The importance of glycemic control in regulating clot properties in CAD patients with concomitant diabetes

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DOI: 10.33963/v.phj.100887

Received:
May 13, 2024

Accepted:
May 13, 2024

Early publication date:
June 4, 2024

Densely packed clots with a stiffer network arrangement, reduced pore size and increased resistance to lysis have been consistently found in a variety of cardiovascular diseases, including arterial thrombotic, venous thrombotic, and thromboembolic diseases, as well as in atherosclerosis itself [1]. In addition, recent prospective evidence suggests a causal role for this type of clot structure in predicting disease severity and outcomes, such as increased mortality in acute coronary syndrome (ACS) patients, recurrent deep vein thrombosis in first-event patients, and recurrent thromboembolic events in antiphospholipid syndrome [reviewed by 1].

This prothrombotic clot phenotype has also been observed in individuals with type 2 diabetes mellitus (T2DM), but with some variability in the findings. Some studies report that worsened glycemic control affects clot properties [2, 3] while others indicate that duration of diabetes has comparatively greater effect [4]. Others found no differences in structural clot properties between individuals with and without T2DM when clots were prepared in plasma [3, 5]. In addition, Pieters and colleagues demonstrated that achieving glycemic control in individuals with T2DM who previously had uncontrolled glucose levels resulted in a significant reduction in fibrinogen glycation and improved clot properties in a purified model [6], but not in plasma [5]. Finally, denser fibrin clot structures were associated not only with hyperglycemia but also with hypoglycemia in diabetes [2, 7]. Prospective evidence also shows an increased risk of long-term cardiovascular mortality in T2DM patients who form denser clots that are resistant to lysis [8]. The mechanisms behind the observed associations are complex and not fully understood. These include the downstream consequences of insulin resistance, increased levels of coagulation factors such as fibrinogen, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor, reduced plasmin generation at the fibrin clot surface, oxidative stress, and post-translational modifications such as glycation of plasminogen and/or fibrinogen, resulting in altered fibrin cross-linking and lysis [8, 9].

To date, only a limited number of studies have investigated whether T2DM has an additional effect on clot properties in the presence of pre-existing coronary artery disease (CAD). For example, Undas et al. [10], reported that ACS patients with either hyperglycemia or a history of T2DM had increased local thrombin generation and platelet activation as well as hypofibrinolysis, whereas reduced clot permeability was found only in patients with previously diagnosed T2DM. Bochenek et al. [11] found that CAD patients with T2DM formed less permeable clots that took longer to lyse than CAD patients without diabetes, and that platelet and endothelial markers contributed to this altered clot phenotype. Neergaard-Petersen et al. [12] also found that CAD patients with T2DM formed more compact clots with impaired lysis rates compared to CAD patients without diabetes and that this clot phenotype was associated with altered fibrinogen concentration, with possible influence of inflammatory proteins such as C-reactive protein, complement C3, and

interleukin-6. These findings suggest an increased risk of thrombotic complications in CAD patients with T2DM. In support of this hypothesis, Sumaya et al. [13] found that impaired fibrin clot lysis was associated with increased cardiovascular death and myocardial infarction in recent acute coronary syndrome patients with T2DM.

In this issue of the *Polish Heart Journal*, Siniarski and colleagues [14] added to the limited literature available on CAD patients with concomitant T2DM by investigating fibrin clot properties, thrombin generation and platelet activation in angiographically proven CAD patients with dysglycemia. They included 31 CAD patients without dysglycemia, 42 CAD patients with impaired fasting glucose and/or impaired glucose tolerance as a prediabetic group (diagnosed by oral glucose tolerance test according to the European Association for the Study of Diabetes guidelines), and 43 CAD patients with diagnosed T2DM who formed part of the CASCARA trial. An important characteristic of the CAD with T2DM group was that their diabetes was well controlled with a median glycated hemoglobin (HbA1c) of 5.9% (IQR, 5.7%–6.3%). They measured soluble CD40 li-gand and platelet factor-4 as markers of platelet activation and tumor necrosis factor-alpha and interleukin-6 as markers of inflammation. For coagulation markers, they measured fibrinogen concentration, performed a thrombin generation assay, and determined clot permeability (Ks) and clot lysis times using a turbidity-based assay. No significant differences in thrombin generation, fibrinogen concentra-tion, fibrin clot characteristics, or platelet activation markers were found between the 3 groups. When the study divided participants into quintiles according to glucose and HbA1c levels, elevated interleukin-6 was observed in both the highest and lowest glucose concentration quintiles and there was a significant increase in endogenous thrombin potential in the highest HbA1c quintile. The authors concluded that individuals with established CAD and concomitant prediabetes or well-controlled T2DM had a similar fibrin clot phenotype, thrombin generation potential, and platelet activation compared to CAD patients without dysglycemia. These results highlight the importance of tight glycemic control as part of the management of T2DM, even in high-risk cardiovascular disease patients with established CAD, as it can potentially attenuate additional adverse effects on the coagulation system.

Article information

Acknowledgements: I would like to thank Dr Zelda de Lange-Loots for critical reading of the editorial.

Conflict of interest: None declared.

Funding: None.

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