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Changes in primary hemostasis in patients with angina and diabetes mellitus

Abdullaev A.Kh [1,*] and Imankulova D.A. [2]

[1] *Tashkent State Medical University, Tashkent, Uzbekistan*
[2] *Republican Specialized Scientific and Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan.*

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Abstract

Objective: To assess primary hemostasis disorders in patients with stable angina pectoris (SAP) and type 2 diabetes mellitus (T2DM).

Materials and Methods: A total of 112 patients with SAP were examined: SAP+T2DM (n=56) and SAP without T2DM (n=56). Platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), hs-CRP, HbA1c, and ADP-induced platelet aggregation were evaluated.

Results: The groups were comparable in age (62.1±8.7 years); 46% were women. In the SAP+T2DM group, HbA1c was 7.8±1.1% vs 5.6±0.4% (p<0.001), and hs-CRP was 3.9 (2.1–6.2) vs 2.3 (1.2–3.8) mg/L (p=0.002). MPV was 10.9±1.0 vs 10.1±0.9 fL (p<0.001), PDW was 13.6±2.1 vs 12.3±1.8% (p=0.001), and ADP-induced aggregation was 63±12 vs 54±11% (p<0.001). MPV ≥10.5 fL was associated with high platelet aggregation (OR 2.6; 95% CI 1.3–5.3).

Conclusion: T2DM in SAP is associated with a proaggregatory platelet phenotype and enhanced primary hemostasis.

Keywords: Stable Angina Pectoris; Type 2 Diabetes Mellitus; Primary Hemostasis; Platelets; Aggregation; MPV.

1. Introduction

Stable angina, as a clinical manifestation of chronic coronary syndromes (CCS), remains one of the leading causes of reduced quality of life and cardiovascular complications, despite substantial progress in anti-ischemic and secondary preventive therapy. Current recommendations of the European Society of Cardiology emphasize that the main goal of managing patients with CCS includes not only symptom control but also the prevention of thrombotic events, making antithrombotic strategy a key component of long-term risk management. At the same time, the balance between ischemic and hemorrhagic risks requires an individualized approach and the search for accessible markers that allow more precise stratification of thrombotic predisposition in an individual patient [1].

Type 2 diabetes mellitus (T2DM) significantly modifies the course of ischemic heart disease, increasing the likelihood of atherothrombosis and creating a marked “residual” risk of events even under standard therapy. This phenomenon is based on a complex set of metabolic and inflammatory disturbances, among which platelet dysfunction occupies a particularly important place. It has been shown that “diabetic” platelets are characterized by hyperreactivity and relative resistance to endogenous inhibitory signals, such as nitric oxide and prostacyclin, which contributes to the formation of a prothrombotic environment and accelerates the progression of vascular complications [2]. At the molecular level, hyperglycemia, insulin resistance, and oxidative stress lead to remodeling of the platelet proteome and signaling cascades, enhancing adhesion and aggregation, as well as platelet interactions with the endothelium and

* Corresponding author: Abdullaev A.Kh.

leukocytes [3]. Recent reviews further emphasize the role of insulin resistance as a systemic driver of platelet hyperactivity and the inflammatory functions of platelets in diabetes [4,5].

Since functional platelet tests are not always available in routine clinical practice, there is growing interest in simple laboratory indicators of primary hemostasis. Mean platelet volume (MPV) and platelet distribution width (PDW), obtained from a standard complete blood count, are considered surrogate markers of platelet activation and heterogeneity of the platelet population. Observational studies demonstrate associations between extreme MPV values and derived indices with adverse cardiovascular outcomes in patients with T2DM, supporting the concept of the clinical significance of the platelet "phenotype" in diabetes [6]. Similarly, PDW is regarded as an independent prognostic marker of mortality and complications in various high-risk populations, indirectly indicating its association with platelet-mediated hemostatic activity and inflammation [7].

However, data on the specific characteristics of primary hemostasis in patients with stable angina against the background of T2DM remain heterogeneous. Comparative studies combining platelet indices such as MPV and PDW, inflammatory and metabolic parameters, and functional assessment of aggregation are therefore especially relevant for practical cardiology. Clarifying these relationships may provide a rationale for more accurate stratification of thrombotic risk and contribute to the personalization of antithrombotic strategy in patients with CCS and T2DM in real-world clinical settings [1,2]. In this regard, the present study is aimed at evaluating the features of primary hemostasis in patients with stable angina against the background of T2DM and identifying clinical and laboratory determinants of increased platelet reactivity.

