**Review article**

**Alterations in Hematological Parameters: Could it be a Marker in Diabetes Mellitus?**

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**Abstract**

This review discussed the mechanism by which hyperglycemia produces changes in blood constituents, the effect of hyperglycemia on different blood constituent with special stress on anemia, as well as its influence on immunological changes and cancer susceptibility. The predictive value of changes in these blood constituent and the development of diabetic complications as well as blood constituent changes produced by drugs used in diabetics (hypoglycemic agents, lipid lowering agents, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and anti platelet agents) were also dealt with. Lastly, the reversible changes in blood constituent on improving glycemic control were mentioned.

**Introduction**

Diabetes mellitus (DM) affects about 383 million adults, i.e. 8.3% of adult population worldwide and is the fifth leading cause of death worldwide [1].

Diabetes is generally characterized by hyperglycemia and hyperinsulinemia, often coupled with a reduced metabolic effect of insulin (insulin resistance) in peripheral tissues [2].

Recurrent hyperglycemia causes non-enzymatic interaction between the carbonyl group of the reducing sugar and the primary amino group of a protein. The final consequence of these reactions is compounds known as advanced glycation end products (AGEs) [3]. The molecules linked to AGEs acquire new properties and become oxidants. This leads to the production of reactive oxygen species (ROS), which increase oxidative stress and prevent nitric oxide (NO) release. AGEs may also reduce the bioavailability and activity of endothelium-derived nitric oxide [1].

**Mechanism of Hyperglycemia Induced Blood Constituent Change**

Some of these AGE cause externalization of platelet membrane phosphatidylserine leading to activation of surface clotting factor and enhancing the thrombogenic state [3]. Hyperglycemia also causes activation of protein kinase C, a transduction pathway mediator for many proaggregatory platelet agonists as well as release larger platelets with more GP Ib and GP IIb/IIIa receptors and a higher thromboxane forming capacity [3].

Persistent hyperglycemia results in glycation of prothrombin, fibrinogen, other proteins involved in clotting mechanisms and plasminogen [4,5]. Plasminogen glycation decrease plasmin generation and lower plasmin catalytic efficiency [5].

Hyperglycemia alter red cell membrane lipid composition and red cell deformability, impair red cell filterability and increase red cell adhesion as a result of decrease in red cell Na/K-ATPase activity, protein structure modifications by oxidation and the accumulation of AGEs on the red cell membrane [6].

Leukocyte phagocytosis and bactericidal activity were impaired with increase in blood glucose levels [7].

**Hyperglycemia and blood constituent changes**

**Anemia**

Anemia was reported in 7.2% of diabetics with normal renal function and in about 20% of diabetics with renal insufficiency [8]. Approximately 70% of diabetics with anemia were over the age of 65 years. This observation was confounded by presence of anemia of ageing, increased prevalence of low glomerular filtration rate “GFR” and albuminuria in elderly patients [9].

The etiology of anemia in diabetes is multi factorial and includes anemia of chronic disease, nutritional deficiencies, concomitant autoimmune disorders, medications, both erythropoietin (EPO) deficiency and ineffectiveness, pro inflammatory cytokines, hormonal changes and kidney disease [10]. Decreased renal function and pro inflammatory cytokines are the most important determinant of anemia in those patients [11]. Anemia may be apparent before demonstrable decline in renal function. A

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normochromic, normocytic anemia has been observed in diabetics without overt renal disease [9]. In early diabetes, renal blood flow is increased leading to hyperfiltration. Increased renal oxygen delivery (blood flow) may act to suppress EPO production in the diabetic kidney [9].

Renal Cause

Approximately 40% of diabetics are affected by kidney diseases [11]. Diabetics with renal impairment were nearly twice likely to have anemia as their counterpart non-diabetic people. Anemia also develops earlier in diabetics than in patients with renal impairment from other causes [9]. Anemia was present in 52% of macro albuminuric, 28% with micro albuminuria and less than 8% of normoalbuminuric patients. Anemia is evident in diabetics, when the estimated GFR falls below 90 ml/min/1.73 m² for men or below 70 ml/min/1.73 m² for women. By the time the estimated GFR declines to less than 60 ml/min/1.73 m², more than one in five diabetics has anemia. Anemia can be observed even earlier in macro albuminuric patients [3].

