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Article · March 2024

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Elite Journal of Medicine. Volume 2 issue 2(2024), Pp.1-17
https://epjournals.com/journals/EJM

Platelet Dysfunction in Diabetes Mellitus

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Abstract

Platelet dysfunction in diabetes mellitus is a multifaceted issue with significant implications for vascular health. The interplay of hyperglycemia, oxidative stress, abnormal lipid profiles, endothelial dysfunction, inflammation, and medications can collectively disrupt platelet function. This dysfunction not only raises the risk of thrombosis and cardiovascular complications but also underscores the importance of comprehensive diabetes management. By controlling blood sugar levels, addressing associated risk factors, and working closely with healthcare providers, individuals with diabetes can mitigate the adverse effects of platelet dysfunction and reduce the likelihood of cardiovascular events.

Keywords*: Platelet, Dysfunction and Diabetes Mellitus*

Introduction

The diabetes mellitus epidemic, as a serious global health threat, is associated with various adverse outcomes and an increased risk of premature death and disability. Diabetes imposes considerable economic pressure on individuals, families, health care systems and societies. It causes premature death, disability, job losses, and disruption to education, which all have negative economic effects on countries. These indirect costs contribute to approximately one-third of total costs, an estimated US$ 1.31 trillion [1].

Diabetes mellitus (DM) is a group of conditions that contribute significantly to the increasing health and financial burden in many Countries around the world and it also contributes to medical morbidity and mortality worldwide, especially in developing countries like Nigeria [2,3]. The latest evidence shows that DM continues to be a significant global health challenge and is likely to continue to grow substantially in the next decades, which would have major implications for healthcare expenditures, particularly in developing countries [4]. The worldwide existing prevalence of DM is about 425 million people, of whom 279 million are in urban areas and 146 million are in rural zones [5]. According to IDF in 2015

more than 321,100 deaths in the Africa Region could be attributed to diabetes; 79.0% of those deaths occurred in people under the age of 60, the highest proportion of any region of the world. In Nigeria, the prevalence of DM has varied from 0.65% in rural to 11.0% in urban areas [6].

DM increases the risk of developing different comorbidities and other health complications including cerebrovascular accidents, hypertension, retinopathy and other ocular diseases, nephropathy, cardiovascular diseases, mental health conditions (e.g. anxiety and depression), skin infections, and lower-limb compromise, among others [4].There are 3 main types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus, with T2DM responsible for about 90% of all diabetes [1].

Platelets are small, anucleated, discoid-shaped cells that emanates from precursor cells known as megakaryocytes which are part of the hemopoietic cell line [7,8]. They play major role in maintaining homeostasis [9]. Among platelet indices, mean platelet volume (MPV) reflects changes in either platelet stimulation or the rate of platelet production. Platelet distribution width (PDW) is a measure of platelet heterogeneity, which in turn may be due to aging of platelets or heterogeneous demarcation of megakaryocytes. The third platelet index, platelet large cell ratio (P-LCR) is the measure of larger platelets [10].

platelet activation is considered to play an important role in the pathogenesis of thrombotic complications in patients with DM [11]. Platelet activation has been linked with pathological processes in T2DM while a combination of platelet indices involving the plateletcrit (PCT), platelet distribution width (PDW) and mean platelet volume (MPV) has been identified as efficient marker of platelet activation [12]. Platelet indices, which consists of platelet count, mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCT) has become part of the current routine hematological examination. There is a change of morphology and platelet function in diabetic patients resulting in changes in platelet indices. MPV describes the size of platelets associated with the risk of thrombosis. PDW illustrates how platelet and PCT sizes measure total platelet mass in which the increase can also describe the presence of atherosclerosis and thrombosis [13].

Classification of Diabetes Mellitus

The classification of diabetes mellitus in 2020 still starts with 2 major types, that is, type 1 and type 2, but each of these now includes a few uncommon variants [14]. DM was classified based on clinical manifestations as juvenile or adult onset. In 1979, the National Diabetes Data Group proposed a new 3 category classification based on clinical manifestations and insulin requirement necessary to prevent ketosis: Insulin-dependent DM (IDDM, or juvenile DM, prone to ketosis), noninsulin-independent (NIDDM, or mature onset DM, including Mature Onset Diabetes of the Young [MODY], not prone to ketosis), and others (DM secondary to pancreatitis, endocrinopathies, drugs, and other causes). Impaired glucose tolerance (IGT) and Gestational DM were classified separately [15]. Diabetes can be classified into the following general categories:

Type 1 Diabetes Mellitus

T1DM is an autoimmune disorder characterized by several immune markers, in particular autoantibodies. These autoantibodies are associated with the immune mediated β-cell destruction, characteristic of this disease. The autoantibodies include glutamic acid decarboxylase autoantibodies (GADAs) such as GAD65, islet cell autoantibodies (ICAs) to β-cell cytoplasmic proteins such as autoantibodies to islet cell antigen 512 (ICA512), autoantibodies to the tyrosine

phosphatases, IA-2 and IA-2α, insulin autoantibodies (IAAs), and autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8) [16].

