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Review on the Bidirectional Relationship of Type 2 Diabetes Mellitus (T2DM) with Major Depressive Disorder (MDD) and its Impact on the Vascular Complications

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a disease with a high prevalence of 8.3 % globally. Major Depressive Disorder (MDD) is another disabling disease that is highly prevalent worldwide. There exists a bidirectional relationship between diabetes and depression. The prevalence of MDD in T2DM patients has been found to be as high as 40%.

T2DM is associated with microvascular and macrovascular complications. These in turn, occur due to hyperglycemia, insulin resistance and release of inflammatory markers, all of which are characteristic of T2DM. MDD is also associated with cardiovascular risk. Platelet activation act as the connecting link between MDD and its vascular complications. The aim of this review was to explore the bidirectional relationship of T2DM and MDD and to evaluate their impact on the vascular complications, with special emphasis on the platelet hyperactivation, associated with these diseases.

As we tried to obtain maximum knowledge, we have gone through as many articles as possible from the databases PubMed and Google Scholar, related to the topic. We have not followed any particular inclusion or exclusion criteria, and whichever articles was found appropriate, after the primary analysis by the authors, were read in detail and information gathered.

We reached a conclusion that, due to the bidirectional relationship, the vascular complications increased multiple fold in patients with comorbid depression and diabetes. However, the studies in this field are grossly inadequate. Identifying novel therapeutic strategies for preventing platelet hyperactivation can reduce the vascular complications, thus improving the quality of life of patients.

Keywords: Type 2 diabetes mellitus, major depressive disorder, platelet activation, platelet function

Introduction

Type 2 Diabetes Mellitus (T2DM) is defined by the World Health Organization as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1].It is estimated to have a prevalence as high as 8.3% globally, which is expected to rise up to 9.5% by 2030 [2].India is expected to have the maximum number of diabetic patients in the world by that year[1]. The etiological factors leading to T2DM include obesity, sedentary lifestyle, genetic and environmental factors and stress. The disease is characterized by insulin resistance, which later leads to insulin deficiency and impaired functioning of β cells [3].

Major Depressive Disorder (MDD) is a disease attributed to multifactorial etiology including psychological, social, biological risks and associated stressful events. Depression will be the major contributor to the global burden of diseases by 2030 [4].MDD is associated with alterations in biological systems and pathways such as changes in psychomotor, emotional, autonomic, cognitive, neurochemical and neuroendocrine systems [5].

The neurobiological abnormalities identified in the pathophysiology of the disease include abnormal neurotransmission of the monoaminergic system, decreased levels of brain-derived neurotrophic factor (BDNF), increased levels of inflammatory cytokines, dysregulated hypothalamic-pituitary-adrenal axis (HPA), cerebral functional disorders, cortical and subcortical anatomical changes and some gene alterations [6].

Both T2DM and MDD are highly disabling diseases. The prevalence of MDD in T2DM patients has been found to be as high as 40% [7].

MDD further worsens T2DM by increasing the risk of non-adherence of patients to the dietary managements and lifestyle modifications for glycemic control. MDD patients are known to have less adherence to any treatment modality too [8]. Hormonal, Neurobiological and inflammatory mechanisms contribute to the co - existence of the two diseases and will be described later.

Diabetes Mellitus can lead to both microvascular and macrovascular complications. Diabetic Neuropathy, Retinopathy and Nephropathy are the major microvascular complications seen in diabetic patients [9]. Increased incidence of coronary artery disease (CAD), Peripheral vascular disease (PVD) and Cerebrovascular disease (CVD) resulting from accelerated atherosclerosis are some of the macrovascular complications [10].

Increased risk of cardiovascular diseases is seen in patients with MDD also. Platelet hyperactivity and endothelial dysfunction are the major etiological factors that link MDD and CVD. Various studies have elucidated the complex mechanisms by which platelets are activated and endothelium is damaged in subjects with MDD [11].

The vascular complications are expected to increase several folds in patients with comorbid diabetes and depression.The aim of this review is to explore the bidirectional relationship of T2DM and MDD and to evaluate their impact on the vascular complications, with special emphasis on the platelet hyperactivation, associated with these diseases.

Methodology

As we tried to obtain maximum knowledge, we have gone through as many articles as possible from the databases PubMed and Google Scholar, related to the topic. We have not followed any particular inclusion or exclusion criteria, and whichever articles was found appropriate, after the primary analysis by the authors, were read in detail and information gathered.

