Investigating the Impact of Oral Anti-Diabetic Agents on Hemostasis in Diabetes Mellitus

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Citation: Rohan K. Bhattacharya, Shruti P. Nair, Shraddha R. Joshi, Aashna S. Kale (2025). Investigating the Impact of Oral Anti-Diabetic Agents on Hemostasis in Diabetes Mellitus. Psychiatria, 17(11), 10-26. https://doi.org/10.5281/zenodo.19096630

ABSTRACT

Thrombotic events in diabetics contribute for almost 65-80% of cardiovascular events. Diabetes affects the platelet, the coagulation factors and fibrinolytic system leading to a state of hypercoagulation and hypofibrinolysis resulting in to thrombosis. Oral drugs commonly used in management of type II diabetes mellitus are antidiabetics like metformin, PPARγ agonist and DPP-4 inhibitor. They rarely produce hypoglycemia. Metformin has been proved to prevent release of mtDNA from arachidonic acid stimulated platelets, reduce membrane damage and mitochondrial ROS production in the platelets. Similarly processes like platelet adhesion, activation and aggregation on collagen coated surfaces which initiate thrombosis are prevented by metformin. PPAR- γ agonists like pioglitazone and rosiglitazone have anti atherogenic effect. They decrease the expression of inflammatory markers and affect the coagulation markers like factor VII: C and inhibit platelet activation. Pioglitazone also reduces the VLDL, triglycerides and increases HDL which further contributes in attenuation of atherosclerosis. DPP-4 inhibitors, which are relatively newer class of antidiabetics, having minimum potential for hypoglycemia induction, due to their novel mechanism of action. Studies have proved that long term use of DPP-4 inhibitors have reduced cardiac mortality by their lipid lowering action, increased release of NO from endothelium and inhibition of TNF- α, PAI-1 and VCAM expression. Increased levels of stromal cell derived factor - 1α helps to maintain endothelial homeostasis and vascular repair. Decreased oxidative stress, inhibition of inflammatory genes like IL6, IL-12, TNF- α provide additional benefit. Destabilization of vasculo-atherosclerotic plaque is prevented by DPP-4 inhibitors. Thus these oral antidiabetics drugs offer many benefits beyond blood glucose control which prevent atherosclerosis, inhibits hypercoagulable state and enhances fibrinolysis which translates into decreased cardiac complications in diabetes.

Keywords: Oral Antidiabetics, Meformin, mtDNA.

INTRODUCTION

Diabetes mellitus has attained an epidemic proportion as number of diabetics is increasing world-wide. By the year 2025, it is estimated that 324 million population will be diabetic[1]. Morbidity and mortality in type 2 Diabetes mellitus arise from microvascular complications like nephropathy, neuropathy and retinopathy and macrovascular complications like coronary artery diseases, cerebrovascular strokes and peripheral artery disease[2-6]. Thrombotic events in diabetics contribute for almost 80% of cardiovascular events[7,8]. Hypercoagulability and hypofibrinolysis in diabetes mellitus correlate with vascular complications[2].

Endothelial changes in Diabetes Mellitus The endothelium plays an important role in the prevention of intravascular coagulation through the generation of nitric oxide [NO], prostacycline and by stimulating tissue plasminogen activator and fibrinolytic system[9]. Endothelial dysfunction in diabetes mellitus, hypertension and hyperlipidemia triggers inflammatory process leading

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to atherosclerosis[10]. Diabetic hyperglycemia through the formation of advanced glycation end products (AGE's) injures endothelium by irreversible glycation of collagen and subendothelial proteins[11]. AGEs damage blood vessel basement membrane[12]. Levels of plasma thrombomodulin (TM) a membrane protein are increased in Type II diabetes mellitus and correlate with vascular injury[13-15]. Von willebrand factor (vWF), a glycoprotein synthesized by megakaryocytes and endothelial cells is increased in type II diabetes mellitus[16-18]. It is a marker of endothelial injury and bears a positive correlation with progressive micro and macro vascular complication in diabetes[15,16,19].