The mechanism of impaired renal EPO response to anemia in diabetics is not established. It may result from defect in the regular processes that enable oxygen sensing through hypoxia-inducible factor-1α [12] secondary to renal interstitium damage or vascular lesions [13]. Other mechanisms include loss of appropriate EPO production due to severe autonomic neuropathy and efferent sympathetic denervation of the kidney [9], systemic inflammation and inhibition of EPO release [13]. Advanced glycation products may alter EPO responsiveness by glycation of EPO or its receptor or by induction of suppressive inflammatory cytokines [9]. The inflammatory situation created by the kidney disease interferes with intestinal iron absorption [11]. Finally, proteinuria results in urinary loss of endogenous EPO and reduced plasma EPO levels [9]. Higher prevalence of early EPO-deficiency anemia occurs more in type 1 diabetes (T1DM), in women and is unrelated to iron stores [13].

Non Renal Causes

- Blood loss and iron deficiency associated with autoimmune gastritis may occur in T1DM [9].

- Helicobacter pylori infection may be associated with presence of endoscopic lesions and chronic gastritis. Marked fluctuations in iron stores can occur in diabetics [9].

- Diabetes is associated with potential sources of occult blood loss such as cancer colon in T2DM and occult hematuria in micro albuminuric and macro albuminuric patients with both type 1 and type 2 diabetes [9].

- T1DM patients are at increased risk of latent pernicious anemia (especially in the presence of autoimmune thyroid disease) and are strongly associated with celiac disease. Celiac disease may produce anemia through iron, folate, vitamin B12 or trace elements malabsorption. Serological testing for celiac disease should be incorporated in the workup of unexplained anemia in T1DM patient [9].

- Anemia might also result from diminished bone marrow responsiveness to EPO stimulation. EPO resistance in diabetes may result from systemic inflammation, microvascular damage in the bone marrow, tryptophan metabolites, inhibition of hemopoesis by AGEs and induction of inflammatory cytokines [6].

- Interleukin (IL)-6 changes the sensitivity of progenitors to EPO and promotes apoptosis of immature erythrocytes and decrease erythrocytes number [11].

- Microangiopathic hemolytic anemia is observed in the setting of accelerated hypertension, in long-standing diabetics and in advanced microangiography.

- Hyperglycemia modifies erythrocyte metabolic and functional abnormalities and induces exposure of the aminophospholipid phosphatidylserine on the red cell surface [6], leading to red cell (senescence) recognition. An extra-cellular oxidative milieu can activate erythrocyte caspase-3 in T2DM which impairs the maintenance of erythrocyte shape and function [14]. Increased osmotic stress as a consequence of sorbitol accumulation by the activated polyol pathway [15]. These changes contribute to reduced erythrocyte survival and their removal by the reticuloendothelial system [14].

- It is possible that serum triglycerides influence the shortening of red cell half-life in diabetes through its effect on red cell aggregation and membrane fluidity [9].

- Poor diabetic control may be associated with chronic fluid retention and hemodilution [9].

- Functional iron deficiency with relatively normal iron indices in dialyzed patients [6].

- Many antidiabetic drugs such as metformin and thiazolidinediones may exacerbate anemia associated with diabetes [10].

- Testosterone deficiency contributed to an increased frequency of anemia in men with T2DM and low testosterone. Testosterone stimulates erythropoiesis via production of hematopoietic growth factors and possible by iron bioavailability improvement [16].

Fallacies Warning In Hba1c Measurement In Anemia

Measurement of HbA1c is invalid in the presence of anemia [17].
Caution must be taken when diagnosing diabetes and pre diabetes among people with high or low Hb when the HbA1c level is near 6.5% or 5.7%, respectively, as changes in erythrocyte turnover may alter the test result [18].

HbA1c levels fall as hemoglobin levels fell, independent of the decline in renal function [9].

HbA1c may be spuriously elevated in anemia because EPO deficiency results in tardy access into the circulation of newly produced erythrocytes which are less exposed to a hyperglycemic environment [9].

EPO therapy artificially lowers HbA1c while blood glucose levels remained unchanged [10].

Iron deficiency may artificially increase HbA1c [17] by changing the shape of hemoglobin molecule, promoting terminal valine glycation or by lowering erythrocyte turnover, allowing more time for hemoglobin glycation to occur [19].

