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Review Article

A review of relationship between platelet indices and microvascular complications in type 2 diabetic patients

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ABSTRACT

Diabetes is a common metabolic disorder affecting the world population which accounts for major amount of morbidity and mortality mainly due to its micro vascular and macro vascular complications. This is a comparative study which analyses the correlation between the Platelet indices like Mean platelet volume, platelet distribution width, plateletcrit and total platelet count in diabetic patients with micro vascular complications and without complications. This review of the literature was conducted through an Internet search on a public access website like PubMed Google scholar, Medline databases until 2019. Keywords utilized included Diabetes mellitus, Microvascular complications, platelet indices. The major exclusion criteria was studies which included the patients with macrovascular complications and patients taking drugs which alters the platelet indices. All these articles were analysed. Platelet indices like Mean platelet volume and platelet distribution width was significantly higher in individuals with microvascular complications, predominantly Diabetic Nephropathy and Diabetic Retinopathy when compared to those without microvascular complications. Change in platelet indices were found to be statistically associated with diabetic microvascular complications. Hence these parameters can be used to monitor and to predict the risk of microvascular complications.

Keywords: Diabetes, Microangiopathy, Nephropathy, Neuropathy, Platelet indices, Retinopathy

INTRODUCTION

Diabetes is a common metabolic disorder affecting the world population which accounts for major amount of morbidity and mortality mainly due to its micro vascular and macro vascular complications.[1] This is a comparative study which analyses the correlation between the Platelet indices like Mean platelet volume, platelet distribution width, plateletcrit and total platelet count in diabetic patients with micro vascular complications and without complications.

SEARCH STRATEGY

This review of the literature was conducted through an Internet search on a public access website like PubMed Google scholar, Medline databases until 2019. Keywords utilized included Diabetes mellitus, Microvascular complications, platelet indices. The major exclusion criteria was studies which included the patients with macrovascular complications and patients taking drugs which alters the platelet indices.

REVIEW OF LITERATURE

The major mortality and the morbidity of diabetes were because of its complications. The major chronic complications were classified into microvascular complications and macrovascular complications. Among the complications, diabetes-related cardiovascular complications were the leading cause of mortality which was more than fifty percent and about ten percent was due to renal related complications. Individuals with family income below the poverty line had a two-fold higher mortality rate when compared with others.[2] Diabetes increases the mortality in every age group in any group of population.[3] On comparing to the mortalities of various metabolic disorders, diabetes accounts for a large amount of long term complications which leads to a very high amount of morbidity and disability.[4]

The major microvascular complications of diabetes were diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy.

Diabetic retinopathy

Diabetic retinopathy is the most common microvascualar complications of patients with long-standing diabetes and also an important cause for blindness in developing and developed world. About 17.7% of diabetic population will develop visual disturbance as a part of the diabetes-related complication. Duration of diabetes is the most important risk factor for retinopathy and about 90% of retinopathy was considered to be preventable 8 by adequate care. Diabetic retinopathy and diabetic macular edema account for about 12% of blindness each year which is significantly high.[5] Endothelial abnormality and dysfunction are considered to be the cornerstone of the pathogenesis of diabetic retinopathy and macular edema. This was also supported by an abnormality in the fluorescent angiographic picture of fundus in diabetic patients.[5] Increased extracellular matrix component, loss of pericytes and Increase in thickness of the basement membrane are the key pathological features of diabetic retinopathy and maculopathy which ultimately lead to disruption of retinal blood barrier. Abnormal retinal blood flow autoregulation leads to a preferential diversion of blood and also damaged capillary basement membrane leads to a formation of microaneurysms. Various pathological mechanisms including the oxidative stress and upregulated inflammatory response and finally the failed retinal blood autoregulation lead to blockage of retinal microvasculature thereby leading to retinal microinfarcts. This retinal ischemia leads to the release of multiple growth factors like vascular endothelial growth factor (VEGF) and proliferative diabetic retinopathy (PDR). These newly formed vessels were week and fragile. They ultimately burst due to varied reasons leading to vitreous haemorrhage and finally tractional retinal detachment and vision loss. Timely diagnosis and rapid treatment are some of the most important management strategies. It was identified that early treatment had a better clinical outcome. Routine ophthalmoscopic and slit-lamp examination was the most commonly used diagnostic modalities but the Fluorescent fundus angiogram is considered as the gold standard investigatory and preferred option provided the renal function is adequate American diabetic association recommends at least yearly once screening for diabetic retinopathy at least for high-risk population.[6,7] Based upon the ophthalmoscopic and angiographic finding diabetic retinopathy is classified into five stages, which comprises of three stages of low risk, stage four of diabetic non-proliferative retinopathy and fifth stage of proliferative retinopathy.[8] Glycemic control stands in the mainstay of treatment of diabetic retinopathy, but once retinopathy has progressed to the high stage, pan-retinal or grid photocoagulation has opted.[9] Nowadays many clinical reviews are coming to support the use of Anti-VEGF for retarding the progression of diabetic retinopathy like Intravitreal bevacizumab, intravitreal pegaptanib, and intravitreal ranibizumab, since they have a wide range side effect, they are lest preferred.[10-12] As a last resort surgery is preferred.

