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PERSPECTIVE PAPER

TYPE 2 DIABETES MELLITUS, PLATELET ACTIVATION AND ALZHEIMER'S DISEASE: A POSSIBLE CONNECTION

Manuel Glauco Carbone, Nunzio Pomara, Camilla Callegari, Donatella Marazziti, Bruno Pietro Imbimbo

Abstract

Type 2 diabetes mellitus DM (T2DM) is associated with a 70% increased risk for dementia, including Alzheimer's disease (AD). Insulin resistance has been proposed to play a pivotal role in both T2DM and AD and the concept of "brain insulin resistance" has been suggested as an interpretation to the growing literature regarding cognitive impairment and T2DM. Subjects with T2DM present an abnormal platelet reactivity that together with insulin resistance, hyperglycaemia and dyslipidaemia effect the vascular wall by a series of events including endothelial dysfunction, oxidative stress and low-grade inflammation. Activated platelets directly contribute to cerebral amyloid angiopathy (CAA) by promoting the formation of β-amyloid (Aβ) aggregates and that Aβ, in turn, activates platelets, creating a feed-forward loop suggesting the involvement of platelets in the AD pathogenesis. Moreover, islet amyloid polypeptide deposition, co-localized with Aβ deposits, is a common finding in the brain of patients with T2DM. These observations raise the intriguing prospect that traditional or novel antiplatelet therapeutic strategies may alleviate fibril formation and could be used in the prevention or treatment of AD subjects with diabetes.

Key words: type 2 diabetes mellitus, Alzheimer's disease, platelet activation, β-amyloid, perivascular inflammation, neuroinflammation

Manuel Glauco Carbone[1,2], M.D.
Nunzio Pomara[3], M.D. (Nunzio.Pomara@nki.rfmh.org),
Camilla Callegari[1], M.D. (camilla.callegari@uninsubria.it),
Donatella Marazziti[2,4], M.D., (dmarazzi@psico.med.unipi.it),
Bruno Pietro Imbimbo[5], Ph.D., (B.Imbimbo@chiesi.com).

[1] Department of Medicine and Surgery, Division of Psychiatry, University of Insubria, Viale Luigi Borri 57, 21100 Varese, Italy
[2] Pisa-School of Experimental and Clinical Psychiatry, University of Pisa, Italy Via Roma 57, 56100.
[3] Geriatric Psychiatry Department, Nathan Kline Institute, and Departments of Psychiatry and Pathology, NYU Grossman School of Medicine, 140 Old Orangeburg Road Orangeburg, New York 10962.
[4] Saint Camillus International University of Health and Medical Sciences - UniCamillus - 00131 Rome, Italy.
[5] Research & Development Department, Chiesi Farmaceutici, Parma, Italy.

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Corresponding author
Manuel Glauco Carbone
E-mail: manuelglaucocarbone@gmail.com

1. Introduction

Diabetes mellitus (DM), defined by elevated glycemic markers, has reached an epidemic level worldwide and its prevalence continues to climb. Findings from the 10th edition of the International Diabetes Federation Atlas confirm that diabetes is one of the fastest growing global health emergencies of the 21st century. In 2021, it is estimated that 537 million people have diabetes, and this number is projected to reach 643 million by 2030, and 783 million by 2045. In addition, 541 million people are estimated to have impaired glucose tolerance in 2021 (International Diabetes Federation, 2021).

There are three main types of diabetes mellitus:

- Type 1 diabetes (T1DM) is characterized by an inability of the pancreas to produce sufficient amounts of insulin due to apoptosis mechanisms of the β-cells, assigned to secrete this hormone (Chwalba et al., 2021). Once known as "juvenile diabetes", it affects about 3-5% of people with diabetes and generally occurs in childhood or adolescence but can also occur in adults (International Diabetes Federation, 2021). Factors triggering apoptosis processes are very diverse and currently not fully explained. Genetic and environmental factors would seem to induce a specific autoimmune response against β-cells, confirmed by the appearance of autoantibodies in the blood, that leads to an absolute insulin deficiency (Roep et al., 2016; Xie et al., 2014;

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Zheng et al., 2017).

