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Review

Thrombotic and cardiovascular risks in type two diabetes; Role of platelet hyperactivity

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ABSTRACT

One of the most commonly identified chronic illnesses in many countries is type 2 diabetes mellitus (T2DM). T2DM denotes an independent risk factor for cardiovascular disease (CVD). Heart disease is one of the causes of mortality in patients with diabetes, mainly due to the macrovascular complications. One of these macrovascular complications in diabetes is atherosclerosis, which involves a complicated pathophysiological process. Besides hyperglycemia, oxidative stress plays a significant role in the pathogenesis of diabetes and its associated risk of CVD. There are many other factors including molecular, metabolic, lipid, fibrinolytic, and platelet function disorders precipitate to thrombotic and CVD risks in T2DM. Also, Platelets have an increased response to procoagulants in patients with diabetes. Platelet hyperactivity, in the presence of oxidative stress, has a major effect on the progression of thrombotic and CVD events. This review will discuss the impact of the above factors and the potential effects of platelet hyperactivity on thrombotic and cardiovascular risks.

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Contents

Abbreviations: AC, anthocyanin; CVD, CVD; T2DM, T2DM; NO, nitric oxide; IGM, impaired glucose tolerance; OS, oxidative stress; CHD, coronary heart disease; IHD, ischemic heart disease; ADP, adenosine diphosphate; AS, atherosclerosis; EC, endothelial cell; PGI_2, prostaglandin I2; AA, arachidonic acid; TXA_2, thromboxane A2; PAI, plasminogen activator inhibitor 1; VWF, von Willibrand factor.

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1. Introduction

T2DM is one of most commonly identified chronic illnesses worldwide and is developing at a high incidence rate, partly because of the current sedentary lifestyle, obesity, and weight gain [1]. CVD represents a risk factor for mortality in patients with diabetes and is due to macrovascular complications. Atherosclerosis is one of these macrovascular complications in diabetes [2]. The pathophysiology of T2DM involves oxidative stress, and is responsible for many conditions, including impaired uptake of glucose by the muscle, impaired oxidation of lipids, and endothelial dysfunction, resulting in activation of platelets, thrombotic risk, and cardiovascular complications [3,4]. Inflammation, oxidative stress, and hyperactivation of platelets are principle factors in the pathophysiology of many diseases like atherosclerosis, heart disease, and T2DM [5]. The pathophysiological correlation between platelet hyperactivity and thrombotic and CVD risks will be potentially covered by the following sections.

2. Role of platelets in diabetes

2.1. Platelet function

Through their aggregation, platelets release constituents from their granules, which are necessary for thrombus formation. Platelet activation leads to a change in expression of surface glycoproteins (GP). During the stimulation and activation phase of platelets, P-selectin translocates from alpha granules and Weibel-Palade bodies of endothelial cells to the cell membrane [6]. On the platelet surface membrane, GPIIb-IIIa undergoes activation dependent conformational change which allows it to bind to fibrinogen [7]. Also, the binding of thrombospondin to GPIV is elevated, and the von Willebrand factor binding site on GPIb-IX complex is down-regulated in thrombin-activated platelets [8]. Recognition of these alterations that occur on the membrane of platelets has been applied for analysis of platelet activation by specific antibodies [9]. Some platelet receptors and their corresponding agonists are shown in Fig. 1.

The most important antiaggregants, such as prostaglandin I2 (PGI2) and nitric oxide (NO), are released by the healthy vascular endothelium and regulate the activity of proaggregants to prevent the formation of thrombi in intact blood vessels [9]. Unlike antiaggregants and proaggregants which apply their effects by attaching to specific receptors on the plasma membrane of platelets, NO crosses the membrane and stimulates guanylate cyclase. Diabetes, hypertension, heart disease, and atherosclerosis share the characteristic of the high risk of thrombus due to platelet activation. Researchers believe that procoagulant mechanisms are not the single reason behind increased platelet action. Loss of the preventive effect of antiaggregatory actions can lead to hyperactivity of platelets as well. The resistance of platelets to the suppressive effect of insulin and the decreased endothelial release of antiaggregants (including NO and PGI2) result in the loss of control of the platelets and reduced platelet contact with the

