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Platelet indices and glucose control in type 1 and type 2 diabetes mellitus: A case-control study

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Abstract *Background and aims:* The relationship between platelet indices and glucose control may differ in type 1 (T1DM) and type 2 (T2DM) diabetes. We aimed to investigate differences in mean platelet volume (MPV), platelet count, and platelet mass between patients with T1DM, T2DM, and healthy controls and to explore associations between these platelet indices and glucose control.
Methods and results: A total of 691 T1DM and 459 T2DM patients and 943 control subjects (blood donors) were included. HbA1c was measured in all subjects with diabetes and 36 T1DM patients further underwent 24 h-continuous glucose monitoring to estimate short-term glucose control (glucose mean and standard deviation). Adjusting for age and sex, platelet count was higher and MPV lower in both T1DM and T2DM patients vs control subjects, while platelet mass (MPV $\times$ platelet count) resulted higher only in T2DM. Upon further adjustment for HbA1c, differences in platelet count and mass were respectively 19.5 $\times$ 10^9/L (95%CI: 9.8–29.3; $p < 0.001$) and 101 fL/nL (12–191; $p = 0.027$) comparing T2DM vs T1DM patients. MPV and platelet count were significantly and differently related in T2DM patients vs both T1DM and control subjects; this difference was maintained also accounting for HbA1c, age, and sex. Platelet mass and the volume-count relationship were significantly related to HbA1c only in T1DM patients. No associations were found between platelet indices and short-term glucose control.
Conclusion: By accounting for confounders and glucose control, our data evidenced higher platelet mass and different volume-count kinetics in subjects with T2DM vs T1DM. Long-term glucose control seemed to influence platelet mass and the volume-count relationship only in T1DM subjects. These findings suggest different mechanisms behind platelet formation in T1DM and T2DM patients with long-term glycaemic control being more relevant in T1DM than T2DM.

Abbreviations: CGM, Continuous glucose monitoring; MPV, Mean platelet volume; PLT, Platelet count; PM, Platelet mass; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; TX, Thromboxane.

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Introduction

Diabetes mellitus is a metabolic disorder associated with a 2-fold increase of micro- and macro-vascular atherothrombotic complications as compared to subjects without diabetes [1,2]. Platelet activation is known to contribute to atherothrombosis development and acute major arterial events [3]. Consistently, an increased urinary thromboxane (TX)A_2 excretion, a biomarker of *in vivo* platelet activation, was documented in type 2 diabetes mellitus (T2DM) patients with macrovascular complications already two decades ago [4]. Since then, many different platelet functional and/or morphological abnormalities have been reported *in vivo*, *ex vivo*, or *in vitro* in T2DM, altogether consistent with increased platelet activity and/or reduced antiplatelet drug responsiveness phenotypes [5]. Conversely, data on platelets in type 1 (T1)DM, are more limited. Recently, we have reported in young T1DM patients an increased TXA_2 generation *in vivo* associated with microvascular damage [6].

Among different platelet morphological indices, a high mean volume (MPV) of peripheral platelets is considered a marker associated with increased platelet activity *in vivo*, mainly related to the larger volume of newly-released platelets which display an increased pro-thrombotic activity [7]. High MPV has been associated with incident coronary heart disease events in T2DM [8] and in the general population [9]. Moreover, MPV has been reported to independently predict a reduced pharmacological response to low dose aspirin in T2DM [10]. Consistently, a higher immature platelet fraction has been reported in T2DM patients with cardiovascular complications [11] and has been associated with macrovascular events in patients without diabetes [12]. Moreover, higher levels of immature platelets have been associated with a reduced response to antiplatelet drugs in patients without [13,14] and with T2DM [10].

Based on the above observations, the MPV has been often proposed as biomarker of poor outcomes and/or antiplatelet drug responsiveness in T2DM. However, not all the studies have been consistent in reporting an increased MPV in T2DM vs non-T2DM subjects [15–19]. In addition, platelet morphometric indices other than MPV, such as platelet count (PLT) and/or platelet distribution width have been investigated in T2DM and non-T2DM subjects, with inconsistent findings [15]. Data on platelet indices on T1DM are far more limited [20–22].

Under steady-state conditions of physiological megakaryopoiesis, the platelet size is inversely related to the platelet count, and these parameters are inversely regulated to keep the platelet mass (PM = PLT × MPV) constant [23]. Therefore, the measure of only one morphometric platelet index might be poorly informative of the kinetics of platelet generation *in vivo* and be potentially misleading or give inconsistent findings. Furthermore, previous studies on T2DM and a single platelet morphometric index often lacked of adjustment for potential confounders known to affect MPV, PLT and PM, independently of diabetes [24], such as age, gender and ethnicity [25]. Moreover, whether and how glycaemic control can affect the kinetics of platelet production *in vivo* is also unclear. Recently, high fasting glucose levels have been associated with high MPV in a large male population [24]; however, one fasting glucose measurement is poorly informative of the short- and long-term regulation of glucose metabolism or of the type of underlying metabolic defect (T1DM, T2DM, glucose intolerance) [26]. Finally, investigating T1DM separately from T2DM is potentially relevant, since hyperglycaemia in T1DM generally does not cluster with other metabolic alterations or comorbidities as in T2DM.

To help clarify these aspects, we performed a large, retrospective, case-control study including T1DM, T2DM and healthy subjects and investigated MPV, PLT, PM and their relationships in physiological and different diabetes conditions. We also investigated the effect of long- and short-term glucose control on the same platelet indices.

Methods

Population

The present study is a retrospective analysis of the database from T1DM and T2DM subjects of the outpatient diabetes clinic of the "A. Gemelli" Hospital, Catholic University School of Medicine, Rome. For subjects with T1DM and T2DM, data collected during one calendar year (2013) were anonymously extracted from hospital datasets providing that there were information on age and sex, and HbA1c, MPV and PLT values from samples collected on the same day. In our outpatient Unit, T1DM is diagnosed as the presence of at least one of the diabetes-related autoantibodies (IA-2 protein tyrosine phosphatase, glutamic acid decarboxylase, or insulin antibody) in subjects needing insulin treatment and T2DM is diagnosed according to the American Diabetes Association criteria [27]. Patients with end-stage renal failure and on dialysis were excluded. For the control group, we used an anonymised database including all blood donor volunteers during the same period (year 2013) and we extracted data with available information on age, gender, MPV and PLT.

For the short-term glucose control study, a group of 36 uncomplicated (absence of macro- and micro-vascular disease and neuropathy) T1DM consenting patients were consecutively enrolled to undergo a 24-h continuous glucose monitoring (CGM) (CGMS® Guardian REAL-Time, Medtronic MiniMed, Northridge, CA, USA). The glucose sensor was inserted subcutaneously in the abdominal wall and patients were instructed to perform the required sensor calibration procedure according to manufacturer's instructions; at the end of CGM, fasting blood samples were taken to measure haemocromocitometric and biochemical variables. Resting systolic blood pressure was measured with a random-zero sphygmomanometer by a trained nurse; body mass index was computed as the ratio of weight in kilograms to the square of height in meters; waist circumference was calculated as the average of 2 measurements taken after inspiration and expiration at