Type 1 diabetes results from autoimmune destruction of the pancreatic islet, due to interaction between genetic susceptibility, perturbed immunology and environmental factors [17]. Type 1 diabetes represents around 10% of all cases of diabetes, affecting approximately 20 million people worldwide. Although type 1 diabetes affects all age groups, the majority of individuals are diagnosed either at around the age of 4 to 5 years, or in their teens and early adulthood [18].

Type 1 DM, also known as type 1A DM or as per the previous nomenclature as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, constitutes about 5-10% of all the cases of diabetes. It is an autoimmune disorder characterized by T-cell-mediated destruction of pancreatic β-cells, which results in insulin deficiency and ultimately hyperglycemia [16]. The disease recognizes two major subtypes: 1A (autoimmune) and 1B (idiopathic) [19].

i. Immune-Mediated Diabetes Mellitus: This form of T1DM results from cell-mediated autoimmune destruction of the pancreatic β-cells. In people, markers of the immune destruction of β-cells include several islet cell autoantibodies (GAD65, IA-2, and ZnT8) and autoantibodies to insulin. Ninety-eight percent of T1DM people are autoantibody positive. Two or more of these autoantibodies are present in 85-90% of T1DM patients when fasting hyperglycemia is detected, and antibodies can be detected years before onset of clinical disease. The antibody profile is highly predictive of the rate of progression to overt DM [15]. Autoimmune destruction of β cells has multiple genetic factors and is also related to environmental factors that are still poorly defined. The disease has strong HLA associations, with linkage to the DQB1 and DRB1 haplotypes, and genetic screening has been used in some research studies to identify high risk populations. Specific alleles in these genes can be either predisposing or protective, and account for most of the heritability observed in T1DM. Several genes involved in T-cell function, including PTPN22, CTLA4, and IL2RA, also impart risk of T1DM. The insulin gene, INS, is another major non-HLA susceptibility gene, and polymorphisms in INS are strongly associated with the presence of insulin autoantibodies at diagnosis [15,20].

T1DM also is associated with other autoimmune disorders, including endocrine diseases as well as myasthenia gravis, autoimmune hepatitis, and inflammatory bowel disease [15].

ii. Idiopathic Type1 Diabetes: Some forms of type 1 diabetes have no known etiologies. These individuals have permanent insulinopenia and are prone to DKA but have no evidence of b-cell autoimmunity. However, only a minority of people with category. Individuals with autoantibody negative type1diabetes of African or Asian ancestry may suffer from episodic DKA and exhibit varying degrees of insulin deficiency between episodes (possibly ketosis-prone diabetes). This form of diabetes is strongly inherited and is not HLA associated. An absolute requirement for insulin replacement therapy in affected individuals may be intermittent [20].

Type 2 Diabetes Mellitus

Type 2 diabetes and its complications are classical examples of polygenic and complex diseases as a result of interactions between multiple genetic and environmental factors [17]. Type 2 diabetes is characterized by several biochemical and pathophysiologic defects associated with hyperglycemia [14].

Type 2 diabetes continues to be a serious and highly prevalent public health problem worldwide. In 2019, the highest prevalence of diabetes in the world at 12.2%, with its associated morbidity and mortality, was found in the Middle East and North Africa region. In addition to a genetic predisposition in its population, evidence suggests that obesity, physical inactivity, urbanization, and poor nutritional habits have contributed to the high prevalence of diabetes and prediabetes in the region. These risk factors have also led to an earlier onset of type 2 diabetes among children and adolescents, negatively affecting the productive years of the youth and their quality of life [21]. T2DM progresses very slowly and asymptomatically with even mild hyperglycemia developing over years and as such remains largely undiagnosed until the appearance of classic symptoms associated with severe hyperglycemia such as weight loss, growth impairment, blurred vision, polyuria, and polydipsia in the advanced stages of the disease [16].Two major pathophysiological mechanisms characterize T2DM insulin resistance, especially in skeletal muscle and liver, and defective insulin secretion from the pancreas. However not all disease causing pathways are completely understood, as T2DM is a complex disorder resulting from an inter play between genes and environment [22]. According to Redondo *et al* (2020) Type 2 diabetes occurs when acquired insulin resistance usually from obesity exists in the setting of innate and acquired inadequacy in beta cell function and also Chronically high insulin demand triggers relative beta cell dysfunction [23].

Gestational Diabetes

Gestational diabetes mellitus (GDM) is an increasing public health concern that affects approximately 5-20% of pregnancies, and its prevalence is progressively rising. It has been defined as any glucose intolerance with the first onset or recognition during pregnancy [24]. The documented prevalence of GDM varies substantially worldwide, ranging from 1% to >30%. Owing to a lack of consensus and uniformity in the screening standards and diagnostic criteria for GDM, it is challenging to compare the prevalence across countries and regions [25]. GDM is the abnormal glucose metabolism that does not reach the dominant diabetes level during pregnancy, which accounts for over 90% of pregnancy diabetes mellitus, and 20% to 50% of the development of type 2 diabetes mellitus (T2DM) in postpartum. The occurrence of gestational diabetes mellitus will increase the probability of complications of pregnant women, such as: abortion, polyhydramnios, macrosomia, diabetic ketoacidosis (DKA), infection, pregnancy-induced hypertension, etc., as well as shoulder dystocia, prolonged labor, postpartum hemorrhage caused by fetal overgrowth during the production process. Because of the high blood sugar environment in the mother during pregnancy, the risk of fetal malformation, macrosomia and growth restriction will also increase [26].