Complications of Anemia

Anemia has direct mitogenic and fibrogenic effects on the kidney and the heart, associated with expression of growth factors, hormones and vasoactive reagents. Many of which are also implicated in the diabetic microvascular disease [20]. McCullough and Lepor [21] coined the term “the deadly triangle” for the combination of anemia, renal insufficiency, and cardiovascular disease.

Anemia is associated with rapid progression of renal disease in diabetics [10]. Low EPO predicted the subsequent increase in serum creatinine concentration in diabetic patients with normal baseline serum creatinine [22].

Anemia is an independent risk factor for diabetic retinopathy (DR) [10].

Treatment

Hemoglobin target of 11-12 g/dl is theoretically appropriate for all patients. However, patients with congestive heart failure, severe symptomatic coronary heart disease or symptomatic cerebrovascular disease may need rHuEPO dosage allowing them to reach a hematocrit level higher than usually recommended [13].

Early correction of anemia in diabetics before the onset of renal failure may improve mortality risks. Early EPO therapy may reduce anemia-induced organ damage, such as cardiac ischemia, and retard the progression of kidney failure [10]. EPO Supplementation has been associated with reduction in macular hard exudates and edema in diabetics in a previous study [20]. A cautious approach is recommended towards raising hemoglobin concentration to levels more than 12 g/dl in diabetics with concurrent peripheral vascular disease [23]. Pentoxifylline has been shown to improve anemia in patients with kidney failure who had developed recombinant EPO resistance [10].

Leukocytes

A rise in leukocyte count, even within the normal range, can predict the number of and the severity of complications in T2DM patients [24]. Monocyte and neutrophil counts also increased in parallel with the progression of complications [4].

The chemotactic, phagocytic [25] and bactericidal activities of neutrophils of diabetics are impaired. Lysosomal enzymes release [7], myeloperoxidase activity [26] and ROS production by neutrophils are all decreased [7]. These enzymes changes may affect the susceptibility to infection. The increased severity of infections in diabetics might be attributed to the following abnormalities during inflammation: decreased leukocyte-endothelial cell interactions, reduced number of leukocytes in inflammatory lesions, low superoxide generation, reduced leukocytes release of TNF-α, IL-1β and prostaglandin E2 upon exposure to lipopolysaccharide; and low content of arachidonic acid in neutrophils [7].

Platelets

Conflicting results have been reported for platelet count in diabetes [28]. Increased platelet aggregability and adheresiveness among diabetics, are due to reduced membrane fluidity, increased intracellular calcium mobilization, decreased intracellular magnesium, increased arachidonic acid metabolism, increased TXA2 synthesis, decreased prostacyclin and nitric oxide production, decreased antioxidant levels and increased expression of GPIIIb-IIIa and P-selectin [29]. The higher baseline calcium and lower cAMP make the platelets more reactive and aggregate at lower levels of agonist stimulation [3]. Additionally, platelets from diabetic patients show impaired sensitivity to prostacyclin and NO that normally blunt platelet activation, this increases platelet reactivity further [3].

The increased GPIIb-IIIa expression enhances fibrinogen binding and aggregability in diabetic platelets. The enhanced surface expression of adhesion molecules suggests that platelets can also communicate with leukocytes and possibly play a role in inflammation mediated tissue damage in the vasculature [29].
Coagulation

Hyperglycemia and insulin resistance induce qualitative and quantitative changes in clotting factors resulting in denser clot structure resistant to fibrinolysis [12]. AGEs can induce an intracellular oxidative response, which results in tissue factor (TF) expression of endothelial cells [30]. Elevated kallikrein, factor XII, factor XI, factor VIII activity, ristocetin cofactor activity, and von Willebrand antigen (vWF) are reported [31].

Thrombin markers, prothrombin fragment 1 + 2 and thrombin–antithrombin complexes are high. The anticoagulant ATIII levels are normal, increased, or decreased [31] and protein C levels are low [32].

