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A Review on Microvascular and Macrovascular Complications of Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is associated with a range of vascular complications that can significantly impact patient health and quality of life. Microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy, arise from the prolonged exposure of blood vessels to elevated glucose levels, leading to endothelial dysfunction, inflammation, and subsequent damage to small blood vessels. These conditions can cause vision impairment, kidney damage, and neuropathic pain, respectively. Macrovascular complications, such as coronary artery disease, cerebrovascular disease, and peripheral artery disease, result from atherosclerosis driven by insulin resistance, dyslipidemia, and hypertension. These conditions increase the risk of myocardial infarction, stroke, and limb ischemia. Effective management of blood glucose levels, along with control of blood pressure and lipids, is crucial in preventing or mitigating these complications. Understanding the pathophysiology of these vascular complications is essential for developing targeted interventions and improving outcomes in individuals with T2DM.

Keywords: *Type 2 Diabetes Mellitus, Microvascular complications, Macrovascular complications, Insulin resistance.*

I. Introduction

Diabetes mellitus is a widespread health issue impacting a significant segment of the population. It is marked by consistently high blood sugar levels and disturbances in the metabolism of carbohydrates, fats, and proteins, resulting from either inadequate insulin production or decreased insulin effectiveness. Long-term effects on the eyes, kidneys, and nerves are known as microvascular complications, while macrovascular complications such as heart disease, stroke, and peripheral artery disease also more frequent in diabetic individuals. The majority of health problems and fatalities related to diabetes are a result of these microvascular and macrovascular issues. Key contributing factors include poor management of blood sugar and the length of time a person has had the condition. Research also suggests that ethnic differences may influence the likelihood of developing these complications.[1]

II. MICROVASCULAR COMPLICATIONS

Research on the occurrence of diabetic retinopathy in India has consistently indicated a lower prevalence compared to Western populations. [2,3] In the population-based Chennai Urban Rural Epidemiology (CURES) study, 17.6% of individuals who self-reported having diabetes were found to have retinopathy. [4] Diabetic nephropathy presents with symptoms such as small outpouchings of retinal blood vessels, Round or blot-like bleeding within the deeper layers of the retina, Streaky haemorrhages resembling flames in the superficial retinal layers, Accumulation of fluid causing swelling in the retina, Lipid-rich deposits forming in the retina due to leakage from blood vessels, Soft, white patches caused by microinfarctions in the retinal nerve fibro layer, and macular oedema. [5,6]

The UKPDS study highlighted that high blood sugar levels and elevated blood pressure are the two major risk factors for retinopathy in diabetic patients. [7] Diabetic nephropathy can develop in up to 40% of diabetes cases, primarily due to glomerular damage caused by prolonged hyperglycaemia and hypertension. [8] This results in increased microalbuminuria and proteinuria, leading to a gradual decline in kidney function. Studies, such as the UKPDS on Type 2 diabetes patients, have demonstrated that tight control of blood sugar levels can prevent the onset of microalbuminuria and maintain glomerular filtration rate (GFR). [8,9] The DCCT study also supports these findings. [7,10,11]

2.1 DIABETIC RETINOPATHY

Diabetic retinopathy is a microvascular complication often seen in individuals with long-standing diabetes. It can lead to vision loss and, in severe cases, complete blindness. In the United States, diabetic retinopathy is the primary cause of blindness among diabetic patients, regardless of age. This condition is categorized into two stages: background retinopathy and pre-proliferative retinopathy. Background retinopathy is marked due to a partial obstruction of the retina's tiny blood vessels, which causes microaneurysms to develop in the walls of the capillaries. Pre-proliferative retinopathy is characterized by the total blockage of these small blood vessels, leading to the damage of retinal capillaries. [12]

2.2DIABETIC NEPHROPATHY

Diabetic retinopathy is a microvascular complication often seen in individuals with long-standing diabetes. It can lead to vision loss and, in severe cases, complete blindness. In the United States, diabetic retinopathy is the primary cause of blindness among diabetic patients, regardless of age. This condition is categorized into two stages: background retinopathy and pre-proliferative retinopathy. Background retinopathy is marked due to a partial obstruction of the retina's tiny blood vessels, which causes microaneurysms to develop in the walls of the capillaries. Pre-proliferative retinopathy is characterized by the total blockage of these small blood vessels, leading to the damage of retinal capillaries. [12]