Other Specific Types

1. Monogenic Defects of the β-Cells: Several forms of DM are associated with monogenic defects in b-cell function [15]. This is further divided into;

I. Maturity-onset diabetes of the young: Maturity onset diabetes of the young (MODY) are monogenic forms of diabetes characterized by autosomal dominant inheritance, early-onset diabetes (usually<25yearsofage), preservation of endogenous insulin secretion with no signs of autoimmune process or insulin secretion [27]. MODY (Maturity Onset Diabetes of the Young) is a type of diabetes resulting from a pathogenic effect of gene mutations. Up to date, 13 MODY genes are known. Gene HNF1A is one of the most common causes of MODY diabetes (HNF1A-MODY; MODY3). This gene is polymorphic and more than 1200 pathogenic and non-pathogenic

HNF1A variants were described in its UTRs, exons and intron [28]. It often manifests in adolescents or young adults, usually before age 30. It is estimated to account for 1% to 2% of all patients with diabetes [14].

It is a group of autosomal dominant disorders characterized by non ketotic and/or non- acute presentation, typical of type 2 diabetes, but occurring at a younger age, usually before the age of 25 years and most of the evidence points to multiple mutations/variants implicated in pathways predominantly linked to b-cell biology [17]. HNF1AMODY is one of the most common subtypes of the Maturity Onset Diabetes of the Young (MODY). MODY was defined as monogenic form of diabetes with an autosomal dominant inheritance that occurs before the age of 25 years due to a defect in the function of β cells. The subtypes of MODY traditionally include mutations of the genes ABCC8, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, NEUROD1, PDX1, BLK, KLF11 and PAX4 [28]. Genes implicated in MODY are crucial in β-cell development, function and regulation, as well as glucose sensing, and include the insulin gene 18 The causative mutations are inherited in an autosomal dominant pattern. Up to 80% of MODY cases are caused by mutations in the glucokinase and hepatocyte nuclear factor (HNF1A and HNF4A) genes. Treatment varies based on the underlying genetic defect [15].

II. Neonatal Diabetes: Diabetes occurring under 6months of age is termed “neonatal” or congenital diabetes, and about 80–85% of cases can be found to have an underlying monogenic cause [20]. Neonatal diabetes can either be transient neonatal DM which is characterized by hyperglycemia that begins in the neonatal period and resolves by 18 months of age and the most common cause is a genetic defect at the 6q24 locus, resulting in over expression of the genes that regulate insulin secretion, b-cell proliferation, and peripheral insulin sensitivity or permanent neonatal DM which is a distinct condition commonly caused by mutation in the genes (KCNJ11 and ABCC8) that encode subunits of the b-cell KATP channel [15,20].

2. Latent Autoimmune Diabetes of Adults (LADA): Latent autoimmune diabetes of adults (LADA) is typically defined as a new diabetes diagnosis after 35 years of age, presenting with clinical features of type 2 diabetes, in whom a type 1 diabetes associated islet autoantibody is detected. However, the existing LADA definition identifies a group with clinical and genetic features intermediate between typical type 1 and type 2 diabetes [29]. A recent consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes (EASD) defines age of onset (>30years), presence of diabetes associated autoantibodies and absence of insulin requirements for at least 6 months after diagnosis as key diagnostic criteria for LADA. Also, they recommend an individualized approach that differs from the classical management of T1 DM [30].

The prevalence of LADA is highly dependent on the cohort of patients under evaluation and on whether the diagnostic criteria are based on autoimmune antibodies associated with type 1 diabetes alone or on additional genetic testing in which overlap with type 2 diabetes genes is considered. Although LADA patients are often started on oral glucose-lowering agents, these agents usually do not control the glucose level for very long [14].

3. Medication induced diabetes: Many medications can contribute to hyperglycemia, including glucocorticoids, statins, psychotropic agents, and immunomodulatory drugs. Both glucocorticoids and immunomodulatory agents likely contribute to the entity now commonly called post-transplant diabetes [14]. In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral edema. The additional stress of surgery may add to the drug induced insulin resistance,

and cause a relative insulin deficiency, sufficient to cause transient diabetes. Hyperglycemia may be exacerbated if large volumes of intravenous dextrose are given for management of diabetes insipidus. An intravenous insulin infusion is the optimal method to control the hyperglycemia, which is usually transient [31].

Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidol, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than 3 fold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose [31].

Epidemiology of Diabetes Mellitus

Diabetes mellitus (DM) is a major public health problem that is determined with impaired carbohydrate metabolism, protein, and fat due to unstable insulin secretion, insulin resistance secretion, or both. With an 8.5% global prevalence of diabetes in 2014; various estimates suggest that the number of affected people will be risen from 422 million to 642 million in the world by 2040 [32]. Diabetes Federation (IDF) Diabetes Atlas, by end of 2013, there were 382 million (or 8.3% of adult world population) people worldwide with diabetes of which 80% live in low- and middle-income countries; this number is estimated to reach 592 million in <25years (by 2035) [33]. The (International Diabetes Foundation (IDF) 2013), shows that 382 million people were living with diabetes globally with Africa bearing 4.9% of this burden. According to IDF (2015) more than 321,100 deaths in the Africa Region could be attributed to diabetes; 79.0% of those deaths occurred in people under the age of 60, the highest proportion of any region of the world [6]. An estimated 90-95% of diabetic cases are type 2 diabetes. Both type 1 and type 2 diabetes have far-reaching effects on the health and economies of communities [34].