Fibrinolysis

Fibrinolytic activity has yielded varying results in diabetes [31]. While impaired fibrinolysis was reported in T2DM [33], fibrinolytic activity is not adversely affected in T1DM, and it has no relationship with the degree of metabolic control [34]. Plasminogen level was normal in insulin-dependent diabetics. tPA antigen levels have been reported to be normal, increased or decreased [31]. The fibrinolytic inhibitor A2PI (alpha 2 plasmin inhibitor) was normal, while PAI-1 was increased [31].

Markers of fibrinolytic activity and activation in diabetics also yield variable results. D-dimers level was increased or decreased. Fibrinopeptide A (FPA) was elevated or normal [31].

Clot lysis from diabetic subjects is slower compared with controls, which is related, partly, to reduced plasminogen binding to the fibrin network coupled with impaired plasmin generation [12].

Hyperglycemia And Immunological Changes

Diabetics often exhibit decreased innate and adaptive immune responses and increased susceptibility to infections. Decreased CD19+ B cells have been reported in poorly controlled subjects and may be due to mobilization of B cells from the blood to the reticuloendothelial system to produce auto antibodies. Alterations in immunocompetent cells are common in T1DM, but only limited data are available for T2DM [25].

Hyperglycemia And Cancer

T2DM have mild-to-moderate increased odds of developing NHL with increased odds of PTCL but not DLBCL or follicular lymphoma: the odds of leukemia was increased, with no association with myeloid or lymphoid leukemia: and there was a trend toward increased odds of myeloma. The odds of hematologic malignancies in T2DM depend on the geographic area [35]. For solids tumors, a definitive association is only available for cancer of the pancreas and liver [9,36]. Cancer of the breast [9], colorectum, bladder, and endometrium also occur more commonly in diabetics [37]. While for prostate cancer, most studies report a reduced risk in diabetes [2].

Diabetes was associated with less favorable tumor characteristics including larger tumor size, more poorly differentiated grade, and more advanced tumor stage [2].

Malignant transformation of cells and tumors progression in T2DM patients is favored by hyperglycemia, insulin-like growth factor (IGF) over production, up regulation of IGF-1 receptor and inflammatory cytokines over secretion [35].

Hyperinsulinemia has been also implicated because exocrine pancreatic cells which give rise to most pancreatic cancers are exposed to very high insulin concentrations because of the common blood supply with the adjacent insulin secreting islets. The quantification of the role of insulin in promoting cancer risk in the different organs is not known owing to the heterogeneity and complexity of different tissue exposure to hyperinsulinemia in diabetic individuals [2].

Increase oxidative stress with poor metabolic control predisposes susceptible cells to malignant transformation by producing permanent pro-inflammatory condition and reduction of intracellular anti-oxidant capacity. Mitochondrial dysfunction in diabetes also increase ROS production and provide low, energy supply insufficient for DNA repair [2]. TNF-α produced by the adipose tissue with insulin resistance induces development and progression of many tumors by strongly activating nuclear factor-kappa B (NF-kB) [2].

However, T2DM and cancer share common risk factors, such as age, sex, overweight, obesity, waist-to-hip ratio, physical activity, dietary habits, smoking and alcohol intake, making it difficult to discern the oncogenic effect of each specific risk factor. Association of diabetes and its treatments with risk of cancer incidence or prognosis was not supported or refuted [35].

Moreover, cancer patients with pre-existing diabetes are at increased risk for all-cause mortality compared with non-diabetics [37]

Diabetic Complications And Blood Constituent Changes

Hemoglobin level

- Anemic patients with T1DM were more than twice as likely to have IHD, irrespective of renal impairment or albuminuria [20].
- T2DM patients with Hb level less than 12 g/dl have 2-fold increased risk of background DR and a 5-fold increased risk of proliferative or proliferative retinopathy, compared with those with higher Hb levels. It may be due to retinal hypoxia leading to up-regulation of vascular endothelial growth factor and other genes involved in neo angiogenesis, capillary permeability and
apoptosis [20].

**Red Cell Indices**

- A positive correlation is reported between high RDW and increased incidence of macro- and micro vascular complications in diabetics without marked vascular complications [38].

- A positive correlation was established between RDW-CV and blood pressure in T2DM in Lagos. RDW-CV (RDW-coefficient of variance= Standard deviation of red blood cell volume ÷ mean cell volume x100)[39].

**Leucocytes**

- Leukocytes play an important role in the progression of diabetic complications [24].