- Type 2 DM (T2DM) is the most prevalent form of diabetes and accounts for approximately 90-95% of the total diabetes cases (International Diabetes Federation, 2021). T2DM is characterized by progressive insulin deficiency and impairment of β-cell function, superimposed on insulin resistance (Aviles-Santa et al., 2020; Eizirik et al., 2020; Saeedi et al., 2019).
- Gestational diabetes mellitus (GDM) is the third main form and has been defined as any degree of glucose intolerance with an onset, or first recognition during pregnancy (Alfadhli, 2015). In women with gestational diabetes, blood sugar usually returns to normal soon after delivery (Lende & Rijhsinghani, 2020). However, there is a higher risk of suffering from T2DM if you have had GDM (Mack & Tomich, 2017).

Considering T2DM, it is a multisystem disease associated with both micro-vascular and macro-vascular complications (Chawla et al., 2016). It is generally associated with an increased incidence (two to fourfold) of ischemic cardio- and cerebro-vascular events (Dal Canto et al., 2019). Insulin resistance, hyperglycemia, and release of excess free fatty acids, along with other metabolic abnormalities affects vascular wall by a series of events including endothelial dysfunction, platelet hyperactivity, oxidative stress and low-grade inflammation (Kaur et al., 2018). Interestingly, not only long-term, continuous hyperglycemia but also transient, acute hyperglycemic spikes may contribute to the enhanced risk of stroke, amputation, and death (Hanssen et al., 2020). Platelet hyper-responsivity has been identified as one of the mechanisms of enhanced arterial thrombosis in T2DM; specifically, an acute, short-term hyperglycemia enhances platelet activation and, in particular, high-shear stress-induced activation (Gresele et al., 2010). Excessive platelet activation may play a key role in the pathogenesis of first or subsequent transient ischemic attack or stroke (Kinsella et al., 2013), perivascular or inflammatory diseases (Berbudi et al., 2020; Kannan et al., 2019) and also neurodegenerative disorders (Hassan et al., 2020; Randriamboavonjy et al., 2014; Rawish et al., 2020; Umegaki, 2012).

Alzheimer's disease (AD), the most common neurodegenerative disease (Santiago & Potashkin, 2021), is characterized by neurotoxic β-amyloid (Aß) plaque formation in brain parenchyma and cerebral blood vessels known as cerebral amyloid angiopathy (CAA) (Vickers et al., 2016). Besides CAA, AD is strongly related to vascular diseases such as stroke and atherosclerosis. As already said, platelets are not only the major players in haemostasis and thrombosis processes, but they were the peripheral primary source of Aß peptides (Chen et al., 1995). Considering these observations, it appears tempting to hypothesize that platelets could be the link between T2DM, vascular risk factors/atherosclerosis and AD.

1.1 Type 2 Diabetes Mellitus and Alzheimer's dementia

T2DM is associated with a 70% increased risk for dementia (Gudala et al., 2013). A recent large longitudinal cohort study with a median follow-up of 32 years has shown that younger age at onset of diabetes was significantly associated with higher risk of subsequent dementia (Barbiellini Amidei et al., 2021). Insulin resistance has been proposed to play a pivotal role in both type 2 diabetes and AD (Sebastiao et al., 2014). The concept of 'brain insulin resistance' has been proposed as a potential interpretation to the growing literature regarding cognitive impairment and neuropathological abnormalities in T2DM, obesity, and insulin resistance (Arnold et al., 2018). A large study has shown that cognitively normal subjects with untreated diabetes present greater tau pathology than both treated diabetics and normoglycemic subjects, and that they progress to dementia at significant higher rates than controls (McIntosh et al., 2019; Reddy et al., 2017). This suggests that abnormal glucose metabolism may drive AD pathogenesis (Chen et al., 2011; Kuehn, 2020).

Insulin resistance, hyperglycaemia and the release of excess free fatty acids, along with other metabolic abnormalities effects the vascular wall by a series of events including endothelial dysfunction, platelet hyperreactivity, oxidative stress and low-grade inflammation (Freeman & Pennings, 2021; Grandl & Wolfrum, 2018). These events further enhance vasoconstriction and promote thrombus formation, ultimately resulting in the development of atherosclerosis (Faselis et al., 2020; Sapra & Bhandari, 2021). Atherothrombosis, the result of the progression of atherosclerosis, and its major manifestations (cerebro- and cardiovascular strokes, myocardial infarction and peripheral arterial ischemia) account for the 80% of deaths in these patients (Gu et al., 1998; Kautzky-Willer et al., 2016; Martin-Timon et al., 2014).

It is well known that platelet hyperactivity plays a pivotal role in the initiation and progression of atherosclerosis processes, generating a prothrombotic and proinflammatory state (Badimon et al., 2012; Borchers & Pieler, 2010; Bray, 2007; Gaiz et al., 2017; Lebas et al., 2019).