Discussion

Bidirectional Relation of Major Depressive Disorder and Diabetes Mellitus

The coexistence of T2DM and MDD have been neglected for a long time in the past. But recent studies have established, that there exists a bidirectional relationship between T2DM and MDD [12]. Incidence of T2DM in depressed patients might be due to the behavioral risk factors associated with depression such as obesity, smoking and lack of physical activities. Dietary habits of depressed patients are found to be extremely unhealthy, with excess carbohydrate, cholesterol and calorie intake, making them prone to diabetes [13].

Dysregulation of the hypothalamo- pituitary axis is another common pathway connecting MDD and insulin resistance. Acute stress, as in depression, are known to activate the hypothalamo-pituitary axis and sympatho medullary axis. Stress also activates the Norepinephrine (NE) neurons in locus coeruleus. The release of corticotropin-releasing hormone (CRH) from the cerebral cortex and hypothalamus is enhanced. Subsequently, Adrenocorticotrophic hormone (ACTH) is increasingly synthesized and released from the anterior pituitary. As a result, release of cortisol and other glucocorticoids from the adrenal cortex is triggered, subsequently raising blood glucose with associated insulin resistance [14].

Abnormality of the sympatho medullary axis is another mechanism by which depression leads to insulin resistance and T2DM. Increased norepinephrine metabolites suggestive of heightened sympathetic activity is characteristic of depression. This is associated with corresponding decrease in parasympathetic activity. The disturbance in sympathetic: parasympathetic equilibrium results in insulin resistance and elevated insulin levels. The increase in basal sympathetic output considerably leads to increased circulating free fatty acids, further deteriorating insulin resistance [15].

On the other hand, insulin resistance as such can set in depression. The functions of insulin in the brain include neuromodulation and transmission of important neurotransmitters. Brain insulin resistance has been associated with depressive behavior due to change in neuronal functions.

Circadian rhythm has been related to glucose homeostasis and mood regulation. Dysregulation of this ultimately leads to insulin resistance, diabetes and depression [16].

The inflammation associated with depression and diabetes also play a role in the pathogenesis of comorbid MDD and T2DM. Elevated levels of proinflammatory cytokines like TNF-α induce the production IL-6. The metabolic effects of these cytokines include inhibition of lipoprotein lipase, inducing dyslipidemia and insulin resistance. These cytokines are known to directly impair the insulin signaling pathway by its effect on insulin receptor as well as insulin receptor substrate phosphorylation. The increased levels of free radicals further accentuate the release of inflammatory mediators by the activation of mitogen activated protein kinase

(MAPK) and nuclear factor kb (NF-kβ) pathways. The free radicals damage the neurons and pancreatic β cells worsening both diabetes and depression [17]. Moreover, the oxygen and nitrogen free radicals, effect intracellular signaling pathways, mitochondrial, endoplasmic pathways. The protein kinase B (Akt) pathway which has a central role in maintaining hepatic glucose output, triglyceride release from liver and insulin sensitivity, is impaired. Akt is also the modulator to prevent cell death during free radical attack. All these together leads to a diabetic environment within the body [18].

A leptin hypothesis of depression is already proposed. Leptin, secreted from the adipose tissues modulates hunger through its action on brain. The serotonin and dopamine neurons in the brain contain large number of leptin receptors on their surface and leptin could affect the availability of these two monoamines in the synaptic cleft. Leptin is known to have an antidepressant effect.But metabolic syndrome and T2DM are often associated with leptin resistance. This can ultimately lead to depression [19].

Ghrelin is another peripheral hormone which is related to food intake. When energy level is low, the hormone induces hunger by its action on the hypothalamic circuit. Activation of ghrelin signaling pathway may be a mechanism to cope up with stress. Stress hormones are known to mediate this action by acting on the ghrelin releasing cells. As a result, there is increased food intake, termed as stress eating, increasing the risk factor for obesity and consequent diabetes [20].

The correlation between T2DM and MDD has been established in the genetic level also. Genes such as NR3C1, NR3C2 and MC4R are involved in the pathogenesis of both diabetes and depression [21]. Thirty four single nucleotide polymorphisms (SNPs) associated with diabetes, have been known to be associated with MDD [22]. In this way, diabetes and depression can co-exist in a person through various interrelated mechanisms.