- Higher leukocyte count was correlated with macro vascular and micro vascular diabetic complications [24].

- Higher prevalence of retinopathy and cardiac events was observed with higher leukocyte counts [24].

- Leukocytes play an important role in the initiation and progression of diabetic nephropathy. It causes proteolytic and oxidative damage of mesangial cells. Plasma cortisol and the changing insulin levels in renal disease may stimulate leptin secretion from adipocytes causing increase in neutrophil influx from marrow storage and decreasing their efflux from the blood stream [40]. Another theory is stimulation of neutrophil production in bone marrow by low blood insulin level [24].

- WBCs in diabetics may be activated by AGEs or ROS and cytokines. Activated leukocytes secrete cytokines and transcription factors that have a crucial role in inflammation. TNF-α, NF-κB, IL-1b, transforming growth factor b, released superoxide radicals and proteases, will all promote oxidative stress. The latter can then activate NF-κB transcription in peripheral mononuclear blood cells [40].

**Platelet Indices**

- Increased mean platelet volume (MPV) indicates subclinical platelet activation. Increased platelet size may be one factor in accelerating atherosclerosis and may be associated with both micro- and macro vascular disease. It may be increased in myocardial infarction (MI), coronary artery disease, cerebral ischemia and peripheral arterial disease [41].

- Platelet distribution width (PDW), platelet large cell ratio (PLCR), and plateletcrit (PCT) are also important in atherosclerosis and thrombosis [41].

- High MPV and PDW are likely to be associated with an increased risk of micro vascular complications including retinopathy and micro albuminuria. However, the relationship between MPV and diabetes macro vascular complications is still controversial [42].

- Mean platelet indices (i.e., MPV, PDW and PLCR could be a beneficial prognostic marker of DR in T2DM patients [41].

- Elevated MPVLR (Mean platelet volume -to-lymphocyte ratio) indicates worse angiographic features i.e. a greater thrombus burden [43].

**Coagulation**

- Fibrinogen levels are further increased in the presence of micro or macro vascular disease, implicating this protein in the pathogenesis of diabetic complications [29].

- FVII level is raised in the metabolic syndrome and in micro albuminuria, independent of triglyceride levels, by mechanisms that are not entirely clear [29].

- Very high vWF level is present in diabetics with micro albuminuria [31].

- It has been suggested that increased plasma level of D-dimer is associated with the formation of atherosclerotic plaque in diabetes.

- ATIII increased in diabetics with retinopathy [31].

- low glucose levels are also associated with changes in coagulation factor levels and clot structure/lysis [12].

**Fibrinolytic System**

- Increased tPA activity has been shown in T2DM subjects with peripheral vascular disease while decreased local tPA production has been linked to the development of diabetic neuropathy [29].

- PAI could be considered a prognostic factor in the follow-up of diabetic patients since it can detect early development of a prothrombotic state particularly in non-insulin dependent diabetics [32].

- A2PIC (alpha 2 plasmin inhibitor C terminal peptide) levels were elevated in diabetics with proteinuria. This increase was correlated with lipoprotein a in diabetics with nephropathy [31].

**Drugs Used In Diabetics And Blood Constituent Changes**

**Hypoglycemic agents**

None of the studied hypoglycemic agents showed a significant effect on RDW [14].
**Sulphonylurea** inhibits platelet aggregation independent of its hypoglycemic action [33]. Glimipiride and glibenclamide inhibited Ca2+ elevation induced by arachidonic acid in a dose-dependent manner [33]. Gliclazide inhibits platelet aggregation via the serotonin pathway, independently of the metabolic control per se [44]. However, there are reported cases of severe thrombocytopenia and bleeding tendency related to glibenclamide treatment [33].

**Metformin** is associated with decrease absorption of folic acid and vitamin B12. In a 16-week placebo-controlled study, metformin reduced serum vitamin B12 levels by 14% and folate by 7% [10]. Patients taking metformin on a continuous basis occasionally develop vitamin B12 deficient megaloblastic anemia [9]. Rare metformin-induced hemolytic anemia has been reported [45]. Metformin lowers FVII and PAI-1 levels, and also interferes with both levels and activity of FVIII [12]. It has a cardioprotective effect which may be related to fibrinogen protein level reduction, enhanced fibrinolytic potential of the clot [12], its inhibitory effect on platelet aggregation and is independent of its hypoglycemic action [46].

