortality ratio and major adverse cardiovascular events at long term, and this hazard was considerably higher than in nondiabetics.[5] In the treatment of NSTEMI, the primary aim should be the revascularization of infarct-related coronary artery (IRA). The most important step is to provide reperfusion by percutaneous coronary intervention (PCI) in the early period.[6]

There are several factors associated with success with PCI in patients with ACS. Syntax score, calculated by taking into account properties such as lesion number, location, and functional importance, provides important information in the evaluation of the CAD extent.[7] Thrombus load in the IRA is an important anatomical factor for successful PCI. It is usually quantified according to the thrombolysis in myocardial infarction (TIMI) thrombus grading system on a 7-point scale.[8] There is a direct relationship between the thrombus load in infarct-related coronary and the outcomes, and it is also incorporated in the Syntax Scoring System.[9-11]

T2DM with unregulated plasma glucose levels may cause worsening of the prognosis in CAD via different mechanisms such as endothelial dysfunction, impaired blood fibrinolysis, and increased platelet activity.[12,13] T2DM is one of the most important clinical parameters that contribute to the thrombus load in diseased coronaries.[14] Hemoglobin A1c (HbA1c) is considered to be a reliable indicator of blood glucose levels within the past 8–10 weeks period, which may be influenced by acute stress.[15] Increased HbA1c level is directly related with increased mortality in patients with T2DM.[16]

In the present study, the aim was to show the relationship between HbA1c and coronary thrombus burden expressed as TIMI thrombus grade, in NSTEMI patients.

MATERIALS AND METHODS

Ninety NSTEMI patients with T2DM who underwent early PCI (within 24 h after beginning of the anginal symptoms) in our center were recruited into the study. The study was approved by the Institutional Ethics Committee, and informed consent was obtained from all patients. Patients with severe anemia (Hb <7 g/dL), recent history of acute blood loss or blood transfusion, hemoglobinopathies, severe infection, hypercoagulability, pregnancy, or those in postpartum period; patients with a history of marijuana, cocaine or synthetic drug use, ST-elevated MI; patients with a metallic valve prosthesis; and patients who received glycoprotein IIb/IIIa inhibitor during their treatment were excluded from the study. Patients were given medical treatment according to the ESC NSTEMI guidelines.[17]

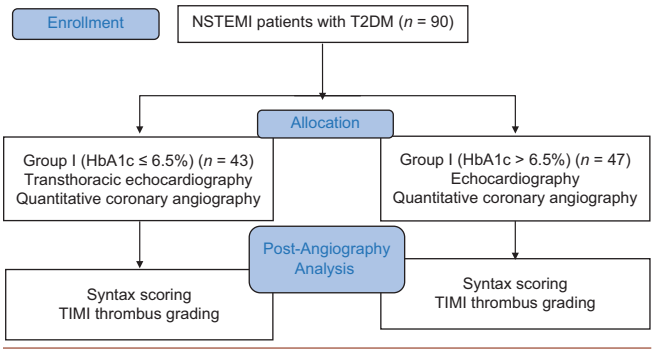
Patients were assessed in terms of cardiovascular risk factors. After referral to the cardiology intensive care unit, blood samples were obtained from all patients for complete blood count and biochemical parameters. Patients were divided into two groups according to the HbA1c levels: Group I included the patients with optimal glycemic control with HbA1c ≤6.5% and Group II included subjects with suboptimal glycemic control, with HbA1c >6.5% [Table 1].

Diagnosis of NSTEMI was made after the evaluation of the clinical symptoms, electrocardiogram (ECG) findings, and cardiac markers. Patient history, 12-lead ECG, echocardiography and coronary angiography (CAG) findings, accompanying systemic diseases, and drugs during the treatment were recorded. The diagnosis of hyperlipidemia was made whenever low-density lipoprotein >100 mg/dl or presence of any antihyperlipidemic drug in patients' history. The blood pressures of the cases were measured and the diagnosis of hypertension was made in case of the systolic pressure >140 mmHg or diastolic pressure >90 mmHg or any antihypertensive drug history.