Diabetes Mellitus and Endothelial Dysfunction

This part of the review analyses the pathophysiology of the vascular complications in T2DM patients. The state of hyperglycemia itself triggers the damage of vascular endothelium. The pathophysiological mechanisms underlying include increased production of Advanced Glycation End Products (AGE), enhanced expression of the Receptors for Advanced Glycation End products (RAGE) on endothelium, augmented hexosamine pathway, overactivation of polyol pathway and increased Protein Kinase C (PKC) activation. Simultaneously, the Endothelial Nitric Oxide Synthase (eNOS), which normally functions to maintain the vascular tone by producing NO, switch to produce Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), the levels of both of which are increased in diabetic subjects [23].

ROS and RNS can directly damage DNA and produce ADP ribose polymers. ADP ribose polymers reduce glyceraldehyde-3-phosphate dehydrogenase activity.

The glycolytic intermediates upstream of glyceraldehyde – 3-phosphate dehydrogenase enzyme are elevated. These intermediates are known to injure endothelium [24]. Biomarkers of Oxidative stress and endothelial injury like Asymmetric Dimethyl Arginine (ADMA), oxidized low density lipoprotein (ox LDL), P-selectin (s P-selectin), soluble E-selectin (s E-selectin), vWF PAI-1, CRP and F2-isoprostanes are elevated in diabetic subjects [25].

Activation of the nuclear factor-κB (NF-κB) pathway is another mechanism of vascular dysfunction in T2DM.

NF-κB is the mediator of RAGE activation on endothelial cells. Upon activation, NF-κB translocates to the nucleus and enhances the translation of proinflammatory and prothrombotic genes. The resultant rise in inflammatory mediators accelerate vascular damage [26].

Insulin Resistance associated with T2DM can aggravate endothelial injury. Normally, insulin enhances NO production through PI3K-dependent pathway. But when insulin resistance sets in, the MAPK pathway gets activated which leads to production of Endothelin 1 (ET-1), a potent vasoconstrictor resulting in endothelial dysfunction [27].

Diabetes Mellitus and Hyperactivation of Platelets

Platelets contain alpha granules and delta granules in the cytosol, both of which degranulate on activation. Alpha granules contain Throm Bo globulin, vWF, fibrinogen, Throm bospondin, platelet factor 4 (PF 4), CD 40L, CD 154 etc. Delta granules contain small molecules like adenosine diphosphate (ADP), ionized calcium and serotonin (5-HT). Activated platelets cross link with the help of fibrinogen or von Willebrand Factor which ultimately leads to platelet aggregation by recruiting additional platelets to the site of injury [28].

Hyperglycemia has direct effects on platelet activation. Formation of Advanced Glycation End products (AGE) results in activation. Externalization of phosphatidyl serine due to glycation can activate coagulatory cascade. Glycation of platelet surface receptors decreases membrane fluidity and enhances cellular adhesion [29]. Protein Kinase C pathway of platelet activation resulting in intracellular calcium release is activated by hyperglycemia [30]. Hyperosmolarity associated with hyperglycemia can activate GP IIb/IIIa receptors with associated enhancement of P-selectin expression [31]. Hyperglycemia can also activate the coagulation cascade by increasing release of prothrombotic molecules. It inhibits fibrinolysis by decreasing the levels of Plasminogen Activator Inhibitor -1 (PAI-1) [32].

Platelet surface expression of GP IIb/IIIa and GPIb levels are found to be correlated with HbA1c levels in the blood. Hyperglycemia results in larger platelets with more surface area and increased expression of surface receptor proteins [28]. Apart from GP IIb/IIIa and GPIb, expression of other receptors like P2Y12 are also increased on platelets with T2DM [33].

Platelets do have insulin receptors (IR) on their surface. Insulin normally inhibits platelet aggregation induced by thrombin, and decreases production of vasoconstrictors like thromboxane β2. Insulin also increases the secretion of antiatherogenic molecules like Plasminogen Activator Inhibitor (PAI) and the expression of PGI2 [34]. There is alteration in insulin signaling pathway in the platelets of subjects with T2DM. Insulin resistance leads to decreased levels of intraplatelet cAMP and hyperactivation of platelets [33]. Hyperinsulinemia in early stages of diabetes is harmful due to IRS independent reduction in number as well as sensitivity of platelet surface receptors to nitric oxide and prostacyclin [35].

The impairment of lipid metabolism in T2DM plays a role in platelet hyper aggregation. The apoprotein E on VLDL interacts with the LDL receptor on the platelets resulting in their activation [36]. The decrease in HDL molecules retards the cholesterol efflux from platelet cell membrane, hence promoting their aggregation [37].