Diabetic dyslipidemia contributing to endothelial dysfunction possibly arises from difficulty in binding of lipoprotein lipase to an endothelium[20].

Platelet changes in Diabetes

Platelets form a plug as a reaction to endothelial injury through platelet aggregation, adhesion triggered by platelet aggregators like ADP, thromboxane and activation of glycoprotein IIb/IIIa receptors which help the platelet binding with each other through fibrinogen[21,22]. Number of circulating platelets in DM patients remains unaffected[7]. The hyperglycemia induced osmotic effect in DM increases the platelet aggregation and degranulation[23]. Glycation of platelet membrane proteins increases platelet reactivity and number of GpIb, IIb and III a molecules and reduces the fluidity of the platelet membrane[24,25]. Increased platelet activation in type II diabetes mellitus is due to increased

levels of markers of platelet activation stored in them like beta thromboglobulin and platelet factor IV in the plasma[10]. P-selectin on the platelet surface which is also a platelet activation marker, correlated to the thrombus formation and is found to be increased in diabetic patients[26]. Platelet plug gets supported by the formation of fibrin clot which helps to stop the bleeding[27].

Changes in coagulation factors

In type II diabetes mellitus patients, increased levels of factor VII is correlated to diabetic dyslipidemia. Factor VII circulates in the plasma bound to VLDL rich in triglycerides which results in to prolongation of the plasma half life of factor VII[10,16,28]. The factor VIII /vWF is increased in diabetes mellitus and in patients with insulin resistance as a result of endothelial dysfunction and inflammation[10,11,16].

About 95% of factor VIII which circulates in plasma is bound to vWF. Plasma levels of vWF are regulated by it's endothelial secretion and by TNF induced by inflammation[16]. Increased plasma levels of factor VIII is an independent risk factor for thromboembolism[29]. Another independent risk factor, fibrinogen for cardiovascular disorders is also increased in DM[11,16,20,28,30]. Hyperglycemia induced glycation of fibrinogen results into denser fibrin clot resistant to firbinolysis. The binding of the glycated fibrin is less to tissue type plasminogen activator resulting into reduced generation of plasmin and increased binding to α2 antiplasmin[7,10]. Prothrombin fragment 1 & 2, thrombin- antithrombin complex and fibrinopeptide which are the markers in hypercoagulability are found to be increased in diabetics[2,7,8,31,32].

Changes in natural anticoagulation in Diabetes Mellitus

Process of formation of thrombus is counter regulated by natural anticoagulants like 1) serine protease inhibitors such as antithrombin (AT), heparin co factor 2 and tissue factor pathway inhibitor (TFPI) and 2) inhibitors of activated protein C (PC) and its co factors protein S (PS)[33]. Decreased levels PC, PS and AT form the risk factors for thrombotic events[29]. In diabetics hyperglycemia results into decreased activity of AT which favours prothrombotic state[34-36]. *Changes in fibrinolytic system*

Hyperglycemia stimulates plasminogen activator inhibitor -1[PAI-1] production which favours the persistence of fibrin clot and development of thrombus[20,37,38]. Elevated levels of PAI-1 have also been considered as risk factor for the development of type II diabetes mellitus as they were found to be increased before the onset of type II diabetes mellitus[10].

Hypercoagulation and hypofibrinolytic state in diabetes favours thrombus formation as there was increase in the hypercoagulability markers such as fibrinopeptide A, prothrombin fragment 1 and 2, thrombin-anti thrombin complex, fibrinogen, soluble vWF, soluble thrombomodulin, D-diamer and PAI-1[11,13,15,27]. Type II diabetes mellitus initiates the process of endothelial dysfunction, atherosclerosis and vascular thrombotic complications[39-43]. Similarly, increased concentration of coagulation factors has been reported in type II diabetes mellitus.[39,44,45,46].

