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

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Article type: Editorial
Received: May 13, 2024
Accepted: May 13, 2024
Early publication date: June 4, 2024
The importance of glycemic control in regulating clot properties in CAD patients with concomitant diabetes

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Related article
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Densely packed clots, with a stiffer network arrangement, reduced pore sizes and enhanced resistance to lysis have consistently been found in a variety of cardiovascular diseases including arterial thrombotic, venous thrombotic and thromboembolic diseases, as well as in atherosclerosis itself [1]. Additionally, more recent prospective evidence also points to a causal role for this type of clot structure in predicting disease severity and outcomes, e.g., higher mortality rate in acute coronary syndrome (ACS) patients, recurrence of deep vein thrombosis in first-event patients, and recurrent thromboembolic events in antiphospholipid syndrome patients [1].

This prothrombotic clot phenotype has also been observed in individuals with type 2 diabetes mellitus (T2DM), however, with some variation in the findings. Some studies report worsened glycemic control to affect clot properties [2, 3] while others indicate duration of
diabetes to have a comparatively bigger 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 decrease in fibrinogen glycation and improved clot properties in a purified model [6], but not in plasma [5]. Lastly, denser fibrin clot structures were not only associated with hyperglycemia, but also hypoglycemia in diabetes [2, 7]. Prospective evidence furthermore demonstrates an increased risk for 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 yet fully elucidated. These include the downstream sequelae of insulin resistance, increased levels of coagulation factors such as fibrinogen, plasminogen activator inhibitor-1, and thrombin-activatable fibrinolysis inhibitor, reduced plasmin generation on the fibrin clot surface, oxidative stress, and post-translational modifications such as glycation of plasminogen and/or fibrinogen resulting in altered fibrin crosslinking 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). Undas et al. [10] for instance, reported that ACS patients with either hyperglycemia or a history of T2DM, had increased local thrombin generation and platelet activation as well as hypofibrinolysis, while 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 with CAD patients without diabetes and that this clot phenotype was related to altered fibrinogen concentration, with possible influence of inflammatory proteins such as C-reactive protein, complement C3 and interleukin-6. These findings suggest increased risk for thrombotic complications in CAD patients with T2DM. In support of this hypothesis, Sumaya et al. [13] found impaired fibrin clot lysis to be 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 established CAD patients with dysglycemia. They included n = 31 CAD patients without dysglycemia, n
42 CAD patients with impaired fasting glucose and/or impaired glucose tolerance as a prediabetic group (diagnosed by oral glucose tolerance test in accordance with the European Association for the Study of Diabetes guidelines) and n = 43 CAD patients with diagnosed T2DM who formed part of the CASCARA trial. An important distinction of the CAD with T2DM group was that their diabetes was well-controlled with a median glycated haemoglobin (HbA1c) level of 5.9% (IQR, 5.7%–6.3%). They measured soluble CD40 ligand and P-selectin as platelet activation markers and tumor necrosis factor-alpha and interleukin-6 as inflammatory markers. Regarding 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 concentration, fibrin clot properties, or platelet activation markers between the three groups were found. When dividing the study participants into quintiles according to glucose and HbA1c level, elevated interleukin-6 in both the highest and lowest glucose concentration quintiles were observed and there was a substantial increase in endogenous thrombin potential in the highest HbA1c quintile. The authors concluded that individuals with established CAD and concomitant prediabetes or well-controlled T2D exhibited a similar fibrin clot phenotype, thrombin generation potential, and platelet activation when compared to CAD patients without dysglycemia. These results highlight the importance of strict glycemic control as part of T2D management, even in high-risk cardiovascular disease patients with established CAD, as it may 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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