There is increasing evidence that metformin may have broad activity against cancer. The antitumor activity of metformin may be mediated through its regulatory effect on hormonal, metabolic, and immune functions [47].

**Thiazolidinediones (TZD)** are associated with volume expansion as much as 6% and hemodilution. The total red cell count and oxygen-carrying capacity are retained while blood viscosity is decreased. TZD induced anemia is normochromic normocytic and is considered a benign dilutional anemia similar to brunnner's anemia. A drop in hemoglobin level as much as 1 g/dl has been reported with rosiglitazone and pioglitazone use [10].

Glitazones inhibit platelet aggregation independently of their hypoglycemic action [33] and can lower FVII, fibrinogen and PAI-1 levels, which reduces thrombosis potential and improves fibrinolysis [12].

Troglitazone is associated with a beneficial effect on fibrinolysis by causing significant fall in plasma PAI 1 antigen concentrations in NIDDM patients [48].

**Repaglinide** was associated with diminished platelet and endothelial activity in the fasting state [33].

**Insulin** can regulate platelet function via a functional insulin receptor found on human platelets [3]. Insulin therapy in T2DM patients may lead to paradoxical increase in platelet reactivity in vivo. Hyperinsulinemia is not protective but potentially detrimental to platelet reactivity in patients with insulin resistance. Insulin has adverse prothrombotic effects. Induced hyperinsulinemia, particularly in combination with hyperglycemia, leads to a procoagulant state by increasing level of TF procoagulant activity, decreasing factor VII/VIIa and increasing factor VIII and prothrombin fragment F1.2. In addition, there is upregulated platelet expression of CD40L and increased monocyte-platelet aggregates, indicative of platelet activation [3]. Fall in FPA was reported in type II diabetics placed on insulin therapy [31].

**Acarbose** may be beneficial for primary prevention of atherothrombosis in T2DM. It may significantly decrease plasma platelet-derived micro-particles and decrease soluble P-selectin and L-selectin [33].

**Dipeptidyl Peptidase-4 (DPP-4) Inhibitor**

Sitagliptin have advantageous effects on platelet function. It has a significant concentration-dependent anti-platelet activity, mostly attributable to its inhibitory effect on intracellular free calcium and tyrosine phosphorylation. A significant reduction in platelet aggregation was shown 1 and 3 months after treatment.

N.B. Available data on the impact of the other categories of oral hypoglycemic agents on platelet function are limited [33].

**Lipid-Lowering Agents**

**Fibrates** have been associated with anemia by blocking alpha peroxisome proliferator activator receptor [9]. They protect against initiation of thrombus formation by reducing fibrinogen levels, probably secondary to gene transcription inhibition and down regulating TF expression on monocyte and macrophages [12].

**Statins** can modulate thrombosis potential through inhibition of platelet activation [43], inhibition of TF pathologic expression by endothelial cells, reduction in FVII activity, FXIII activation and FV a generation. In addition, statins affect the fibrinolytic system through up regulation of thrombomodulin expression and reduction in plasma PAI-1 levels. Indirect effects on the coagulation system are related to lowering cholesterol levels which may be associated with reduced PAI-1 and improved tPA release [12].

**Ezetimibe** treatment was associated with a small non statistical significance increase in TF levels [12].

**Angiotensin Converting Enzyme (ACEI) Inhibitors And Angiotensin Receptor Antagonists (ARB)**

Both are associated with a dose-dependent reduction in hematocrit within the first month of therapy. Both may have direct effects on erythroblast proliferation. No significant link has been found between ACEI use and hemoglobin levels [9]. Both reduce fibrinogen levels, thereby reducing the risk of cardiovascular events. ACEI can also modulate PAI-1 levels in diabetic subjects, whereas ARB has a less consistent effect [12].
**Antiplatelet Agents**

**Aspirin**

Its main antithrombotic action is related to decreased platelet aggregation as a result of inhibition of cyclo-oxygenase-1 activity and reduction of thromboxane A2 production. Aspirin can modulate thrombin production and affects FXIII activity. Aspirin has also been shown to acetylate fibrinogen, resulting in a less compact clot structure that is easier to lyse [12].

