

**A REVIEW ON DOMINATING DIABETIC COMPLICATIONS AND THEIR
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Article Received on 02/03/2021

Article Revised on 21/03/2021

Article Accepted on 11/04/2021

ABSTRACT

Diabetes, the most common global burden affecting people of all age groups. It is a chronic metabolic disorder, results in elevated levels of blood glucose. This could be due to beta cell destruction/dysfunction. Diabetes results in variety of Complications, among them, the micro and macro vascular complications are more predominant. The incidence of diabetes complications varies with genetic factors, environment, gender and race. Diabetic retinopathy is associated with loss of pericytes and it is classified as non-proliferative and proliferative types. Diabetic neuropathy is the inflammation of neurons causing burning and tingling sensation especially in arms and feet. Diabetic nephropathy refers to the damage of nephrons due to hyperglycemic condition which progress to end stage renal failure where GFR is reduced to less than 15ml/min. Microalbuminurea is the hallmark of nephropathy. Nephropathy and hypertension are correlated in diabetic individual by altered Renin-angiotensin-aldosterone system mechanism. Oxidative stress pays the way for endothelial dysfunction which further worsens the condition by resulting in insulin resistance. The insulin resistance cause perivascular fibrosis which is characterized by ventricle hypertrophy leading to cardiomyopathy. Plaque deposit trigger the incidence of heart failure and one among the risk factor for development of stroke. Occurrence of stroke is predominant due to inflammation of cerebral blood vessels. Antioxidants play a vital role in prevention of severity of complications. There is no cure for diabetes hence, proper adherence, life style modifications and regular screening help in eliminating the risk of mortality due to complications.

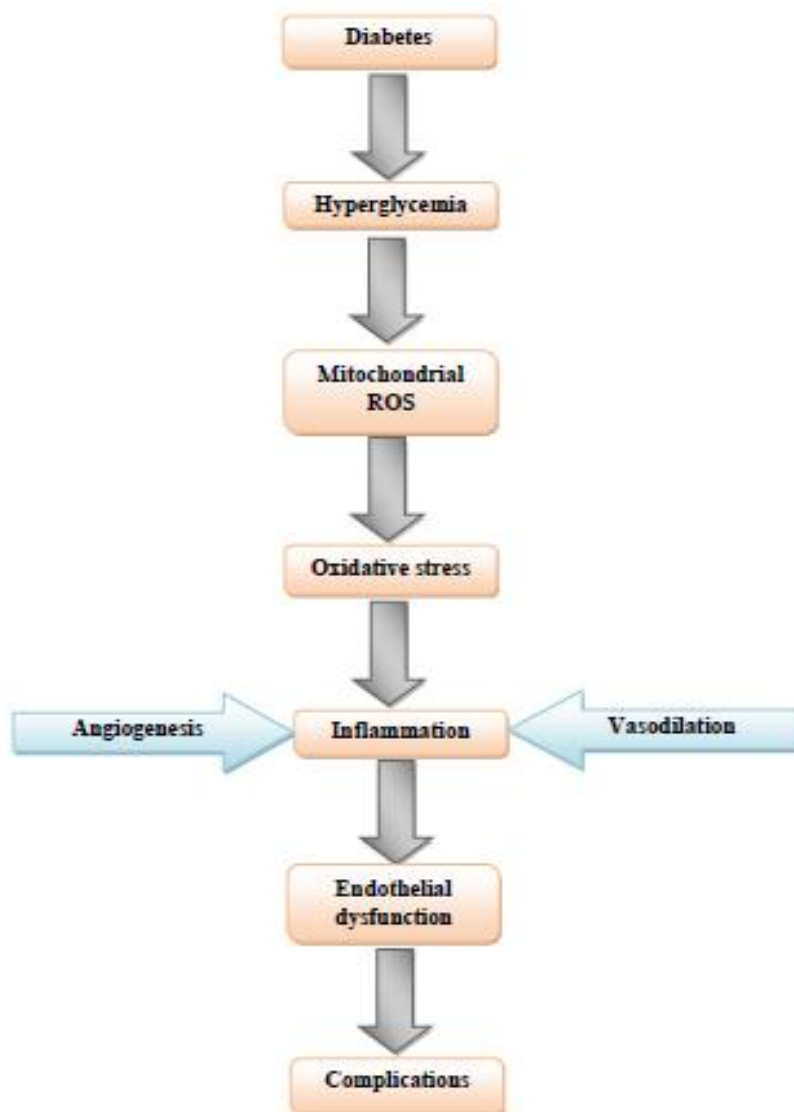
KEYWORDS: Complication, Diabetes, Endothelial dysfunction, Macrovascular, Microvascular, Oxidative stress.**INTRODUCTION**

Diabetes can be defined as chronic, metabolic disorder resulting from destruction in beta cells of pancreas leading to rise of blood glucose levels.^[1] It is estimated that about 9.3% of people are diagnosed with diabetes worldwide which seems to be a rise by 62% in past 10 years.^[2] Complications are common among both type 1 and type 2 diabetes patients which may also responsible for various morbidity as well as mortality in diabetics. These are classified into micro vascular and macro vascular complications.^[3] Type 2 diabetes accounts for 95% of all diabetes. Hypertension is the major risk factor that accelerates the incidence of micro and macro vascular complications. Patient with diabetic hypertension are at high risk of developing insulin resistance that substantially worsen hyperglycemic condition.^[4] Microvascular complications are of long term duration that affects tiny blood vessels. Macrovascular complications include disease of coronary and peripheral arteries. Diabetes increase the risk of stroke about 5 times, of these, cardiovascular disease is the major burden that increase the rate of mortality.^[5,6] Kidney disease remains major risk factor for

development of cardiovascular disease in type 2 diabetes individuals.^[7] In the present review, the predominant complications of diabetes viz., micro and macro vascular complications and their management are discussed.