2.3DIABETIC NEUROPATHY

Diabetic neuropathy refers to a range of nerve disorders caused by prolonged high blood sugar levels, affecting both the somatic and autonomic nervous systems. It leads to nerve damage in peripheral (sensory motor), autonomic, and spinal nerves. The main types include sensory motor neuropathy, which causes numbness, pain, and muscle weakness in the limbs, and autonomic neuropathy, which disrupts involuntary functions like digestion and heart rate. Chronic high blood sugar is the primary cause, and managing blood sugar levels is key to slowing its progression. Sensory motor neuropathy primarily impacts the distal nerves, particularly in the lower limbs, while autonomic neuropathy leads to a wide range of dysfunctions affecting nearly all bodily organs and systems. Maintaining proper blood sugar levels and performing islet cell transplants from the pancreas can help delay or prevent the onset of neuropathy. [14]

III. VISUAL COMPLICATIONS

3.1GLAUCOMA

Glaucoma is the leading cause of permanent blindness, with a global prevalence estimated at 3.54%. The most common form, open-angle glaucoma, is marked by a gradual increase in intraocular pressure and a progressive loss of peripheral vision due to nerve fiber damage. Open-angle glaucoma is most prevalent in Africa (4.2%) and least prevalent in Asia (2.1%), a notable statistic considering the projected rise in diabetes cases in these regions. Key risk factors for open-angle glaucoma include age, ethnicity, family history, and myopia, with elevated intraocular pressure being the only adjustable factor. Although the link between diabetes and glaucoma remains debated, there is a plausible mechanistic connection through autonomic dysfunction, leading to impaired autoregulation, fluctuating intraocular pressure, and a heightened vulnerability of retinal ganglion cells to apoptosis. [15]

3.2CATARACTS

Cataracts account for 51% of treatable blindness worldwide, with diabetes, metabolic syndrome, and low vitamin D levels being key risk factors. A "snowflake" cataract is commonly seen in younger individuals with Type 1 diabetes. In some cases, cataracts that develop rapidly in young patients can be reversed with better management of blood sugar levels. [16]

IV. MACROVASCULAR COMPLICATIONS

Approximately 80% of individuals with Type 2 Diabetes Mellitus (T2DM) who die do so due to cardiovascular disease (CVD). [17] Asian Indians are particularly susceptible to coronary artery disease (CAD), often experiencing triple vessel disease and earlier onset compared to white patients. [18] They also face a 40% higher mortality rate following acute coronary events, largely due to “atherogenic dyslipidaemia” (high triglycerides, small dense LDL, and low HDL) and elevated insulin resistance. [19,20] While peripheral vascular disease (PVD) is rare among Indian diabetics, largely due to lower smoking rates and younger onset, diabetic foot infections and ulcers are common, causing over 30% of hospitalizations in this group. [21,22] Around 25% of diabetics will develop a foot ulcer during their lifetime. [23] Furthermore, diabetes and tuberculosis often coexist, with diabetes affecting about 25% of tuberculosis patients. [24] Diabetics with tuberculosis may show atypical symptoms and have lower cure rates compared to those with tuberculosis alone. [25]

4.1PATHOPHYSIOLOGY

Atherosclerosis, which narrows arterial walls, is the main pathological mechanism behind macrovascular complications in T2DM. Key factors in these complications include insulin resistance and increased blood glucose. Insulin resistance leads to a prothrombotic state due to reduced inhibition of thrombosis and increased platelet aggregation, exacerbated by higher calcium levels in platelets. Elevated PAI-1 disrupts fibrinolysis, increasing vascular occlusion risk. Hyperglycaemia further contributes by generating ROS, which inactivate nitric oxide, causing endothelial dysfunction and atherosclerosis. ROS also activate protein kinase C (PKC), which disrupts vascular homeostasis and fosters thrombotic processes. This creates a vicious cycle of increased ROS production and worsening macrovascular complications. [26]