Platelets obtained from T2DM are hyperactive and demonstrate exaggerated aggregation and adhesion as well as thrombus generation (Chen et al., 2017; Eibl et al., 2004; Ferreiro et al., 2010; Kakouros et al., 2011; Pretorius et al., 2018; Rodriguez & Johnson, 2020; Yngen et al., 2004; Zhu et al., 2012). There are many different consequences that have been attributed to the diabetes-associated enhanced platelet activation, such as a loss of the anti-platelet effect of insulin, insulin resistance, hyperglycaemia, oxidative stress, elevated vascular shear forces, increased binding of fibrinogen, altered expression of glycoprotein receptors, proteins attached to the platelet surface, obesity, dyslipidaemia and increased systemic inflammation (Baghersalimi et al., 2019; Hu et al., 2017; Kaur et al., 2018; Pretorius, 2019; Randriamboavonjy, 2015; Schneider, 2009; Vaidyula et al., 2006).

1.2 Insulin resistance and platelet activation

Insulin, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-2 (IGF-2) exert their actions through structurally similar receptors, including insulin receptor isoforms (IRs) and IGF-1-receptor (IGF1R) (Belfiore et al., 2017; Ullrich et al., 1985). Platelets express this receptor pool and its functions are directly regulated by insulin, thus raising the possibility that platelets may be sites of insulin resistance (Hunter & Hers, 2009).

In the prediabetic stage this insulin resistance is initially associated with a compensatory increase in insulin production by pancreatic β-cells sufficient to maintain fasting euglycemia. In susceptible individuals, the pancreatic β-cells under the increased demand, undergo apoptosis leading to a reduction in β-cell

mass (Weir & Bonner-Weir, 2004). Consequently, the hyperinsulinemia characteristic of the early stages of DM2 progressively gives way to a related and eventually absolute insulin deficiency.

Several studies showed that insulin inhibits platelet aggregation, impairs the interaction with collagen and also reduces its sensitivity to proaggregants (Ferreira et al., 2006; Hers, 2007; Hiramatsu et al., 1987; Westerbacka et al., 2002). Firstly, insulin decreases thrombin-induced increase in Ca2+ and attenuates agonist-induced platelet aggregation (Randriamboavonjy, 2015). Insulin also mediates the anti-platelet effect by activation of the AMP-activated protein kinase (AMPK) and the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway inducing inhibition of aggregation and promoting synthesis of nitric oxide, cyclic GMP, and cyclic AMP (Ceriello et al., 1995; Jones, 1985; Kahn et al., 2003; Rauch & Nemerson, 2000; Trovati et al., 1994; Vaidyula et al., 2006).

At the same time, insulin decreases the release of proaggregatory factors in healthy non-obese subjects, an effect that is blunted in obese individuals, which induces plasminogen activator secretion and increases expression of prostaglandin I2 (PGI2) (Westerbacka et al., 2002). Moreover, in non-diabetic obese women, there is a direct correlation between platelet reactivity assessed by thromboxane A2 generation and insulin resistance (Basili et al., 2006). Insulin binding to IR activates insulin receptor substrate 1 (IRS-1) via tyrosine phosphorylation and mediates its association with Giα-subunit. This leads to decreased activity of Gi that results into decreased platelet activity (Ferreira et al., 2004; Trovati et al., 1997).

T2DM patients have a loss of responsiveness to insulin that leads to increased platelet reactivity and reduced response to antiplatelet agents (Marin et al., 2009).

All of these considerations imply that an impaired platelet response to insulin is often present in T2DM subjects and may lead to an abnormal platelet reactivity.

1.3 Hyperglycaemia and platelet activation

Hyperglycaemia contributes to greater platelet reactivity through direct effects and by promoting glycation of platelet proteins (Lee & Bergmeier, 2017).

Hyperglycaemia, inducing nonenzymatic glycation of proteins on the platelet surface, decreases membrane fluidity and increases platelet reactivity (Watala et al., 1998; Winocour et al., 1992). This hyper-reactivity may be further enhanced by the osmotic effect of glucose which promotes the expression of platelet GP IIb/IIIa, P-selectin and CD40 ligand as well as soluble markers (sP-selectin) (Ghoshal & Bhattacharyya, 2014; Keating et al., 2003; Undas et al., 2008; Vaidyula et al., 2006; Yngen et al., 2001).