2. Materials and Methods

A single-center comparative observational study was conducted at the Republican Specialized Scientific and Practical Medical Center of Therapy and Medical Rehabilitation, Tashkent, Uzbekistan. The study consecutively included 112 patients aged 40–80 years with stable angina, functional class I–III, who were divided into two comparable groups: stable angina with type 2 diabetes mellitus (SA+T2DM, n=56) and stable angina without diabetes mellitus (SA without T2DM, n=56).

The exclusion criteria were acute coronary syndrome or revascularization within the previous 3 months, active bleeding, severe hematological disorders, thrombocytopenia ($<150\times10^9$/L) or thrombocytosis ($>450\times10^9$/L), severe hepatic failure, eGFR <30 mL/min/1.73 m^2, acute infections or exacerbation of inflammatory diseases within the previous 4 weeks, use of oral anticoagulants, and recent use of non-steroidal anti-inflammatory drugs, except for low-dose acetylsalicylic acid.

Demographic data, risk factors, and concomitant therapy were recorded for all patients. Blood samples were collected in the morning after overnight fasting. Platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), high-sensitivity C-reactive protein (hs-CRP), glycated hemoglobin (HbA1c), and ADP-induced platelet aggregation, expressed as maximum amplitude (%), were assessed.

Statistical analysis included testing for normality, between-group comparisons using the Student's t-test or Mann–Whitney U test, the χ^2 test for categorical variables, correlation analysis, and logistic regression to identify predictors of high platelet reactivity. Statistical significance was accepted at $p<0.05$.

The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants.

3. Results and Discussion

The study included 112 patients with stable angina, divided into the SA+T2DM group (n=56) and the SA without T2DM group (n=56). The groups were comparable in terms of age (62.1±8.7 years), sex distribution (women: 46% vs 45%; p=0.87), body mass index (29.1±4.2 vs 28.3±4.0 kg/m^2; p=0.28), prevalence of arterial hypertension (82% vs 79%; p=0.66), smoking status (21% vs 18%; p=0.67), and use of baseline cardioprotective therapy: acetylsalicylic acid (88% vs 91%; p=0.59), statins (93% vs 89%; p=0.47), β-blockers (75% vs 71%; p=0.64), and ACE inhibitors/ARBs (84% vs 80%; p=0.58). This reduces the likelihood of a systematic influence of concomitant factors on platelet-related parameters.

As expected, metabolic and inflammatory parameters differed between the groups. In the SA+T2DM group, HbA1c was 7.8±1.1% compared with 5.6±0.4% in the non-diabetic group (p<0.001), while fasting glucose was 8.3±1.9 vs 5.3±0.6 mmol/L, respectively (p<0.001). The hs-CRP level was also higher in patients with diabetes: 3.9 (2.1–6.2) vs 2.3 (1.2–3.8) mg/L (p=0.002), reflecting a more pronounced chronic low-grade inflammatory background.

Analysis of platelet indices showed no significant difference in platelet count (PLT): 236±54 vs 228±49×10^9/L (p=0.41). However, parameters characterizing the morphofunctional activity of platelets were significantly higher in the presence of T2DM: MPV was 10.9±1.0 vs 10.1±0.9 fL (p<0.001), and PDW was 13.6±2.1 vs 12.3±1.8% (p=0.001). These findings indicate a predominance of larger and more heterogeneous platelets by volume, which generally possess increased reactivity and a higher density of granules. This is biologically consistent with the concept of a "proaggregant" platelet phenotype in T2DM (Table 1).

Functional assessment of primary hemostasis confirmed enhanced platelet reactivity: ADP-induced aggregation was higher in the SA+T2DM group than in the group without diabetes (63±12% vs 54±11%; p<0.001). The proportion of patients with "high platelet reactivity," defined as an aggregation threshold of ≥60%, was 57% in the SA+T2DM group compared with 30% in the non-diabetic group (p=0.004). Correlation analysis showed that ADP-induced aggregation was positively correlated with HbA1c (r=0.38; p<0.001), hs-CRP (r=0.29; p=0.002), and MPV (r=0.41; p<0.001), and to a lesser extent with PDW (r=0.22; p=0.02). These associations highlight the integrative role of metabolic decompensation and inflammation in maintaining platelet hyperactivity.