Currently, sub–Saharan Africa is estimated to have 20 million people with diabetes, about 62% are not diagnosed and the number is expected to reach 41.4 million by 2035 or an increase of 109.1% [33]. Several years ago, South Africa and Ethiopia were said to have more diabetes cases than Nigeria. However, currently, Nigeria has the highest incidence of diabetes in sub-Saharan Africa [35].

Records from the World Health Organization (WHO) reveal that Nigeria; the most populous black Nation in the world, has the greatest number of persons living with diabetes in Africa The prevalence of diabetes in Nigeria varies from 0.65% in the rural (North) to 11% in the urban (South) [36]. Studies conducted by Isara and colleague in Nigeria have shown that the prevalence of diabetes varies across different zones of the country but ranges from 2.2-9.8% and diabetes statistics of the International Diabetic Federation (IDF) showed that Nigeria has the highest number of people living with diabetes and impaired fasting glucose (IFG) in Africa [3]. Compared to high income countries (HIC), the increase in the prevalence of diabetes affect slow and middle income countries and adds a burden of excess morbidity, mortality, and health care costs. Specifically, the Middle East and North Africa region (MENA) carried the highest prevalence of diabetes in 2019 at 12.2% and is expected to witness a 96% increase in diabetes prevalence between 2019 and 2045, second only to the African region with a 143% projected rise [21].

Effect Of Diabetes on Platelet and Platelet Indices

Diabetes is characterized by an alteration of platelet function. Indeed, platelets from patients with type 1 or type 2 diabetes are hyperreactive and demonstrate increased adhesiveness as well as exaggerated aggregation and thrombus formation [37]. Platelets from diabetic patients also demonstrate increased surface expression of adhesion proteins such as P-selectin and the αIIbβ3

integrin and reduced membrane fluidity. These changes characteristic of the "diabetic platelet" have been mostly attributed to the metabolic dysregulation associated to the insulin resistance and dyslipidemia. However, given that platelet hyperreactivity has also been found in patients with type 1 diabetes mellitus it is suggested that hyperglycemia alone can account for at least part of the altered platelet response in patients with diabetes mellitus. Oxidative stress which characterizes both types of diabetes has also been shown to be an important factor mediating the phenotypic changes of diabetic platelet [37]. Platelets of diabetic patients are characterized by dysregulation of several signaling pathways and have been suggested to be hyperreactive, showing increased adhesion, activation, and aggregation. Platelets from patients with type 1 and type 2 diabetes exhibit enhanced platelet activity early in the disease course that may precede the development of CVD [38].

Platelet dysfunction in diabetes may be found even before development of visible damage to the vessel wall. Platelets in diabetes respond more frequently even to subthreshold stimuli, and thus contribute to accelerated thrombosis and release of fresh hyperreactive platelets [38]. Diabetes mellitus elevates mean platelet volume (MPV) in diabetic patients indicating larger platelet sizes and suggesting stimulated thrombopoiesis and augmented platelet activation. The mechanism of increased MPV in DM is osmotic swelling due to raised blood glucose and perhaps due to a shorter lifespan of platelets in diabetic patients [39]. Platelet distribution width (PDW) reflects variability in platelet size, and is considered a marker of platelet function and activation. However, platelet dysfunction due to platelet hyperreactivity shows increased adhesion, activation, and aggregation of platelets thereby affecting platelet function and activation and in turn affecting platelet distribution width (PDW) [40,38]. Diabetes may increase the range of platelet size, due to changes in the morphology of platelets as spherically shaped and pseudopodia formed. Another mechanism for higher variability in platelet size is hypercoagulability. During thrombosis, increased platelet destruction and consumption result in declining platelet count, on one hand; and in stimulation of thrombopoiesis with enhanced release of younger larger platelets from the bone marrow into the blood circulation [40]. platelet large cell ratio (P-LCR) is the measure of larger platelets [10]. Hyperglycemia in DM leads to release of larger platelets with more GPIb and GPIIb/IIIa receptors and higher thromboxane forming capacity this results to a higher platelet-large cell ratio (P-LCR), the third platelet index [41].

A study of the platelet indices by Ogbuabor and colleagues revealed significant increase in the mean platelet volume (MPV), platelet distribution width (PDM) and the plateletcrit (PCT) in the type 2 diabetic patients (T2DM) compared to the controls [12]. Another study by Shilpi and Potekar showed that MPV, PDW and P-LCR were significantly higher in diabetics compared to non-diabetic controls [39].

Mechanisms to Platelet Dysfunction in Diabetes Mellitus

Multiple mechanisms caused by metabolic and cellular abnormalities have been suggested to play a role in the increased platelet reactivity observed in patients with DM. These mechanisms can be grouped together into the following aetiopathogenic categories: a) hyperglycaemia, b) insulin deficiency and resistance, c) associated metabolic conditions, and d) other cellular abnormalities [42].