4.2CORONARY HEART DISEASE

Cardiovascular issues account for the highest healthcare expenses among patients with DM, particularly with CHD being closely associated with Type 2 T2DM. The Framingham study found that individuals with DM faced a 2- to 3-fold increased risk of atherosclerotic conditions, especially noticeable in cases of intermittent claudication and congestive heart failure, with women experiencing a higher risk than men. Recent research shows that diabetic patients are at a myocardial infarction (MI) risk comparable to that of nondiabetic patients who have previously had an MI. Specifically, the 7-year Myocardial Infraction risk is 20.2% for diabetic individuals without a history of Myocardial Infraction, compared to 3.5% for their nondiabetic counterparts. For those with a prior MI, the risks are 45.0% for diabetic patients versus 18.8% for nondiabetic patients. This indicates that Diabetes Mellitus serves as a significant risk factor for MI, akin to having had a previous Myocardial Infraction.

"Diabetic cardiomyopathy" (DC) refers to abnormal heart performance or structure in diabetics without CAD, high blood pressure, or notable valvular disease can lead to a condition marked by cardiac hypertrophy and diastolic dysfunction, which may result in heart failure with preserved ejection fraction. While this condition was first identified in diabetic patients experiencing heart failure, its recognition remains a topic of discussion. The U.K. Prospective Diabetes Study indicated that higher levels of HbA1c correlate with an increased risk of heart failure over a decade. [26]

4.3CEREBROVASCULAR DISEASE

Stroke is a significant macrovascular complication of diabetes mellitus (DM). Among various stroke subtypes, those with Diabetes Mellitus are particularly vulnerable to the effects of cerebral small vessel disease. Elevated blood glucose levels increase the likelihood of stroke, and this heightened risk is frequently observed in diabetic patients, leading to worse clinical outcomes, including higher mortality rates, particularly after an ischemic stroke. [26]

4.4ARRHYTHMIAS - SUDDEN CARDIAC DEATH

Persistent elevated blood sugar levels in Type 2 Diabetes Mellitus (T2DM) contribute to several cardiac issues, such as arrhythmias and sudden cardiac death (SCD). The occurrence of arrhythmias in T2DM is mainly related to cardiac autonomic neuropathy. Atrial fibrillation (AF) stands out as the most prevalent and critical arrhythmia in clinical practice, as it correlates with a greater likelihood of cardiovascular and cerebrovascular complications. Recent studies suggest that people with DM face a higher risk of developing AF. [26]

V. Conclusions

In conclusion, Type 2 Diabetes Mellitus (T2DM) is associated with significant microvascular and macrovascular complications. Microvascular issues, such as retinopathy, nephropathy, and neuropathy, arise from chronic hyperglycaemia and lead to severe long-term health problems, including vision loss, kidney failure, and nerve damage. Macrovascular complications result from atherosclerosis and other vascular changes exacerbated by insulin resistance and hyperglycaemia. Both types of complications significantly impact morbidity and mortality, emphasizing the critical need for effective blood glucose management and regular monitoring to mitigate these risks and improve patient outcomes.

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References

[1]. Agrawal RP, Ola V, Bishnoi P, Gothwal S, Sirohi P, Agrawal R. Prevalence of micro and macrovascular complications and their risk factors in type-2 diabetes mellitus. J Assoc Physicians India. 2014 Jun;62(6):504-8. PMID: 25856915.

[2]. Dandona L, Dandona R, Shamanna BR, Naduvilath TJ, Rao GN. Developing a model to reduce blindness in India: The International

Centre for Advancement of Rural Eye Care. Indian J Ophthalmol. 1998 Dec;46(4):263-8.

[3]. Narendran V, John RK, Raghuram A, Ravindran RD, Nirmalan PK, Thulasiraj RD. Diabetic retinopathy among self-reported diabetics in southern India: a population-based assessment. Br J Ophthalmol. 2002 Sep;86(9):1014-8.

[4]. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of Diabetic Retinopathy in Urban India: The Chennai Urban Rural Epidemiology Study (CURES) Eye Study, I. Investigative Ophthalmology & Visual Science [Internet]. 2005 Jul 1;46(7):2328.

[5]. Rema M, Pradeepa R. Diabetic retinopathy: an Indian perspective. Indian Journal Medical Research 2007 Mar;125(3):297-310.

[6]. Franklin SW, Rajan SE. Diagnosis of diabetic retinopathy by employing image processing technique to detect exudates in retinal images. IET Image Processing. 2014 Oct 1;8(10):601–9.