Echocardiography images were taken in the left lateral decubitus position. The measurements were taken 24 h after patients' admission to the hospital with 3 and 5 Mhz transducers and GE Vivid 7 Pro, according to the guidelines of the American Society of Echocardiography.[18] Left ventricle end-diastolic diameter, left ventricle end-systolic diameter, and left ventricle ejection fraction were obtained with the Modified Simpson method from apical four-chamber views.

Quantitative coronary angiographic measurements were taken with ACOM PC Lite version 2.0 (Siemens, München, Germany) program. The number of the diseased and treated vessels was recorded on the template. TIMI scores pre- and postintervention were measured. Preintervention thrombus load in IRA was scored and recorded according to the TIMI thrombus grade.[8,19] All measurements were performed by two independent physicians (DT and ET) separately blinded to the patients' clinical status.

Table 1: Study flow chart



Syntax score was retrospectively calculated by two independent investigators (FVA and TP) using an online software which calculates a point for each lesion, by considering morphological properties of each lesion in CAG (Syntax score calculator version 2.11, www.syntaxscore.com). To decrease interobserver variation, the scores measured by individual angiographers were randomly monitored and reviewed by a senior interventional cardiologist. (MY) In case of disagreement, consensus was made within the group.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (ver. 16.0, SPSS Inc., Chicago, Illinois, USA). Continuous variables were defined as mean ± standard deviation, whereas categorical variables were defined as percentage (%). Among the study groups, variables that show normal distribution were compared with Student's *t*-test, while variables without normal distribution were compared by Mann–Withney *U*-test. Pearson's Chi-square test was used to compare the distribution of categorical variables between the study groups. To determine the parameters that have an impact on the thrombus formation and progression, ordered logistic regression protocol in SPSS was used.

RESULTS

The patient characteristics and labarotory parameters are summarized in Table 2. There was no statistically significant difference in terms of age and gender between Group I (HbA1c ≤6.5%, n = 47 patients) and Group II (HbA1c >6.5%, n = 43 patients) (57 ± 10 vs. 58 ± 10 years, P = 0.59, 74% vs. 53%, P = 0.38). The door-to-hospitalization and time-to-catheterization times were comparable between the study groups (21 ± 5 vs. 22 ± 4 h, P = 0.87 and 27 ± 4 vs. 28 ± 5 h, P = 0.91). Smoking and dyslipidemia rates were similar in the two groups (44% vs. 48%, P = 0.33 and 55% vs. 68%, P = 0.12, respectively). Body mass index (BMI) was not different between Group I and Group II (26 ± 3 kg/m^2 vs. 27 ± 4 kg/m^2, P = 0.18). There was no difference between groups in terms of blood biochemical parameters. Troponin I levels did not differ significantly between the study groups (P = 0.71).

The parameters in transthoracic echocardiography are summarized in Table 3 and CAGs are summarized in Table 4. Left ventricular dimensions and transmitral Doppler velocities were comparable between the two groups. Mean TIMI thrombus grades were significantly higher in the Group II than in Group I (4.7 ± 0.5 vs. 3.2 ± 1.4, P = 0.006) [Figure 1]. The Syntax scores in Group II were significantly higher than the Group I (26.3 ± 3.0 vs. 20.2 ± 3.4, P < 0.001). Frequency distribution of the IRA and number of diseased vessels did not differ between groups significantly [Table 3]. In ordered logistic regression analysis, HbA1c was found to be a significant independent predictor of TIMI thrombus grade in a model consisting of DM, smoking, previous PCI, troponin T, total cholesterol, and mean platelet volume. Platelet count was omitted from the model because of significant collinearity (χ^2 = 16.935, P < 0.05 for overall model) [Table 5].