Chronic and acute hyperglycaemia is able to increase the expression and/or activity of protein kinase C (PKC) (Assert et al., 2001), a central kinase in the regulation of platelet activity. In addition, hyperglycaemia induces a coagulated state by increasing the release of prothrombotic molecules like von Willebrand factor (vWF) and tissue factor, while inhibiting fibrinolysis by raising plasminogen activator inhibitor-1 (PAI-1) concentration (Boden & Rao, 2007; Kessler et al., 1998).

Many of these deleterious glucose-induced effects have been attributed to its metabolite methylglyoxal (MG), a highly reactive dicarbonyl metabolite that is generated endogenously by the nonenzymatic degradation of the glycolytic intermediates (Thornalley, 1993). MG as well as the related advanced glycation end-products (AGEs) through the action on the AGE receptor (RAGE) expressed on platelet surface, increases the plasmatic level of several platelet activation markers such as CD 31, CD49b and CD63 (Gawlowski et al., 2009). Moreover, it was found that glycated haemoglobin (HbA1C) levels and fasting glucose were significantly correlated with P-selectin and CD63 platelet expression (Eibl et al., 2004; Kakouros et al., 2011). Finally, when hyperglycaemia aldose reductase activity increases significantly, it leads to abnormal activation of the polyol pathway and enhanced oxidative and osmotic stress (Tang et al., 2011). In turn aldose reductase increases thromboxane formation and platelet activation (Tang et al., 2011).

1.4 Oxidative stress and platelet activation

Superoxide is considered to be a major factor in oxidant toxicity, and it has been shown to increase platelet reactivity through different mechanisms (Freedman, 2008; Handin et al., 1977). It may increase platelet activity and facilitate platelet aggregation response by enhancing intraplatelet release of calcium after activation (Freedman, 2008). Superoxide increases the production of F2 isoprostanes, which in turn enhance platelet response to agonists. In addition, superoxide limits the biologic activity of NO (Freedman, 2008; Schaeffer et al., 1999) reducing the activity of eNOS. Oxidative stress impairs endothelial function and decreases the production of prostacyclin (Schaeffer et al., 1999). Additionally, superoxide increases signalling of many platelet receptors (Masselli et al., 2020).

The association of T2DM with increased systemic inflammation is well known (Tsalamandris et al., 2019). In T2DM, increased levels of inflammatory markers were observed in comparison with healthy controls (Lim et al., 2004). Inflammatory processes increase the expression of Fcγ receptor type IIa (FcγRIIa), which induces increased platelet activation in response to collagen (Belostocki et al., 2008; Calverley et al., 2003) while attenuation of inflammation decreases expression of FcγRIIa (Belostocki et al., 2008).

Moreover, crosstalk between platelets and leukocytes amplifies leukocyte activation both by platelet activation and by platelet reactivity (Stratmann & Tschoepe, 2005). 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 (Keating & Schneider, 2009).

Therefore, oxidative stress that is associated with diabetes promotes platelet hyperreactivity and inflammation that very often accompanies diabetes and contributes to increased platelet reactivity that, in turn, may further accentuate the inflammatory process.

Elevated shear forces caused by narrowing of the vascular lumen, typical of the micro and macroangiopathic processes of subjects with diabetes, were found to increase platelet aggregability (Rana et al., 2019). High shear forces result in higher downstream platelet adhesion onto three different platelet agonists: fibrinogen, collagen, or von Willebrand Factor (vWF).

Generally, αIIbβ3-fibrinogen-dominated platelet aggregation occurs mainly under low shear rates while the bonds were stabilized by soluble agonists that maintain the activated state of integrins (Rana et al., 2019). At increasing shear range, platelet-platelet interactions become increasingly dependent on vWF and its binding with both αIIbβ3 and GPIbα receptors

(Jackson et al., 2009; Ruggeri et al., 2006). On the other hand, at pathological shear rates, initial aggregation exclusively relies upon vWF-GPIbα bonding, resulting in dominating platelet-platelet interactions that induce "large rolling aggregates" onto immobilized vWF (de Man et al., 2000; Rana et al., 2019). Under extreme shear conditions, enhanced inter-platelet interactions result in a growing transient aggregate (Rana et al., 2019).

P-selectin, GPIIb/IIIa, lysosomal glycoprotein, and phosphatidylserine significantly increased after transient exposure to elevated upstream wall shear strain rates (Rahman & Hlady, 2019).

Definitely, high shear forces induced by the architecture of large thrombi create a feed-forward mechanism that can precipitate occlusive thrombus formation (Rana et al., 2019).