Hyperglycemia

Hyperglycaemia not only defines DM but also plays an independent and important role in the blood abnormalities leading to a prothrombotic state in DM patients [42]. Hyperglycemia can

increase platelet reactivity by inducing non enzymatic glycation of proteins on the surface of the platelet. Such glycation decreases membrane fluidity and increases the propensity of platelets to activate. Osmotic effect of glucose is a second mechanism by which hyperglycemia can increase platelet reactivity by activating platelet glycoproteins GP IIb/IIIa (a platelet surface receptor) and P-selectin expression (a platelet adhesion protein). We found that brief exposure of platelets invitro to hyperglycemia or a similar concentration of mannitol increased their reactivity. Activation of protein kinase C is a third mechanism by which hyperglycemia can increase platelet reactivity. Protein kinase C is an essential mediator of platelet activation [43,42]. The fourth mechanism is glycation of circulating low-density lipoproteins (LDL), which increases intracellular calcium concentration and nitric oxide (NO) production [42].

People with diabetes exhibit increased expression of the surface glycoproteins Ib and IIb/IIIa. These glycoproteins mediate platelet adhesion and adherence. Thus, greater expression would be anticipated to increase the functional activity. Hyperglycemia appears to promote platelet activity by increasing megakaryocyte production of glycoproteins [43].

Insulin Deficiency and Resistance

The vast majority of DM patients can be assigned to two broad aetiopathogenetic categories. Type-1 DM, which accounts for only 5-10% of cases, results from a cellular mediated autoimmune destruction of the β-cells of the pancreas, leading to an absolute deficiency of insulin secretion. Type-2 DM, which accounts for around 90-95% of DM Individuals, is caused by a combination of resistance to insulin action and an inadequate compensatory insulin secretory response, usually having relative (rather than absolute) insulin deficiency [42].

Insulin antagonizes the effect of platelet agonists such as collagen, ADP, epinephrine, and platelet-activating factor. This antagonism is mediated by activation of an inhibitory G protein by insulin receptor substrate (IRS)-1. Insulin resistance reflects impaired insulin signaling, predominantly mediated by IRS. Thus, resistance by the platelet to the effects of insulin (relative insulin deficiency) or absolute deficiency of insulin attenuates insulin-mediated antagonism of platelet activation and thereby increases platelet reactivity. Thus, insulin resistance appears to the activation of platelets, consistent with increased platelet reactivity [43]. Among IRS-dependent factors, insulin resistance causes an increase in intracellular calcium concentration that leads to augmented platelet degranulation and aggregation. The exact mechanism by which the increase in calcium concentration is generated is not yet entirely known and a number of hypotheses have been suggested, such as IRS binding to the calcium ATPase of the sarcoplasmic reticulum in an insulin regulated fashion, or via inhibition of cyclic adenosine monophosphate formation by the inhibitory G-protein of adenylyl cyclase, Gi. Among IRS-independent pathways involved in platelet dysfunction due to insulin resistance, the role of reduced platelet sensitivity to NO and PGI2 is noteworthy, since both molecules released by the endothelium retard platelet activation; thus, an impaired response is associated with enhanced platelet reactivity [42].

As mentioned previously, patients with type 2 diabetes exhibit progressive pancreatic β-cell apoptosis. A consequence of β-cell apoptosis is absolute deficiency of insulin. Accordingly, the relative deficiency of insulin imparted by insulin resistance is magnified by the superimposition of insulin deficiency. Platelet reactivity that is increased in obese subjects manifesting insulin resistance will be greater when type 2 diabetes is manifest and accompanied by absolute deficiency of insulin [43].

Associated Metabolic Conditions

Several metabolic conditions associated with type-2 DM may contribute to the enhanced platelet reactivity observed in these patients, including obesity, dyslipidaemia and increased systemic inflammation [42].

Obesity is a common feature in patients with type-2 DM, and obesity itself may be associated with some degree of insulin resistance, which has relevant implications for platelet reactivity as described above. Nevertheless, other factors present in obese subjects may account for platelet dysfunction, which include: a) elevated platelet count and high mean platelet volume, which is related with platelet reactivity and has prognostic implications in atherothrombotic processes such as stroke and ACS; b) higher serum leptin concentration, which is associated with increased platelet aggregability; c) greater cytosolic calcium concentration, which also boosts platelet reactivity; and d) increased oxidative stress. Overall, these metabolic abnormalities caused by obesity ultimately lead to enhanced platelet reactivity [42].

One feature of diabetes is the presence of dyslipidemia which is characterized by high plasma triglyceride concentration, reduced high density lipoprotein (HDL) concentration, and increased concentration of low-density lipoprotein (LDL) [44]. There is evidence that dyslipidemia contributes to the diabetes associated platelet hyperactivation. By binding to a pertussis sensitive G-protein coupled receptor on platelets, LDL induces an increase in cytosolic [Ca2+]i, IP3 formation and activation of PKC [37]. However, the pro-thrombotic properties of LDL seem to be rather associated to its oxidation. Indeed, oxidized LDL can directly interact with platelets specific receptors such as the lectin like oxidized LDL receptor-1 or the CD36. The latter involves the activation of the MAPK c-Jun N-terminal kinase (JNK)2 and its upstream activator MKK4. Not only are platelets activated by ox-LDL but activated platelets are also known to be able to form ox-LDL via platelet gp91phox (NOX2)-dependent ROS generation suggesting the contribution of platelets to circulating ox-LDL. The formed ox-LDL has been demonstrated to be either uptaken by monocytes [37] or amplify platelet activation [45]. On the molecular levels, LDL activates the platelet arachidonic acid signalling cascade, i.e phosphorylation of p38 MAPK and cytosolic phospholipase A2, leading to increased TXA2 formation [46]. Interestingly, there is less information on the direct effects of triglycerides on platelets. However, the link between hyperlipidemia and platelet hyperactivation is supported by the fact that lipid-lowering agents possess anti-thrombotic properties [37].