CD 41 and CD 61, the glycoproteins normally present on platelet membrane, bind fibrinogen, von Willebrand factor [vWF], fibronectin and vitronectin [38]. Molecules like CD 62P, present in α-granules of resting

platelets and CD63, a lysosomal membrane protein, are translocated to the membrane following activation [39]. Platelet factor 4 (PF4), sP-selectin, β-Throm boglobulin (β-TG),thromboxane B2(TXB2), glycoprotein V (CD42d) and thrombospondin-1 are also markers of platelet activation, found to be high in subjects with T2DM [40].

Major Depressive Disorder and hyperactivation of platelets

As in the case of diabetes, platelet hyperactivation could explain the vascular complications in subjects with Major Depressive Disorder (MDD) [41]. Alteration in serotonergic signaling in MDD, along with dysfunction of the hypothalamic-pituitary-adrenal axis and autonomous nervous system are the major factors involved in the pathophysiology of platelet hyperactivation in patients with MDD [42].

Serotonin, a neurotransmitter, is inevitable for euthymic mood. Low levels of serotonin lead to disorders like depression. It was found that CSF analysis of depressed patients show low levels 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin. The serotonin transporter binding sites in brain are also found to be decreased in post-mortem analysis of patients with MDD [43].

Serotonin is generally a vasodilator in the periphery by increasing the production of Endothelial Derived Relaxing Factor (EDRF). But it turns out to be a vasoconstrictor when endothelium is injured, as no more EDRF is produced [44]. Platelets themselves cannot synthesize serotonin. But they uptake and store high amounts of peripheral serotonin, produced from sources like the enterochromaffin like cells in the gut [45].In addition, there occurs a process known as serotonylation in which serotonin in platelet cytoplasm is trans amidated to small GTPases, catalyzed by transglutaminase, during activation and aggregation.

This further degranulates the platelet granules [46]). Serotonin executes its action through the serotonergic receptors (5-HT2A) and (5-HT3A)on platelet surfaces [47]. Serotonin receptors (5-HT2A) and transporters (SERTs) within platelets share great similarity with those of the brain [48].

Upon ligand binding to the 5-HT2A receptors on platelets, G-protein mediated activation of Phospholipase C (PLC) pathway leads to consequent rise in intracellular calcium levels and platelet activation [49]. Increased expression of 5-HT2A receptors on platelets resulting in enhanced reactivity is seen in MDD [50].

Certain polymorphisms such as T102 homozygosity within the gene for platelet 5-HT2A receptor are known to increase the risk for depression and platelet hypercoagulability [51].

Serotonin transporters (SERT) regulate serotonin reduce synaptic cleft concentration of serotonin and terminate post synaptic transmission in brain tissue. In platelets, they transport serotonin to dense granules. As in the brain, platelets of depressed patients show a reduction in number of SERTs along with decreased serotonin binding sites on serotonin transporters concentrating serotonin at sites of vascular damage and prolong their effect [43]. Similar to platelet 5-HT2A receptors, some polymorphisms within the promoter region of the serotonin receptors (such as HTTLPR) are prone to have MDD along with heightened platelet reactivity [52].

Abnormal functioning of the adrenergic system plays a key role in the pathophysiology of MDD. The α2-adrenergic receptor functioning on platelets is simultaneously altered in subjects with depression. The

downstream signaling pathway involving cAMP formation is consequently impaired. Concurrently, the phospholipase C signaling pathway becomes activated with subsequent calcium release and Protein Kinase C (PKC) activation, which results in the release of serotonin [53].

NO,synthesized in platelets, is known to inhibit the pathways that are activated by serotonin [54]. Low activity of platelet and endothelial Nitric Oxide Synthase with subsequent decrease in NO levels have been established in patients with MDD [55]. The activity of the enzyme Arginase, which functions to reduce the availability of the substrate L-Arginine, has been found to increase in depressed patients [56]. The etiology for this change is attributed to the activation of platelet Arginase by the inflammatory markers which are found to be raised in these patients[57]. Subsequently, the superoxide anions and other free radicals are increasingly produced [58]. Brain is also particularly vulnerable to oxidative damage as it uses nearly 20% of the oxygen supply and has very little amount of anti-oxidants. As a result, depression symptoms further worsens with associated increase in severity of the cardiovascular complications [59].