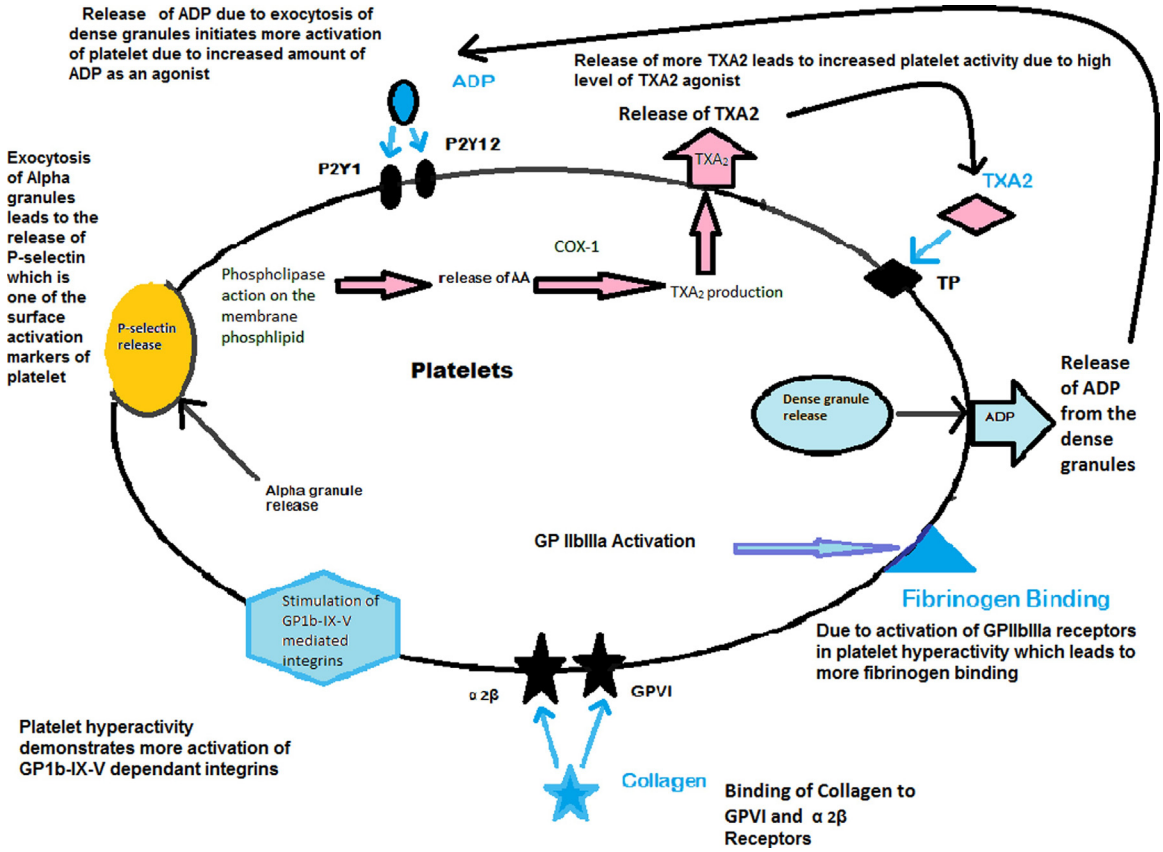

Fig. 1. Platelet receptors and their corresponding agonists. ADP = adenosine diphosphate, TXA2 = thromboxane A2, GPVI = glycoprotein VI, AA = arachidonic acid, COX–1 = cyclooxygenase-1, GP1b = glycoprotein 1b, IX = coagulation factor IX, V = coagulation factor V, P2Y1 and P2Y12 = platelet surface receptors of ADP.

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