Thrombosis that entails platelet activation is intimately intertwined with inflammation. People with diabetes exhibit increased markers of both platelet activation and inflammation. In particular, cross-talk between platelets and leukocytes amplifies leukocyte activation both by platelet activation and by platelet reactivity. For example, the release of platelet-activating factor by leukocytes primes platelets for activation and increases the extent to which they activate in response to other agonists. An additional mechanism by which inflammation can increase platelet reactivity is by increasing expression of proteins that participate in the activation of platelets. For example, subjects with diabetes exhibit increased expression of Fcy receptor type IIa (FcyRIIa) and associated increased platelet activation in response to collagen. Inflammation appears to increase expression of FcyRIIa, and attenuation of inflammation decreases expression of FcyRIIa. Thus, inflammation that accompanies diabetes contributes to increased platelet reactivity that, in turn, contributes to greater inflammation [43].

Other Cellular Abnormalities

The roles of other platelet anomalies common in DM patients that may account for the global hyperreactivity status, includes dysregulation of calcium metabolism, oxidative stress, upregulation of P2Y12 signalling pathway and accelerated platelet turnover [42].

Impaired regulation of calcium metabolism that leads to increased intracellular calcium levels is a major feature of platelets from patients with DM. The mechanisms involved in calcium signalling abnormalities present in DM are not fully elucidated. Factors that have been proposed to play a role in impaired calcium homeostasis and, therefore, in platelet hyperreactivity are: a) excessive influx of calcium through the sodium/calcium exchanger; b) changes in the activity of calcium ATPases; c) impaired sensitivity to insulin, which decreases sarcoplasmic endoplasmic reticulum calcium-ATPase (SERCA-2); and d) augmented oxidative stress, which enhances calcium signalling due to increased formation of superoxide anions and reduced nitric oxide production. The final result of this altered calcium homeostasis is an augmented concentration of cytosolic calcium, which leads to enhanced platelet reactivity and aggregation [42].

With an over production of reactive oxygen and nitrogen species and potent radicals, such as hydrogen peroxide and superoxide anion, that can directly lead to platelet activation. DM patients have higher levels of 8-iso-prostagland in F2α (8-iso-prostane), a product of non- enzymatic arachidonic acid peroxidation and marker of oxidative stress, particularly in association with acute hyperglycemic episodes. Oxidative stress can directly affect platelet reactivity as superoxide anions enhance intraplatelet calcium release upon platelet activation, helping to amplify the platelet aggregation response. The reactive oxygen species enhance the interaction of sugars with proteins during recurrent episodes of hyperglycemia and increase the rate of accumulation of previously mentioned advanced glycation end products (AGEs). These products can interact with AGE receptors (RAGEs) on the endothelium inducing endothelial dysfunction and an inflammatory response. Normal endothelium produces nitric oxide (NO) and prostacyclin which inhibit platelet activation under physiological conditions. Endothelial dysfunction leads to reduced productionon NO and prostacyclin and so contributes to platelet hyper reactivity. NO can be oxidized by superoxide anions, leading to further reductions in its half-life and antiplatelet action [41]. Platelet function can be impaired by alterations in vascular redox status and reactive oxygen species. Diabetes mellitus (DM) is linked to oxidative stress, overproduction of reactive oxygen and nitrogen species, and reduced platelet antioxidant levels. This leads to increased platelet activation, AGE production, and impaired endothelial function, particularly in patients with DM who have diminished sensitivity to vasodilator molecules [42].

The platelet adenosine diphosphate (ADP) P2Y12 receptor signalling pathway has been suggested to be upregulated in diabetic platelets, in particular those with type-2 DM. This suppresses cAMP concentration and, in addition to a lower responsiveness to insulin, leads to increased adhesion, aggregation, and procoagulant activity. Another abnormality in platelet surface molecules is the increased expression of surface proteins such as P-selectin and glycoproteins Ib and IIb/IIIa, which are integrins that mediate adhesion [42].

An accelerated platelet turnover represented by the presence of a higher number of reticulated platelets has been observed in patients with DM. Reticulated platelets are larger and more sensitive, resulting in platelet hyperreactivity and lower response to antiplatelet therapies including aspirin and clopidogrel. In addition, platelets of DM patients are larger, and thus hyperreactive, as platelet size correlates with greater platelet reactivity measured by aggregation and total release of granular content [42].

COMPLICATIONS OF DIABETES MELLITUS

Diabetes is a disease that is strongly associated with both macrovascular complications, including ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, and micro vascular complications, including nephropathy, retinopathy, and neuropathy. This results in organ and tissue damage in approximately one-third to one-half of patients with diabetes [47].