Diabetic nephropathy

From UKPDS it was observed that about 2% of diabetic patients progressed to microalbuminuria and among them, 2.8% progresses to the macroalbuminuria stage and finally, the elevation of creatinine or need of renal replacement therapy was about 2.3 % per year.[13] It was found that Diabetic nephropathy is the leading cause of ESRD and Renal replacement therapy in the modern world. Southeast Asian when compared to the developed nation are at higher risk to develop diabetic nephropathy. The duration of diabetes is significantly and directly related to the occurrence of diabetic nephropathy.[14] The principle hemodynamic alteration in diabetic nephropathy was hyper perfusion followed by hyper filtration in the glomerulus. Elevated glomerular pressure leads to increased glomerular plasma flow rate. this leads to increased alveolar resistance in the kidney finally resulting in mesangial cell overgrowth and leading on to increase in glomerular basement membrane thickness thereby ending in glomerulosclerosis.[15] Pleomorphism is the ACE gene is also responsible for the development of Diabetic nephropathy.[16] At molecular level majorly five pathways are thought to be involved in the pathogenesis which is, increased hexosamine pathway flux, activation of NF-κB, stimulation of ANG II synthesis, activation of the protein kinase C (PKC) pathway, increased polyol pathway flux and, increased advanced glycation end-product formation.[15] Diabetic nephropathy was classified into 5 stages clinically and biochemically. Stage 5 is the stage of end-stage renal disease and stage 4 is overt diabetic nephropathy and stage 3 is the most important and potentially treatable stage of incipient nephropathy.[17]

The major histological features were nodular glomerulosclerosis which is called the KW lesion, increased mesangial proliferation, capillary aneurysm,

capillary adhesion, lipophages, and complete hyalinization. There are diffuse atrophy and dilatation of the tubules in both cortex and medulla of the kidney.[18] Once microalbuminuria is identified or macroscopic proteinuria patients should be evaluated for it by ruling out other causes. There is no definitive evidence for the indication for biopsy. The biopsy is usually considered if there is the presence of proteinuria, unexplained hematuria in the absence of diabetic retinopathy. The main treatment options were strict sugar control and BP control, along with these ACE, ARB can be used alone or in combination with spironolactone was found to be effective in diabetic patients with nephropathy. Control of lipid and the use of Low dose aspirin is still in a debate. The newer drugs like Treatment with High doses of thiamine, ALT-711, protein kinase C inhibitor (ruboxistaurin), Sulodexide, a glycosaminoglycan, Pimagedine, of advanced glycation end products have been tried but not yet approved by FDA.[19]