Coagulation factors VIII and its carrier vWF are increased in diabetics making them susceptible for myocardial infarction [MI][47,48]. Similarly, elevated levels of factor XI is known to be an independent risk factor for thrombotic complications like MI[49-58]. Hyperglycemia and hyperinsulinemia leads to increased activity of tissue factor [TF] and subsequent increase in coronary complications[39,54,59-63]. It activates coagulation pathway through activation of factor VII[41,64,65].

Hyperinsulinemia in diabetes mellitus impairs fibrinolysis even with the normal glucose concentration. Similarly hyperglycemia triggers coagulation which is unrelated to insulin concentration. Thus both hyperglycemia and hyperinsulinemia in type II diabetes mellitus have strong procoagulant effect by triggering coagulation machinery and simultaneous inhibition of fibrinolysis[66].

To summarize, in diabetics the atherosclerosis starts somewhat 20 years earlier as compared with non diabetics. Thrombotic complications constitute cerebrovascular events, coronary artery disease and peripheral vascular disease[67]. Imbalance between coagulation and fibrinolysis along with platelet dysfunction is responsible for thrombosis[68].

Hyperglycemia and insulin resistance in type II diabetes mellitus leads to enhanced platelet aggregation and increased levels of fibrinogen[69-71], vWF and PAI-1. Rise in levels of inflammatory markers like C-reactive protein, cytokines[71] and adhesion molecules[74,75] have been found to be elevated in type II diabetes Mellitus. In type II diabetes mellitus hyperglycemia initiates the problem of thrombogenesis through advanced glycation end products, endothelial dysfunction with decreased NO generation, enhanced platelet aggregation and inhibition of levels of PAI-1 and reduced levels of tissue plasminogen activation (t-PA)[119,120]. AGE increases oxidative stress resulting into endothelial dysfunction with increasing levels of CRP, IL-6, TNF-α, VCAM and ICAM[74,75]. Decreased NO generation adds to endothelial dysfunction. Elevated levels of inflammatory mediators, platelet aggregation and decreased PAI makes the atheromatous plaque unstable. Unstable plaque initiates the coagulation cascade by activating extrinsic factors like tissue factor and Factor VII and intrinsic factors like factor VIII,XI, XII[78]. Enhanced fibrinogen generation as a result of endothelial dysfunction, increased AGE's and heightened oxidative stress helps in clot formation along with plaque rupture and coagulation cascade. There are decreased levels of endogenous anticoagulants like anti thrombin III, protein C and thrombomodulin[71,79].

Type II diabetes mellitus respond therapeutically to oral drugs except where there is confirmed drug failure which necessitates use of insulin. Available oral antidiabetic drugs are categorized as

Oral hypoglycemic drugs like sulphonylureas and meglitinides

Oral drugs which are antidiabetic and are rarely hypoglycemic e.g, biguanides like metformin, PPAR- γ

agonists like thiazolidinediones (pioglitazone and rosiglitazone), DPP 4 inhibitors (siltagliptine) Drugs which inhibit the intestinal absorption of glucose and are anti-hyperglycemics like α- glucosidase inhibitors Sodium glucose transporter- 2 inhibitors (SGLT-2 inhibitors) – glucose excretion enhancers like canagliflozine.

Out of all these drugs biguanides, PPAR –γ agonists and DPP-4 inhibitors are preferred due to their antidiabetic action and lack of hypoglycemic potential.

Metformin

Thrombosis is a major cause of mortality and morbidity in diabetic patients with the incidence of 65%-80%[80-82]. Metformin is a preferred first line drug in type II diabetes mellitus and has been reported to reduce the diabetes related mortality arising out of thrombotic events[83-87]. Diabetes related hyperglycemia triggers mitochondrial hyperpolarization of platelets, increases generation of reactive oxygen species resulting into platelet activation. It has been observed that thrombosis and platelet activation is related to mitochondrial function[88-91]. It was found that changes in mitochondria activate the platelets and these platelets can release mitochondria[90,91].