Macrovascular Complications

Macrovascular complications comprise a group of large blood vessel diseases that occur in diabetic patients. In comparison with non-diabetics, the risk of cardiovascular disease in diabetic patients is four times higher. Coronary artery, cerebrovascular, and peripheral vascular diseases are categorized as macrovascular complication [48].

1. Myocardial infarction (MI)

The risk for a first myocardial infarction (MI) in patients with diabetes is five times greater than in a population with similar risk factors but without diabetes. The risk for a recurrent MI is twice as high than people who previously had an MI but who do not have diabetes. After sustaining a MI, patients with diabetes have a poorer long-term prognosis, increasing the risk for congestive heart failure and death [47].

2. Cerebrovascular disease

Several studies indicated that cognitive dysfunction occurs in T2DM affecting intelligence, attention, memory, learning, and perception [49]. The presence of diabetes adversely affects cerebrovascular circulation by increasing the risk of intracranial and extracranial atherosclerosis [47].

3. Peripheral artery disease

Peripheral artery disease (PAD) is characterized by stenosis and/or occlusion of the lower-extremity arteries. PAD, like the aforementioned vascular diseases, is related to the duration and severity of diabetes. As in other diabetes-related complications, hyperglycemia, specifically glycosylated hemoglobin (HbA1c), appears to be a significant factor in the development of PAD. Sakran *and colleagues* stated that with every 1% increase in HbA1c, there was a 28% increase in the risk of PAD in the United Kingdom Prospective Diabetes Study (UKPDS) [47].

Microvascular Complications

Damage to small vessels (capillaries) during high blood glucose levels can cause microvascular complications in tissues where glucose uptake is independent of insulin such as with neurons, the kidneys, and retina. Hyperglycemia, as the most important risk factor in diabetics, can cause neuropathy, nephropathy, and retinopathy by different mechanisms. Some of these mechanisms are more important in specific complications. Here, we classify microvascular complications into three categories retinopathy, neuropathy, and nephropathy [48].

1. Diabetic Retinopathy: Diabetic retinopathy is the leading cause of blindness in adults. There are two types, non-proliferative diabetic retinopathy (early stage usually left untreated) and proliferative retinopathy (more advanced and usually treated with laser surgery). The deterioration or alteration of small blood vessels in the eye result in loss of vision or blindness [50]. In uncontrolled diabetes, the high blood glucose level in the delicate vessels of the retina increases osmotic pressure, and the vessels get leaked or rupture in some instances resulting in an impaired supply of blood to the retina. To compensate for the ruptured retinoid vessels, collateral blood vessels grow out of the retina and cause scar tissue to form resulting in impaired vision [49].

The earliest pathologic changes associated with retinopathy are termed mild non-proliferative diabetic retinopathy. In type 1 patients, these changes generally begin no sooner than 5 years after diagnosis. The first signs of mild non-proliferative diabetic retinopathy are microaneurysms, which arise most often in areas of capillary occlusion. Subsequently, increasing vascular permeability leads to retinal blot hemorrhages (round, with blurred edges) and hard exudates (sharply defined and yellow). Infarctions of the nerve fiber layer, known as soft exudates or cotton-wool spots, appear as white or gray, rounded swellings. At this early stage of retinopathy, visual acuity is generally unaffected, and the risk of progression to high-risk proliferative diabetic retinopathy is about 15% at 5 years [51].

Proliferative diabetic retinopathy involves neovascularization the growth of fine tufts of new blood vessels and fibrous tissue from the inner retinal surface or the optic head. Early proliferative changes are confined to the retina, but later invasion of the vitreous body constitutes high-risk proliferative diabetic retinopathy; during this end stage, fibrosis and contracture of the neovasculature result in retinal detachment and hemorrhage, the most important determinants of blindness. On occasion, new vessels can invade the iris and anterior chamber, leading to sight-threatening closed-angle glaucoma [51].

2. Diabetic Neuropathy: Damage from hyperglycemia to peripheral nerves, including sensory, autonomic, and motor neurons, can cause neuropathy. Hyperglycemia, disease duration, and genetic factors can increase the risk of this complication. Peripheral neuropathy can be characterized by axonal thickening, axonal loss, loss of microfilaments, neural demyelination, and neural death [48].

By far the most common diabetic neuropathies are chronic sensorimotor distal symmetric polyneuropathy (DPN) and cardiac autonomic neuropathy. DPN is a length-dependent dying back axonopathy, primarily involving the distal portion of the longest myelinated and unmyelinated sensory axons, with relative sparring of motor axons. Therefore, DPN initially affects the distal parts of the lower extremities. With disease progression, sensory loss ascends in the legs and it appears in the hand, causing the typical stocking and glove sensory loss [52].

3. Diabetic Nephropathy (DN): Diabetic nephropathy is a syndrome comprising of persistent proteinuria, hypertension and a low glomerular filtration rate (GFR) [52]. Diabetic nephropathy is characterized by loss of glomerular filtration rate, albuminuria (>300 mg/day), and damage to glumeruli. Diabetic nephropathy can be seen in about 30-40 % of diabetics. Hyperglycemia, hypertension, and hyperlipidemia are the main metabolic risk factors that increase kidney disease by several known metabolic pathways [48]. This life-threatening complication is the leading cause of end-stage renal disease (ESRD). Approximately 40 percent of Type1 diabetics with a diagnosis of 20+ years develop this complication. 5 to 10 percent of Type 2 diabetics are affected with diabetic nephropathy. The first sign of diabetic nephropathy may be protein present in urine [50]. In total, 25-45% of Type1 DM patients develop nephropathy in their lifespan. The peak time to develop nephropathy is 10-15 years from onset of disease. In patients with type2 DM, the prevalence of nephropathy is reported to be lower [52].