Mood disorders are prone to inflammation. Depression itself might cause release of inflammatory markers, cytokines, chemokines and cell adhesion molecules by induction of oxidative stress. Stress is known to reduce antioxidant levels and induce lipid peroxidation [60].CRP has been predicted as a predictor of cardiovascular diseases in patients MDD [61]. There is a chronic systemic inflammatory state in depression associated with activation of cell mediated immune system characterized by T-helper (Th1)- activation and IFN γ. Levels of the inflammatory markers are associated with depression severity [62].

Alteration of the adenosinergic system has been implicated in the pathogenesis of depression. Adenosine is synthesized in the brain through hydrolysis of ATP, ADP and S-Adenosyl Homocysteine (SAH). Via the adenosine receptors on brain, adenosine is known to involve in neuronal functioning and neurotransmission. In subjects with MDD, adenosine synthesis was found to be decreased [63]. There are four types of adenosine receptors, A1, A2a, A2b, and A3 on platelets. Activation of the receptor A2a leads to increased intracellular cAMP with simultaneous reduction in sensitivity to serotonin and inhibition of platelet activation. Patients with MDD have decreased response to adenosine resulting in platelet hyperactivation [64].

Glutamate, an excitatory neurotransmitter in the nervous system acts on the (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptor) and metabotropic glutamate receptors (mGluR1 to mGluR8) [65]. Glutamate signaling is known to be altered in psychiatric disorders like depression. Platelets have glutamate stored in their dense granules. Studies have found that serum levels of glutamate were higher in patients with depression compared to healthy subjects [66]. Glutamate receptors on platelet surface have been found to be hyperactive in depressed patients [67].

Brain derived neurotrophic factor (BDNF), a nerve growth factor helps in the differentiation and survival of neurons. It helps to maintain the strength and morphology of neurons [68]. BDNF and its receptor TrkB, highly distributed in the brain has other functions like intracellular signaling processes, neuronal protection and synaptic plasticity. Decreased BDNF is associated

with atrophy of limbic structures found in depressed patients[69].

Platelets also contain significant amounts of BDNF. It is known to influence endothelial function, thrombin stability and monocyte activation. Platelet levels of BDNF are found to be decreased in patients with depression [70]. Polymorphism of the BDNF gene (e.g. BDNF Val 66 Met polymorphism) has been known to induce a thrombogenic state in experimental mice studies [71].

Platelet activation markers in comorbid Diabetes and depression

Given the incidence of MDD in T2DM and vice versa, it would be wise to assume that the complications associated with these diseases would tend to be severely increased when they co-exist. The vascular complications and platelet function abnormalities increase several folds in comorbid Diabetes and depression. Study by Daniela Zahn et al demonstrated that platelet activation markers CD40, CD62P andsCD40L differed significantly in depressed patients with and without diabetes [72]. Ante Silić et al found out a significant difference in the platelet serotonin levels, serum IL-6 and CRP levels in depressed patients with and without metabolic syndrome, which itself is a risk factor for T2DM [73].

The authors have done a flowcytometry based analysis of platelet activation markers among T2DM subjects with and without depression. We have found that CD63 was significantly higher in patients with comorbid diabetes and depression. CD62P was also high, but not was statistically significant. The expression of these activation markers positively correlated with hs CRP levels, marker of inflammation and with insulin pointing out to the underlying pathophysiology [74].

Considering the involvement of platelets in mediating the vascular complications associated with these diseases, the studies conducted in this area are grossly inadequate. More studies have to be conducted to establish the effect of comorbid depression and diabetes on platelet activation profile and its associated vascular complications. This would help to identify platelets as potential therapeutic targets to prevent the cardiovascular and other microvascular complications resulting from T2DM and MDD.

Conclusion

Type 2 Diabetes Mellitus is a major concern of morbidity in public health scenario. Major Depressive Disorder is another disabling disease associated with cardiovascular complications. There exists a bidirectional relationship between T2DM and MDD. T2DM is associated with microvascular and macrovascular complications. Endothelial injury and platelet hyperactivation play significant roles in the pathophysiology of these complications. MDD is also associated with vascular complications.

Platelet hyperactivation is known to be the causative factor of these complications. Due to the bidirectional relationship, the vascular complications can increase multiple fold in patients with comorbid depression and diabetes. Identifying novel therapeutic strategies for preventing platelet hyperactivation can reduce the vascular complications, thus improving the quality of life of patients.

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