Studies done by Xin G et al has shown that release of mitochondrial DNA [mtDNA] from activated platelets was decreased by metformin. It also inhibited release of mtDNA from arachidonic acid (AA) and thrombin activated platelets. It did not induce platelet apoptosis. Study results suggest that membrane damage of activated platelets was prevented by metformin along with lowering of lipid peroxidation activity arising out of excess load of ROS. Mitochondrial ROS production in platelets was reduced by metformin. The three important key indices of mitochondrial function like intracellular ATP level, mitochondrial routine respiration and level of hyperpolarization of mitochondrial membrane potential were improved in metformin treated ADP activated platelets. It also inhibited complex I activity of respiratory chain in platelet mitochondria[92].

The mitochondrial electron transport chain (ETC) forms an important target and regulates mitochondrial function which includes mitochondrial membrane potential, ROS and ATP levels. Metformin was found to lower mtDNA release from activated platelets, inhibit complex I in ETC and suppress the mitochondrial dysfunction. mtDNA was found to increase platelet aggregation and αIIbβ3 expression which were observed to be reduced by metformin[92].

Release of mtDNA from activated platelets can induce platelet activation possibly through DC-Sign pathway. The three key indicators of platelet activation like αIIbβ3, cytosolic calcium and p-selectin were decreased with metformin which was comparable with the effect of aspirin. Platelet adhesion, activation and aggregation on collagen coated surfaces which initiate thrombosis were also inhibited by metformin[92].

Indices of viscoelastic property of developing clot, thrombogenesis and platelet activation were significantly improved with metformin without influencing prothrombin time, activated partial thromboplastin time , fibrinogen , thrombin time , coagulation factors II,V, VIIXII . Platelet count was observed to be unaffected. Unlike current antithrombotic agents, metformin could prevent thrombotic events without increasing bleeding episodes[92]. Metformin did not have adverse effects of current antiplatelet agents like bleeding episodes, neutropenia, thrombocytopenia and gastrointestinal toxicities[93-95]. The mechanism for decreased ROS production in the platelets due to metformin did not involve NADPH peroxidase I. But metformin decreased ROS generation by inhibiting conversion of superoxide to H_2O_2 by superoxide dismutase. Superoxide dismutase plays an important role in the generation of superoxides[92].

Intracellular ATP levels, hyper polarization level of mitochondrial membrane potential and mitochondrial routine respiration which are the three key indices of mitochondrial function were found to be improved in ADP stimulated platelets with decreased mitochondrial complex I activity and resulted into inhibition of platelet ROS formation[92].

Metformin in low concentration protected the mitochondrial function and inhibited mtDNA release. mtDNA released from activated platelets acts as agonist for platelet activation and thrombosis. mtDNA also plays important role in immune and inflammatory responses and diseases arising out of it[96-100]. Aspirin is most commonly used anti platelet drug to prevent thrombotic episodes in diabetics. But 10-40% of diabetic patients are found to have biochemical resistance to this drug. Hence, newer therapies which can target underlying platelet dysfunction deserve further exploration[101-103,80]. Hence, metformin forms a promising new class of antiplatelet drug in the inhibition of platelet activation and prevention of thrombotic episodes. Platelets are known to play major role in inflammatory and infectious diseases. It is known that bacterial infections are also the predisposing factors for atherosclerosis and thrombosis[104].

Imbalance between the clot formation and its lysis results into vessel occlusion. Augmentation of fibrinolytic process has an impact on clot dissolution. Metformin has shown mild decrease in cholesterol and fibrinogen with increased fibrinolytic activity as monitored by euglobulin clot lysis time. There was fall in the fibrinolytic inhibitor, PAI-1[105-111].