4. Diabetic foot: The diabetic foot is characterized by slowly healing plantar ulcers that result from apparently insignificant trauma. Left untreated, superficial ulcers may penetrate to underlying tissues, leading to complications including cellulitis, abscess formation, joint sepsis, and osteomyelitis. Gangrene may occur, and amputation may be required. In advanced cases, abnormal

loading of the foot can result in repeated painless fractures and the displacement of normal joint surfaces, producing the so-called Charcot foot or Charcot joint [51].

MANAGEMENT AND TREATMENT

It was thought that once a patient is diabetic, he/she is diabetic for a lifetime; however, DM can go into remission. Diabetes can be controlled by changing diet, doing physical exercise, maintaining reasonable body weight, monitoring lipid profile, and having appropriate medication when necessary. Changing diet is effective in controlling diabetes. Taking low glycemic food, complex carbohydrate, protein, and polyunsaturated fatty acid (PUFA) and fiber can help to maintain normal blood sugar. Moderate exercise which decreases obesity helps lowering blood glucose levels through insulin-independent glucose transport into the muscle [49].

1. Pharmacological interventions such as;

i. Metformin: it is one of the most popular and common medications prescribed to delay the onset of diabetes. Metformin belongs to the biguanide class of antidiabetic medication. Metformin decreases fasting plasma glucose (PG) concentration and A1c by suppressing liver glucose production (hepatic gluconeogenesis) or by restoring βcell function [53].

ii. Thiazolidinediones: it targest PPAR-γ. PPAR-γ are ligand activated transcription factors and activation of PPAR-γ results in insulin sensitization and increases glucose metabolism. Thiazolidinedione work by making the adipocytes, liver and muscle cells more sensitive to insulin and by conserving the β-cell function [53].

iii. Incretin-Based Therapies: Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies which are to target this previously unrecognized feature of DM pathophysiology resulting in sustained improvements in glycemic control and improved body weight control [54].

iv. Insulin: Insulin is used alone or in combination with oral hypoglycemic agents. Augmentation therapy with basal insulin is useful if some beta cell function remains. Replacement of basal-bolus insulin is necessary if beta cell exhaustion occurs [54].

v. Dipeptidyl-Peptidase IV Inhibitors: Dipeptidyl-peptidase (DPP) IV inhibitors inhibit dipeptidyl peptidase-4 (DPP-4), a ubiquitous enzyme that rapidly inactivates both GLP-1 and GIP, increase active levels of these hormones and, in doing so, improves islet function and glycemic control in type 2 DM [54].

2. Lifestyle changes: the two most important lifestyle interventions in the management of diabetes are diet and exercise. Diet and exercise contribute importantly to the care of patients with type 1 diabetes. Patients should be educated about balancing calorie intake (diet) with energy expenditure (exercise), and they should understand the basic concepts of insulin therapy as it relates to stress and physical activity. If they are properly managed and sufficiently motivated, diabetic patients should be able to consume the foods they enjoy and participate fully in exercise and sports [51].

3. Monitoring

i.Self-Monitoring of Blood Glucose Concentration: Self-monitoring of blood glucose concentration has revolutionized the management of diabetes. it actively involves patients in the treatment process, allows more rapid treatment adjustment, and reinforces dietary changes [51].

ii. Continuous Glucose Monitoring [51].

iii. Glycohemoglobin: Gycohemoglobin (glycosylated hemoglobin) assays have emerged as the goldstandard" for long term glycemic control. The test does not rely on a patient ability to self-

monitor blood glucose levels and is not influenced by acute glycemic changes or by recent meals [51].

4. Surgical therapy

i. Bariatric surgery: Bariatric surgery mainly works by targeting the calorie intake of the subject which ultimately results in weight loss. As reviewed by Bansal, the most common modalities under bariatric surgery include Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, sleeve gastrectomy, and duodenal switch with bilio pancreatic diversion [53].

ii. Pancreas and Islet transplantation: Pancreas transplantation is conceptually promising in this regard; with growing experience in recent years, there have been substantial improvements in the outcome of pancreas transplantation surgery. Unfortunately, because of the need for long term immunosuppression, pancreas transplantation is currently an option for only a select group of patients, mainly type 1 diabetic patients who already require immunosuppression for a renal allograft [51].

Conclusion

Platelet dysfunction in diabetes mellitus is a multifaceted issue with significant implications for vascular health. The interplay of hyperglycemia, oxidative stress, abnormal lipid profiles, endothelial dysfunction, inflammation, and medications can collectively disrupt platelet function. This dysfunction not only raises the risk of thrombosis and cardiovascular complications but also underscores the importance of comprehensive diabetes management. By controlling blood sugar levels, addressing associated risk factors, and working closely with healthcare providers, individuals with diabetes can mitigate the adverse effects of platelet dysfunction and reduce the likelihood of cardiovascular events.

Conflict of Interest: The authors have declared no conflict of interest.

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