1.5 Obesity and platelet activation

Obesity is a common feature of patients with T2DM and can induce various metabolic abnormalities (count and mean volume of platelets) or exacerbate insulin resistance (Ferreiro et al., 2010; Ferroni et al., 2004; Gaiz et al., 2017; Muscari et al., 2008).

Previous studies involving subjects with central obesity showed that weight loss re-established sensitivity for NO and PGI2 and decrease platelet activation (Russo et al., 2010). Insulin sensitization by pioglitazone in obese women decrease platelet activation (Basili et al., 2006; Kahn & Flier, 2000; Murakami et al., 2007). Moreover, obese patients were reported to have increased plasma CD40L and elevated levels of derived microparticles.

One feature of T2DM is the presence of dyslipidaemia which is characterized by high plasma triglyceride concentration, reduced high density lipoprotein (HDL) concentration, and increased concentration of low density lipoprotein (LDL) (Chehade et al., 2013).

Dyslipidaemia contributes to the diabetes-associated platelet hyperactivation (Randriamboavonjy, 2015).

By binding to a pertussis sensitive G-protein coupled receptor on platelets, LDL induces an increase in intracellular Ca^{2+}, IP3 formation, and activation of PKC (Pedreno et al., 2001). Low HDL-C was observed to be associated with endothelial dysfunction in T2DM patients, leading to increased atherosclerosis (Kuhn et al., 1991).

Furthermore, oxidized-LDL can directly interact with platelets specific receptors such as the lectin-like oxidized LDL receptor-1 or the CD36 that amplify platelet activation (Carnevale et al., 2014; Chen et al., 2008; Chen et al., 2001; Podrez et al., 2007). On the molecular level, LDL activates the platelet arachidonic acid signalling cascade, i.e phosphorylation of p38 MAPK and cytosolic phospholipase A2, leading to increased TXA2 formation (Colas et al., 2011).

Enhanced platelet activity in hypertriglyceridemia may be related to changes in the lipid composition of platelet membranes. Higher plasma cholesterol levels have been shown to decrease the platelet membrane fluidity and these cholesterol-enriched rigid platelet membranes show an enhanced platelet responsiveness by increasing the number and affinity of platelet thrombin receptors (Malle et al., 1991; Shattil & Cooper, 1976; Tandon et al., 1983). Moreover, VLDL may influence the platelet activation status by changing the conformation of the GPIIb-IIIa complex via apoB-100 (Mahley et al., 1979; Mochizuki et al., 1996; van Willigen et al., 1994). At the same time, the VLDL-induced effect might be regulated also by its apolipoprotein E (apoE) content. In fact, apoE-VLDL-rich fractions caused antiaggregative effects, whereas apoE-VLDL-poor fractions produced a strong proaggregative response (de Man et al., 2000; Olufadi & Byrne, 2006; Pedreno et al., 2000). Along with platelet activation, vLDL particles also impair fibrinolysis and disturbs coagulation cascade thus resulting in atherothrombotic risk (Olufadi & Byrne, 2006).

2. Conclusions

A large body of experimental evidence has emerged that highlights the importance of platelets in modulating immune and inflammatory responses. Experimental studies have shown that activated platelets directly contribute to cerebral amyloid angiopathy (CAA) by promoting the formation of β-amyloid (Aβ) aggregates and that Aβ, in turn, activates platelets, creating a feed-forward loop (Donner et al., 2016). The potential involvement of platelets in the pathogenesis of AD raises the intriguing prospect that antiplatelet therapy may alleviate fibril formation in cerebral vessels of AD patients. However, it is important to point out that clinical studies so far have not demonstrated any benefit of antiplatelet therapy using aspirin in patients with established AD (Bentham et al., 2008; Ryan et al., 2020). The appearance of amyloid deposits as a consequence of misfolded proteins is not restricted to AD but is a common finding in a range of pathologies, including diabetes and atherosclerosis (Herczenik et al., 2007). Neuropathological studies have shown that islet amyloid polypeptide deposition, co-localized with Ab deposits, is a common finding in the brain of patients with T2DM (Pruzin et al., 2018). Given the global epidemic of diabetes and cardiovascular disease, in conjunction with the limited efficacy of treatments for AD, it is worth to perform future investigations that will shed new light on the role of platelets in the pathogenesis of AD in subjects with diabetes. Most importantly, unfolding these mechanisms may herald the development of novel therapeutic strategies in the prevention or treatment of dementia in subjects with diabetes.

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