Table 1 Clinical and Laboratory Parameters and Primary Hemostasis Indicators in Patients with Stable Angina According to the Presence of T2DM (n=112)

Parameter	SA+T2DM (n=56)	SA without T2DM (n=56)	p
Age, years (M±SD)	62.1±8.7	61.8±8.5	0.84
Women, n (%)	26 (46)	25 (45)	0.87
HbA1c, % (M±SD)	7.8±1.1	5.6±0.4	<0.001
hs-CRP, mg/L (Me [IQR])	3.9 [2.1–6.2]	2.3 [1.2–3.8]	0.002
PLT, ×10^9/L (M±SD)	236±54	228±49	0.41
MPV, fL (M±SD)	10.9±1.0	10.1±0.9	<0.001
PDW, % (M±SD)	13.6±2.1	12.3±1.8	0.001
ADP-induced aggregation, % (M±SD)	63±12	54±11	<0.001
High aggregation ≥60%, n (%)	32 (57)	17 (30)	0.004

Note: M±SD — mean ± standard deviation; Me [IQR] — median [interquartile range]. The p value was calculated using the t-test/Mann–Whitney U test for quantitative data and the χ^2 test for categorical variables.

In multivariable logistic regression, where high platelet reactivity (≥60%) was used as the dependent variable, MPV ≥10.5 fL (OR 2.6; 95% CI 1.3–5.3; p=0.008) and HbA1c (per +1% increase: OR 1.5; 95% CI 1.1–2.0; p=0.01) were identified as independent predictors after adjustment for age, sex, presence of arterial hypertension, smoking, aspirin use, and statin therapy. hs-CRP retained a trend toward association (OR 1.10 per 1 mg/L; 95% CI 0.99–1.22; p=0.07), which may reflect both a true contribution of inflammation and the limited statistical power of the sample to detect an independent effect when HbA1c and MPV were simultaneously included in the model.

The obtained results have clear clinical interpretation. In patients with stable angina, diabetes mellitus creates a sustained prothrombotic predisposition specifically at the level of primary hemostasis: morphological signs of platelet activation, reflected by increased MPV and PDW, are consistent with the functional enhancement of ADP-dependent aggregation. Pathophysiologically, this corresponds to the effects of chronic hyperglycemia and insulin resistance on platelets, including amplification of intracellular signaling cascades, increased sensitivity to agonists, reduced effectiveness of endogenous antiaggregatory mechanisms such as nitric oxide and prostacyclin, and activation of platelet–endothelium–leukocyte interactions [8]. In practical terms, this may explain the phenomenon of residual ischemic risk in patients with T2DM even under standard secondary prevention and highlights the importance of optimizing glycemic control as a potentially modifiable factor of thrombotic risk. The applied value of platelet indices deserves particular attention. MPV and PDW are available from a routine complete blood count, do not require

expensive testing, and, in our study, were statistically and clinically associated with high platelet aggregation. Therefore, their use may be considered as a simple primary screening tool for identifying patients with probable platelet hyperreactivity who may require more detailed assessment, correction of risk factors, and monitoring of therapeutic response.

4. Conclusions

In patients with stable angina against the background of type 2 diabetes mellitus, pronounced alterations in primary hemostasis were identified, reflecting a proaggregant platelet phenotype. Compared with patients without diabetes, higher values of platelet indices, including MPV and PDW, were observed despite comparable platelet counts, along with a significant increase in ADP-induced platelet aggregation.

Metabolic decompensation and low-grade inflammation, reflected by elevated HbA1c and hs-CRP levels, were associated with increased platelet reactivity, confirming the pathogenetic relationship between hyperglycemia, inflammation, and platelet activation. In multivariable analysis, MPV ≥10.5 fL and increased HbA1c remained independently associated with high platelet reactivity, allowing MPV to be considered an accessible routine marker for the primary screening of patients with potentially increased atherothrombotic risk.

The obtained data substantiate the need for stricter glycemic control, correction of inflammatory and behavioral risk factors, and personalization of antithrombotic strategy in patients with chronic coronary syndromes and T2DM.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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