This response was independent of dosage[111]. Use of metformin was found to be associated with the reduction in coagulation factor VII levels[112] and also the levels of Factor XIII and Factor XIIIA and B sub-unit in the plasma. It also affected fibrin polymerization and its aggregation[113]. The cross linking of fibrin and formation of advanced glycation end products both share common amino acid interaction which is likely to get interrupted by metformin[114].

Type II diabetes patients when treated with metformin were found to have reduced markers of platelet activation like platelet factor IV and beta thromboglobulin resulting in to platelet stabilization[115]. Metformin is also known to exert antioxidant effect on the platelets[116].

Metformin was also found to have action on blood flow in type II diabetes mellitus patients. Patients of type II diabetes Mellitus when treated with metformin for six months were found to have increased hemodynamic

response to L-arginine which is a precursor of nitric oxide[117]. It also lowered the levels of ADMA[118]. There was improved blood flow both in skeletal muscles and adipose tissue[119].

The results of UKPDS study conducted in overweight type II diabetics showed reduced cardiovascular mortality in them with metformin as compared to insulin or sulphonylureas, despite similar improvement in glycemic control[120].

Activated partial thromboplastin time which reflects the function of intrinsic system of coagulation cascade was affected insignificantly by metformin and also the INR, which is a parameter of activity of extrinsic pathway of coagulation[121]. But fibrinogen and PAI-1 were affected significantly by metformin[122].

PPAR γ- agonist thiozolidinediones- glitazone -TZDs

Pioglitazone and rosiglitazone are currently used PPAR γ agonists. They are insulin sensitizers and reduce the cardiovascular risk in type II diabetes mellitus[123].

They have antiatherogenic effect and also have been observed to affect coagulation cascade favourably and maintain vascular homeostasis beyond their antidiabetic effect[124-126]. Their antiatherogenic effect in type II diabetes Mellitus is attributed to their insulin sensitization potential, lowering of blood sugar, decrease in LDL and triglyceride level. Lowering of vascular monocytes and T cell recruitment, decrease in T cell activation and vascular smooth muscle cell [VSMC] migration in the formation of foam cells also contribute to this effect. They also reduce inflammatory biomarkers in the atheromatous plaque[127-128].

By decreasing expression of inflammatory markers and adhesion molecules like VCAM, pioglitazone improved endothelial function and release of NO, and decreased oxidative stress and CRP levels[129-133]. VSMC accelerates the atherosclerosis through accretion of lipid plaque, generation of extracellular matrix and by release of inflammatory cytokines[134]. Pioglitazone reduces VSMC cell migration, proliferation and enhances their apoptosis[135].

Pioglitazone was found to affect coagulation markers like Factor VII:C, VII: Ag, PAI-1 and vWF in type II diabetes mellitus[126,136]. Platelet activation was also observed to be inhibited[137,138]. TNF α mediated stimulation of PAI-1 was seen to be inhibited by both pioglitazone and rosiglitazone[139].

Circulating levels of biomarkers of inflammation and coronary atherosclerosis like CRP, adiponectin, PAI-1 and monocytes chemoreactant protein- 1[MCP-1] a chemokine which regulate migration and infiltration of monocyte/macrophagess and matrix metallopeptidase[MMP-9] which is involved in degradation of extracellular matrix are also reduced by pioglitazone. Pioglitazone directly affect VSMC , endothelial cells and ratio of macrophages/monocytes which plays an important role in the process of atherosclerosis. Pioglitazone is known to influence vWF by affecting its expression from monocytes which also play an important role in the process of atherosclerosis and coagulation[140].

Endothelial dysfunction is improved by inhibiting endothelial cell inflammation and monocytes adhesion by inhibiting VCAM-1 expression on activated endothelial cell by pioglitazone. It also reduces TNF- alpha induced RAGE expression by inhibiting NFkB, an important pro inflammatory transcription factor[141,135].