ADA recommends 81-325 mg of aspirin to be used as a preventive strategy in high-risk diabetics and as a secondary preventive measure in diabetics with large vessel disease (history of MI, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina) [29].

The clinical efficacy of aspirin in diabetics is compromised [12]. A subgroup of patients on therapeutic doses of aspirin experiences thrombotic vascular events. For this group, the term “High on-treatment platelet reactivity” (HTPR) (previously termed aspirin resistance) has been applied. Both glucose and aspirin compete to either glycosylate or acetylate unoccupied amino groups on platelet proteins. There is persistent agonist-induced platelet activation despite aspirin therapy. Activated platelets produce the eicosanoid thromboxane A2, which creates a local positive-feedback loop that amplifies the activation response of platelets to most agonists as well as activating bystander quiescent platelets. Another possibility is that diabetic platelets may be activated by pathways independent of arachidonic acid [49].

**Thienopyridines (Clopidogrel And Prasugrel)**

Clopidogrel 150 mg daily can significantly suppress platelet reactivity in poor aspirin responders. Higher doses of clopidogrel (600 mg loading dose) may overcome HTPR in some patients despite suboptimal glycemic control. Patients on sulfonylureas had more than 2-fold higher rate of HTPR on clopidogrel, possibly due to competition of the two drugs for metabolism by the CYP2C9 cytochrome isoenzyme leading to reduced biotransformation of clopidogrel to its active metabolite [3]. Clinicians must be aware of TTP which occurred within the first 2 weeks of therapy. However, blood monitoring is not required [29].

**Dual Antiplatelet Therapy (DAT)**

Use of aspirin and clopidogrel (DAT) is a rationale in certain patients at high-risk of thrombotic events, such as patients with acute coronary syndrome or undergoing percutaneous coronary intervention (PCI). Two thirds of diabetics have suboptimal response to DAT, defined as more than 50% residual platelet aggregation following ADP agonist stimulation [3].

Diabetics with stable asymptomatic coronary, cerebrovascular, or peripheral vascular disease did not have a reduction of MI, stroke or cardiovascular death with DAT compared to aspirin alone. DAT was associated with increased hemorrhagic events. Addition of clopidogrel to antiplatelet regimen in the presence of diabetic nephropathy was associated with increase in overall cardiovascular mortality, though the pathophysiological mechanism of this finding is unclear [3].

Lower baseline cAMP will lower platelet inhibition by P2Y12 antagonists [3]. Cilostazol is a phosphodiesterase-3 inhibitor that increases intra platelet cAMP levels and theorized can overcome platelet resistance to P2Y12 inhibition. Cilostazol reduced platelet activity more effectively than 150 mg clopidogrel in patients with high platelet activity following clopidogrel loading. Prasugrel (TRITON-TIMI 38) and ticagrelor (PLATO) appear favorable for use in conjunction with aspirin following PCI in DM patients in clinical studies [3].

**Hypoglycemia And Its Influence On Blood Constituent Changes**

Acute hypoglycemia is associated with increased FVIII coagulation activity and accelerated thrombin generation [33]. Insulin induced hypoglycemia in T2DM caused a transient increase in FPA [31].

In patients with type 1 diabetes, hypoglycemia acutely increases circulating levels of PAI-1, vascular, adhesion molecules, IL-6, and markers of platelet activation (P-selectin), thus resulting in activation of pro thrombotic, pro-inflammatory and pro-atherogenic mechanisms. Detrimental action on calcium homeostasis and platelet mitochondrial integrity may partly explains the effect of hypoglycemia on platelet function [33].

**Improving Glycemic Control And Its Influence On Blood Constituent Changes**

Improving glycemic control reduces TF levels, reduces thrombin generation [12], recovers platelet activity [3], lowers RDW [14] and is correlated with improvement of neutrophil functional activity [7]. Decreased plasmin generation and lower plasmin catalytic efficiency are reversible with modest improvement in glycemic control [5]. Improving glycemic control with gliclazide is associated with inhibition of ADP-induced platelet aggregation and fall in PAI-1 levels, thereby enhancing fibrinolysis [44].

In conclusion, regular monitoring of variable hematological parameters is an important item to be considered since it may be a predictor of some of diabetic complications.
References