[7]. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998 Sep 12;317(7160):703-13.

[8]. Stavniichuk R, Shevalye H, Sergey Lupachyk, Obrosov A, John Taylor Groves, Obrosova IG, et al. Peroxynitrite and protein nitration in the pathogenesis of diabetic peripheral neuropathy. Diabetes/metabolism research and reviews. 2014 Nov 1;30(8):669–78.

[9]. 9.Hajhosseiny R, Khavandi K, Jivraj N, Mashayekhi S, Goldsmith DJ, Malik RA. Have we reached the limits for the treatment of diabetic nephropathy? Expert Opinion on Investigational Drugs. 2014 Feb 21;23(4):511–22.

[10]. 10.Factors in development of diabetic neuropathy. Baseline analysis of neuropathy in feasibility phase of Diabetes Control and Complications Trial (DCCT). The DCCT Research Group. Diabetes. 1988 Apr;37(4):476-81.

[11]. Diabetes Control and Complications Trial.

[12]. Nentwich MM. Diabetic retinopathy - ocular complications of diabetes mellitus. World Journal of Diabetes [Internet]. 2015;6(3):489.

[13]. Varghese RT, Jialal I. Diabetic Nephropathy. 2023 Jul 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30480939.

[14]. Amoretti M, Amsler C, Bonomi G, Bouchta A, Bowe P, Carraro C, et al. Production and detection of cold antihydrogen atoms. Nature. 2002 Oct 1;419(6906):456–9.

[15]. Zhang N, Wang J, Li Y, Jiang B. Prevalence of primary open angle glaucoma in the last 20 years: a meta-analysis and systematic review. Scientific Reports. 2021 Jul 2;11(1).

[16]. Harahap J, Rania R. Cataracts Risk Factors and Comparison of Blood Glucose Levels in Diabetic and Non-Diabetic Patients towards the Occurrence of Cataracts. Open Access Macedonian Journal of Medical Sciences. 2019 Oct 14;7(20):3359–62.

[17]. Ali MK, Narayan KM, Tandon N. Diabetes & coronary heart disease: current perspectives. Indian J Med Res. 2010 Nov;132(5):584-97.

[18]. Enas EA, Singh V, Munjal YP, Bhandari S, Yadave RD, Manchanda SC. Reducing the burden of coronary artery disease in India: challenges and opportunities. Indian Heart J. 2008 Mar-Apr;60(2):161-75.

[19]. Mohan V, Venkatraman JV, Pradeepa R. Epidemiology of Cardiovascular Disease in Type 2 Diabetes: The Indian Scenario. Journal of Diabetes Science and Technology. 2010 Jan;4(1):158–70.

[20]. Enas EA, Mohan V, Deepa M, Farooq S, Pazhoor S, Chennikkara H. The Metabolic Syndrome and Dyslipidaemia Among Asian Indians: A Population with High Rates of Diabetes and Premature Coronary Artery Disease. Journal of the Cardiometabolic Syndrome [Internet]. 2007 Sep;2(4):267–75.

[21]. Pradeepa R, Chella S, Surendar J, Indulekha K, Anjana RM, Mohan V. Prevalence of peripheral vascular disease and its association with carotid intima-media thickness and arterial stiffness in type 2 diabetes: The Chennai Urban Rural Epidemiology Study (CURES 111). Diabetes and Vascular Disease Research. 2014 Mar 13;11(3):190–200.

[22]. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nature Reviews Endocrinology [Internet]. 2016 Apr 15;12(6):357–70.

[23]. Singh N. Preventing Foot Ulcers in Patients with Diabetes. JAMA. 2005 Jan 12;293(2):217.

[24]. Viswanathan V, Kumpatla S, Aravindalochanan V, Rajan R, Chinnasamy C, Srinivasan R, et al. Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. PloS One [Internet]. 2012 [cited 2020 Jul 26];7(7): e41367.

[25]. Viswanathan V, A. Vigneswari, K. Selvan, K. Satyavani, R. Rajeswari, Kapur A. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis—A report

from South India. Journal of diabetes and its complications. 2014 Mar 1;28(2):162-5.

[26]. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular complications of type 2 diabetes mellitus. Current Vascular Pharmacology. 2019 Apr 5;18(2).