Human bone marrow megakaryocytes and platelets express PPAR- γ receptors and PPAR- γ agonist inhibit release of thromboxane and inhibit platelet aggregation.

PPAR- γ agonist like TZDS forms the target for antiplatelet therapy[138].

Rosiglitazone also has been found to inhibit PAI-1[126].

Dipeptidyl peptidase 4-[DPP-4] inhibitors

DPP-4 inhibitors like sitagliptine, vildagliptine are antidiabetic drugs used in type II diabetes mellitus. They are found to decrease total cholesterol, LDL and triglycerides and increase high density lipoprotein cholesterol[142]. They have additional cardioprotective effect beyond the glucose control[143,144]. They act through GLP-1 receptors located on endothelium and smooth muscle cells in blood vessels[144]. GLP 1 receptor stimulation in endothelium helps to generate vasorelaxant and antiplatelet NO by drugs like sitagliptine. Inhibition of TNF-α, PAI-1 and VCAM expression was observed with liraglutide[143].

The cytokines and chemokines play an important role in thrombogenesis. Their levels were found to be affected by DPP-4 inhibitors. Stromal cell derived factor -1 α (SDF-1 α) levels are increased by DPP4 inhibitors resulting into stimulation of endothelial progenitor cells (EPCS) helping to maintain endothelial homeostasis and vascular repair. Proinflammatory chemokines like MCP-1 regulate homing of activated monocytes into atherosclerotic plaque. Sitagliptine therapy reduced the levels of MCP-1 and enhanced the levels of SDF-1α and EPCs[145].

NFkB regulates proinflammatory genes and proliferation of VSMCs which play an important role in atherogenesis[146]. DPP-4 inhibition leads to NFkB activation in T cells interacting with caspase recruitment domain family member 11 (CARD-11)[147].

Treatment with DPP-4 inhibitor, vildagliptine resulted into reduced oxidative stress and inhibition of inflammatory, thrombogenic and fibrotic gene expression like ICAM-1, PAI-1 and tissue growth factor in animal models of diabetes[148].

Sitagliptine was found to reduce mRNA expression of inflammatory genes like IL-6, IL-12 and TNF α in adipose tissues and IL-6 and IL 1 and MCP 1 in endocrine glands. Activation of MMPs through toll like receptor pathway plays an important role in destabilization of atherosclerotic plaque resulting into acute vascular event. DPP-4 inhibitors are shown to prevent activation of MMPs[145]. Alogliptine enhanced the release of NO in cultured endothelial cells via activation of the Akt-eNOS pathway and produce vasorelaxation. GLP-1 stimulation itself stimulates generation of NO through eNOS[145].

CONCLUSION

The epidemic of type II diabetes mellitus is threatening human health not only due to hyperglycemia but also due to vasculo-thrombotic events in the vital organs like heart, brain, kidney. Hence it becomes imperative to choose the oral antidiabetic drug which not only should control hyperglycemia but also offer protection against microvascular, macrovascular pathologies and thromboembolic complications. Amongst the oral antidiabetic drugs, biguanides, thiozolidinediones and DPP-4 inhibitors are the promising agents in the prevention of these vascular complications by various mechanisms which inhibit hypercoagulable state and accelerate fibrinolysis. Reduced platelet aggregation, enhanced fibrinolysis and reduced fibrin generation, inhibition of PAI-1, correction of hyperlipidemia, inhibition of inflammatory mediators and generation of ROS and regression of atherosclerosis are the prominent mechanisms through which these drugs can fulfill these goals. Inhibition of platelet mtDNA released by metformin if properly investigated can prove it to be a new antiplatelet agent. Lack of its hypoglycemic potential would facilitate its use in nondiabetic conditions as antiplatelet agent. Emerging resistance to antiplatelet drug aspirin to the tune of 40% compels to consider metformin as antiplatelet drug in type II diabetes.

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