Table 2: Comparison of the clinical and biochemical parameters in study groups

Variables	Group I (HbA1c ≤6.5%) (*n*=47)	Group II (HbA1c>6.5%) (*n*=43)	*P*
Age (years)	57±10	58±10	0.59
Admission time to the hospital (h)	21±5	22±4	0.87
Admission time to the catheterization laboratory (h)	27±4	28±5	0.91
Gender; male/female	35 (74)	23 (53)	0.38
Smoking (*n*,%)	21 (44)	20 (48)	0.33
Dyslipidaemia (*n*,%)	26 (55)	27 (68)	0.12
Total cholesterol (mg/dL)	186±44	199±36	0.16
HDL (mg/dL)	36.1±8.1	40.4±14.2	0.42
LDL (mg/dL)	124.6±36.2	134.9±31.9	0.17
Hypertension (*n*)	13 (23)	11 (32)	0.24
Systolic blood pressure (mmHg)	129±24	130±27	0.84
Diastolic blood pressure (mmHg)	81±14	83±17	0.69
BMI (kg/m^2)	26±3	27±4	0.18
Urea, mg/dL	14.7±3	15±4.7	0.27
Creatinine, mg/dL	0.81±0.2	0.81±0.3	0.95
Hemoglobin, g/dL	13.8±1.8	13.4±1.3	0.37
White blood cell, (10^3/μl)	11.8±3.1	13.0±3.1	0.27
Platelet (×10^9/L)	233.2±55.5	255.1±64.7	0.14
MPV, f/L	8.8±1.01	9.1±0.86	0.32
Troponin I (ng/ml)	75.1±20.8	87±18.1	0.71

LDL=Low-density lipoprotein; HDL=High-density lipoprotein; BMI=Body mass index; MPV=Mean platelet volume; Data are presented as mean±SD. HbA1c=Hemoglobin A1c; SD=Standard deviation

Table 3: Comparison of echocardiographic and angiographic parameters between the study groups

Variables	Group I (HbA1c ≤6.5%) (*n*=47)	Group II (HbA1c>6.5%) (*n*=43)	*P*
LVEDd (mm)	49±3.6	48±3.7	0.27
LVESd (mm)	34±5	32±5	0.26
IVST (mm)	11±1.3	12±1.9	0.38
Mitral E (cm/s)	0.82±0.18	0.64±0.22	0.43
Mitral A (cm/s)	0.72±0.32	0.67±0.27	0.81
LA diameter (mm)	38.4±3.2	39.0±3.0	0.85

LVEDd=Left ventricular end-diastolic diameter; LVESd=Left ventricular end-systolic diameter; IVST=Interventricular septum thickness; Data are presented as means±SD; NS=Nonsignificant (*P*>0.05). SD=Standard deviation; HbA1c=Hemoglobin A1c

Table 4: Comparison of angiographic parameters between the study groups

Variables	Group I (HbA1c ≤6.5%) (*n*=47)	Group II (HbA1c>6.5%) (*n*=43)	*P*
Infarct-related artery			
LAD	18	17	0.139
LCX	10	7	
RCA	28	10	
SVD	24	15	0.346
2-VD	14	14	
MVD	9	14	
TTGS	3.2±1.4	4.7±0.5	0.006
Syntax scores	20.2±3.4	26.3±3.0	<0.001

LAD=Left anterior descending coronary artery; LCX=Left circumflex coronary artery; RCA=Right coronary artery; SVD=Single-vessel disease, 2-VD=Two-vessel disease; MVD=Multi-vessel disease; TIMI=Thrombolysis in myocardial infarction; TTGS=TIMI thrombus grading score; HbA1c=Hemoglobin A1c

Table 5: Predictors of thrombolysis in myocardial infarction thrombus grading score

Variables	Test estimate	*P*
Overall model	16.935	<0.05
Study group (Group 2 vs. Group 1)	1.402 (0.456-9.462)	0.003
Smoking	−0.446 (0.092-0.032)	0.788
Previous PCI	−0.002 (0.785-0.322)	0.927
Hs-TnT	−0.004 (0.012-0.028)	0.944
TC	−0.045 (0.005-0.658)	0.394
MPV	1.402 (0.223-0.041)	<0.001