Diabetic neuropathy

A rural population-based epidemiological study showed the prevalence of diabetic neuropathy is around 26.1%.[20] The occurrence of diabetic neuropathy was positively correlating with the duration of diabetes.[21] Diabetic peripheral neuropathy is a chronic, length-dependent, symmetrical sensorimotor polyneuropathy (DSPN), which is the most prevalent type. Painful diabetic neuropathy is also present but usually misdiagnosed. The next most important one is diabetic autonomic neuropathy which can affect any system in the body and it is potentially fatal.[22]

As the diabetes progress, there will be irreversible damage to the neuron and neuronal loss was there, even though the exact pathological mechanism is not fully understood various theory has proposed. The alterations in the neuronal microcirculation (endoneurial vessels), primary degeneration of the Axons and to some extent of demyelination are the three primary theories proposed. The derangement in the polyol pathway is one of the most widely accepted theory for diabetic peripheral neuropathy as it can lead to NADPH loss and oxidative stress to the neuron. Finally, they have concluded that the major pathogenesis of neuropathy in Type 1 and Type 2 diabetes was different and primary axonal loss was attributed to type 1 and vasculopathy was attributed to type 2 Diabetes.[23] A newer theory is being postulated to identify the newer therapeutic targets like the Nrf2 pathway (a transcriptive factor) which is gaining importance as it can prevent oxidative stress.[24] Even though strict glycemic control plays an important role in the treatment of diabetic neuropathy, TCA, anticonvulsants like gabapentin, pregabalin, topiramate, and SSRI and finally newer Aldolase reductase inhibitor are being used as the therapeutic targets. The antioxidant α-lipoic acid is also under extensive research for the treatment of diabetic peripheral neuropathy.

PLATELET INDICES

Platelet indices were the major morphological representative parameters for platelets, it indirectly signifies both the morphological and as well as the functional status of the platelet. The most commonly used platelet indices were the mean platelet volume, platelet distribution width, plateletcrit, and total platelet count. The normal range of mean platelet volume 8.6 - 15.5 fL and it was influenced by the total platelet count.[25] Platelet distribution width is a commonly used parameter that signifies the changes in the platelet size which has a wide range. The normal range was from 8.3 to 25 fl, this was highly influenced by various factors such as drugs, inflammatory state, young platelet, storage time. Platelet count is the next platelet indices which represent the amount of platelet in circulation, the normal value ranges from 150000 to 400000.

Platelets in diabetes

In recent times platelets are gaining more attention among the diabetic population. Recent studies from literature had found that platelets in diabetic patients behave differently and they have an increased aggregatory response and decreased response to the antiaggregatory substance this is mainly because of the metabolic effect of insulin resistance. Insulin normally downregulates the aggregatory action and up regulates the PGE2/PGI2 receptors in the platelets in the setting of insulin resistance most of the normal actions of platelets were lost and as a consequence of it, there will be accelerated atherosclerosis and other complications.[26,27]

Platelets are not only functionally changed but it was observed that platelets were also structurally altered in the diabetic population, It is shown that patients with diabetes mellitus have an altered platelet indices when compared with normal individuals and its pathological consequences like increased incidence of thromboembolism (Stroke, MI) were under research.[28]

Platelet indices in relation to microvascular complications

The most commonly evaluated platelet indices were platelet distribution width, mean platelet volume, plateletcrit and total platelet count and platelet large cell ratio.

Mean platelet volume

Mean platelet volume is a platelet index which is mainly signifying the size of platelet and if it is increased, it indirectly signifies the increased amount of large reticulated platelets in the circulation and it was found that larger platelet was highly reactive. They had found that mean platelet volume was positively correlating with poor glycemic control and it relating to the occurrence of diabetic retinopathy and diabetic nephropathy.[29,30]

Various studies had found the positive correlation between the Mean platelet value and HbA1C, neuropathy and also in diabetic population when compared to nondiabetic population.[31] Yilmaz et al, had found that Mean platelet volume is correlating directly with the stage of diabetic retinopathy.[32] Mean platelet volume is also correlating with diabetic retinopathy, nephropathy and HbA1C levels.[29,33] Mean platelet volume was also found to be related positively with the microalbuminuria and diabetic nephropathy.[34,35]