Study group (Group 1: HbA1c≤6.5%, Group 2: HbA1c>6.5%).
hs-TnT=High-sensitivity troponin-T; TC=Total cholesterol, MPV=Mean platelet volume; HbA1c=Hemoglobin A1c; PCI=Percutaneous coronary intervention

DISCUSSION

The main finding of the present study was that HbA1c, TIMI frame count pre-PCI, and TIMI frame count post-PCI were significant predictors of the coronary thrombus load and higher Syntax score in NSTEMI patients with T2DM. TIMI thrombus grade in the IRA and the Syntax score of the patient were significantly higher in diabetic NSTEMI patients with HbA1c >6.5% than those with HbA1c ≤6.5%.

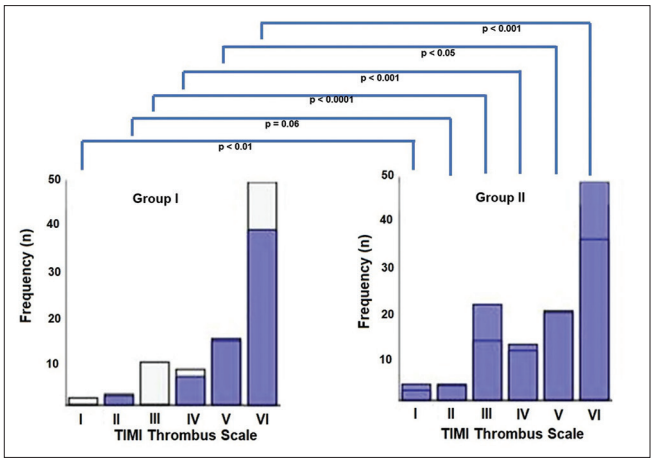


Figure 1: The distribution of the subgroups of the thrombolysis in myocardial infarction thrombus scale in the study groups. When compared between the study groups, in each thrombolysis in myocardial infarction thrombus scale subgroup, thrombus formation was more frequently detected in the group of hemoglobin A1c >6.5% (*P* < 0.001)

The main pathophysiological underlying mechanism of NSTEMI is plaque rupture or erosion with resultant thrombus formation in the vessel lumen. The intracoronary thrombus causes occlusion of epicardial coronary arteries and distal embolization that reduce epicardial blood flow and myocardial perfusion. In NSTEMI patients undergoing PCI, angiographically visible thrombus, distal embolization, and no-reflow phenomenon are related with limited success of coronary intervention, prolonged hospitalization, urgent revascularization post-PCI, and higher mortality.[14] For these reasons, prediction and detection of thrombus formation should have a substantial impact on the treatment, intervention success, and prognosis during the clinical follow-up. In NSTEMI, as PCI is planned, the next step should be the detection of the thrombus load in the diseased coronary segments. TIMI thrombus grading is one of the most widely used methods for this purpose.[20]

T2DM considerably contributes to the formation of the atherosclerotic lesion and thrombus in NSTEMI patients.[21] Mean platelet volume, glycoprotein IIb/IIIa receptor activation, and thromboxane-A2 formation were all found significantly higher in patients with T2DM. While fibrinogen levels and von Willebrand factor vWF activity are increased, antithrombin III and antithrombotic factors such as endogenic heparin are reported to be decreased. Long-term hyperglycemia, hyperinsulinemia, and increased fatty acids induce adverse metabolic alterations within the endothelium which may precede the development of atherosclerosis.[12]

Platelets in diabetic patients demonstrate increased adhesion activity and platelet aggregation. This response was either spontaneous or induced by stimulating agents.[22] Platelet functions measured by aggregometry in

uncontrolled T2DM patients were obviously increased and by antidiabetic therapy, the risk of arterial thrombosis was significantly reduced.[23]

Long-term hyperglycemia induces the production of free oxygen radicals, thus increased oxidative stress, resulting in decreased endothelial nitric oxide production and increased endothelin and angiotensin-2 production and activation of several thrombogenic factors. Furthermore, increased glucose impairs the endothelial layer through inducing dysfunctions in the membranous proteins within the endothelial cells.[24] In atheromatous plaques from diabetic patients, the plaque content was rich in lipids, macrophage infiltration was more intense, and thrombus formation was more severe resulting in an increased risk of plaque rupture and thrombosis. Since all these pathophysiological conditions are due to the oxidant effect of glucose, close monitoring of hyperglycemia in T2DM seems indispensable for the reduction in cardiovascular mortality and morbidity.[15]

HbA1c reflects long-term glycemic control and is less affected by acute stress. Thus, HbA1c levels may provide the relationship between chronic glucose control and disease progression, more accurately. A 10% reduction in HbA1c levels causes a 45% reduction in the risk of complications. Gustavsson and Agardh reported that increased atherosclerotic and inflammatory events are associated with increased HbA1c in diabetic subjects.[25] Different glycemic targets were proposed in T2DM patients with ACS. A recent ACCORD study demonstrated an increased risk of cardiovascular complications with intensive glycemic control with an HbA1c target of 6% versus a less stringent glycemic control with an HbA1c target of 7%–7.9% among young adults, although that difference was not observed among older individuals.[26] Taking into account that lower HbA1c target did not bring further reduction in development of cardiovascular complications as expected, less stringent diabetes control was recommended.

In the present study, the significant relation between high levels of HbA1c and the IRA TIMI thrombus grade may be associated with increased damage to the vascular endothelium of uncontrolled hyperglycemia and increased thrombogenicity.[12,27,28] To our knowledge, the current study is the first in the literature to show that thrombus burden is significantly higher in T2DM with poor glycemic control.

Hyperglycemia plays an important role in the development of many abnormalities including endothelial dysfunction, increased coagulability, fibrinolytic impairment, and platelets hyperreactivity.[29] Glycosylation is a nonenzymatic reaction induced by chronic hyperglycemia and HbA1c is a precursor of advanced glycation end products (AGEs) known as one of glycosylation's products. AGEs induce inflammatory reactions, oxidative stress, and thrombosis, thus associated with vascular damage.[30,31] Many thrombotic conditions have been stated as being coincided with acute hyperglycemia, myocardial infarction, stroke, and venous thromboembolism (VTE). Movahed *et al*.[32] found an odds ratio of 1.27 (95% confidence interval [CI], 1.19–1.35) for the occurrence of pulmonary embolism in diabetic patients. Previously, Tsai *et al*.[33] also found diabetes to be a risk factor for VTE with a hazard ratio (HR) of 1.46 (95% CI, 1.03–2.05), even after adjusting for BMI, a known predictor of VTE.

The study by Ravipati *et al*. found that HbA1c levels in diabetic patients were closely related to the severity of CAD. HbA1c levels increased more than 6.5%, leading to an increase in the number of arteries with stenosis >50% in coronary angiography.[34] In the present study, NSTEMI patients with unregulated T2DM had more severe CAD by distribution and severity as assessed by Syntax score, similar to the previous reports in the literature.

CONCLUSION

TIMI thrombus score and Syntax score of the IRA were found to be significantly higher in Type II DM with HbA1c >6.5% in NSTEMI. The relationship between HbA1c levels and target vessel thrombus load could either be caused as a direct effect of glycated hemoglobin or the thrombogenicity caused by the effect of uncontrolled T2DM on the endothelial layer of the diseased vessel segments. Large-scale prospective trials are needed to unravel the predictive role of the HbA1c levels on thrombotic occlusion of the diseased vessel and the adverse clinical events related with atherosclerotic vessel disease.

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Conflicts of interest
There are no conflicts of interest.

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