Platelet distribution width

Platelet distribution width is a surrogate marker of changes in platelet volume. An increased platelet distribution width signifies platelet anisocytosis. And it is also affected by inflammatory responses and active thrombosis. In diabetic the role of platelet distribution width is controversial. Buch et al had found that platelet distribution width varies significantly in diabetic and nondiabetic population and also it was significantly different in platelet with diabetic microvascular complications.[29] In controversy to the previous study CHEN et al, had found that there is no significant difference in platelet distribution width among patients with diabetic microvascular complications and patients with no complications.[35] Jindal et al, also supported this by saying mean platelet volume and platelet distribution width also relates to the occurrence of diabetic retinopathy.[36] Various studies had found that platelet distribution width was relating positively with diabetic microvascular complications predominantly with diabetic retinopathy and nephropathy, duration of diabetes, HbA1C levels.[29,37,38]

Plateletcrit and total platelet count

Plateletcrit and total platelet count were the two commonly used platelet parameters in clinical practice. Plateletcrit is the volume occupied by the platelet in the blood as the percentage. The number of platelets in the blood is maintained in an equilibrium state by regeneration and elimination.

The normal value of plateletcrit was 0.22-0.24% Although knowledge about plateletcrit is limited in the literature, previous studies have demonstrated the association of plateletcrit with certain inflammatory disease and vascular disease and an adverse impact on clinical outcomes in patients with myocardial infarction. Plateletcirt level was found to be elevated in endometrial carcinoma, papillary thyroid carcinoma some types bronchogenic carcinoma and also associated with shorter survival in pancreatic carcinoma.[39]

DISCUSSION

Recently a number of clinical research studies were analyzing the relationship between the platelet indices and various clinical settings like myocardial infarction, sepsis, trauma, thrombocytopenia, diabetes etc. Since platelet act as a central role in various chronic and acute inflammatory pathologies including diabetes only a few studies were carried out to analyze the relationship between the platelet indices and diabetic microvascular complications. And hence here in this study authors evaluated the platelet indices like mean platelet volume, platelet crit, platelet distribution width and total platelet count in the diabetic population to find out its relation with microvascular complications.

Various studies like walinjkar et al, Jindal et al, and Buch et al, all found out a positive correlation between the micro-vascular complications and mean platelet volume.[29,31,36] Mean platelet volume was also positively correlating with the diabetic retinopathy and its grade, a similar finding was also seen in other studies like Atea et al, Jindal et al, Hekimsoy et al.[28,36,40] Mean platelet volume was also positively correlating with diabetic nephropathy, Unubol et al, showed a significant positive correlation with microalbuminuria and mean platelet volume.

This elevation in mean platelet volume in diabetic with microvascular complications and poorly controlled Diabetics can be attributed as the main mode of energy for platelets is glucose. In the diabetic population, there may be an increased production of glycogen by the platelet which is mainly due to the presence of platelet in the chronic hyperglycemic environment in the diabetic population thereby resulting in increased mean platelet volume.

Platelet distribution width was a direct measure of the platelet size and its variability. Elevated platelet distribution width correlates with larger circulating platelets which are predominantly immature.[41] Various studies like Jindal et al, Dalamag M et al, showed a statistically significant correlation between the platelet distribution width with diabetic retinopathy and nephropathy.[36,42]

This increase in platelet distribution width was attributed to abnormal activation of platelet leading to the formation of pseudo philias which is seen in the people with long standing uncontrolled diabetes which was supported by Vagdatli E et al, and this change can be considered one of the pathogenesis process in diabetic microvascular complications.[43]

Demirtunc R et al, Rajagopal et al, had shown a positive correlation of increase in platelet count in population with diabetic microvascularcomplications.[42] This finding of no correlation between the plateletcrit and total platelet count with other microvascular complications may be due to the influence from other factors like infection, drugs causing thrombocytopenia even though most of these drugs were eliminated, and other systemic illness like dyslipedemia, hypertension and smoking which also can significantly alter the platelet count.

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