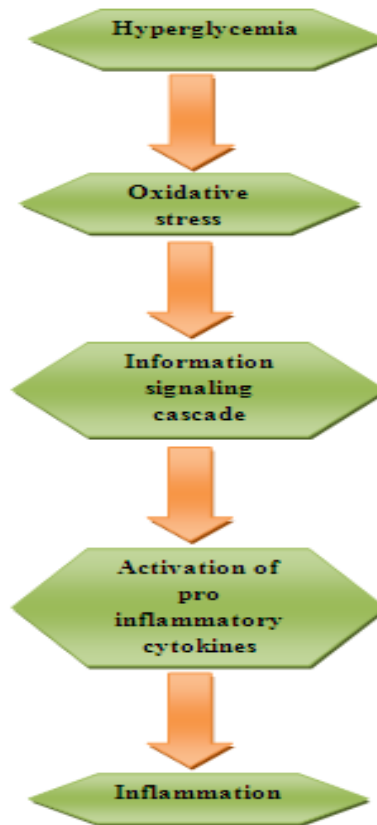
Pathophysiology of complications

Oxidative stress is the vital factor for development of endothelial dysfunction as it involve in damage of DNA, proteins and lipids that contribute to progression of microvascular as well as macrovascular complications.^[8,9] Hyperglycemia leads to excessive reactive oxygen species which oxidize poly unsaturated lipid membrane contributing to plaque formation.^[10] Mitochondrial ROS activates cyclooxygenase 2 gene resulting in overproduction of prostaglandin E2 that is associated with glomerular hyperfiltration which is the character of early stage diabetic nephropathy.^[11]



Microvascular complications

Microvascular complications are most dominant among diabetic population. ROS seems to be the common factor in progress of diabetic complication.^[12] Retinopathy which is leading cause of visual damage is characterized by thickening of basement membrane and increased capillary permeability.^[13] Hyperglycemic condition compromise blood flow in peripheral nerves. This contribute to nerve fiber damage followed by ischemia.^[14]

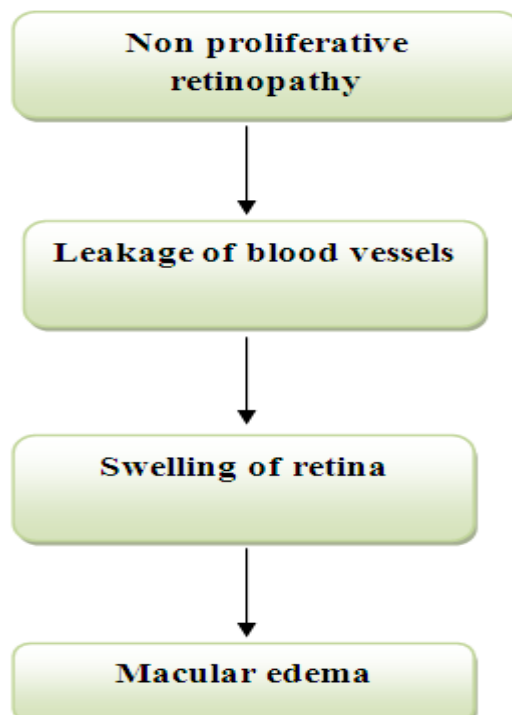


Diabetic retinopathy

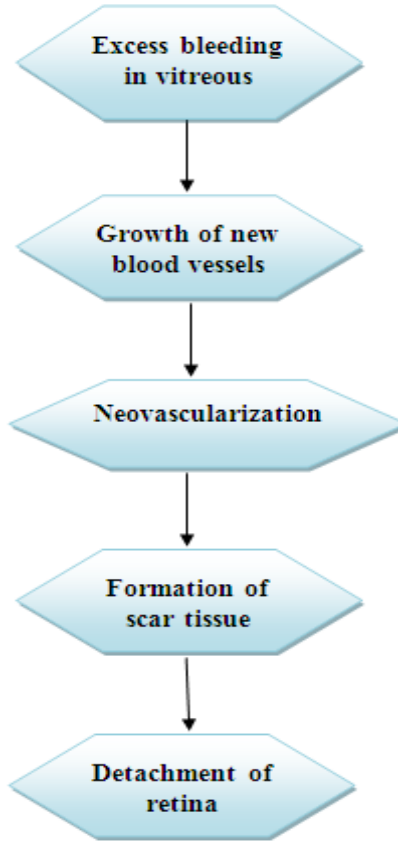
Diabetic retinopathy is one of the major reasons for loss of vision especially in hyperglycemic population and is due to microvascular damage occurring in retina.^[15] Retinal detachment results in partial and complete loss of vision occurs from retinal leakage. Loss of pericytes is

the early marker of diabetic retinopathy.^[16] Non Proliferative Retinopathy is the early stage of eye disorder due to chronic diabetes and Proliferative retinopathy is the term that indicates more advance stage of eye damage.^[17]

Non proliferative retinopathy



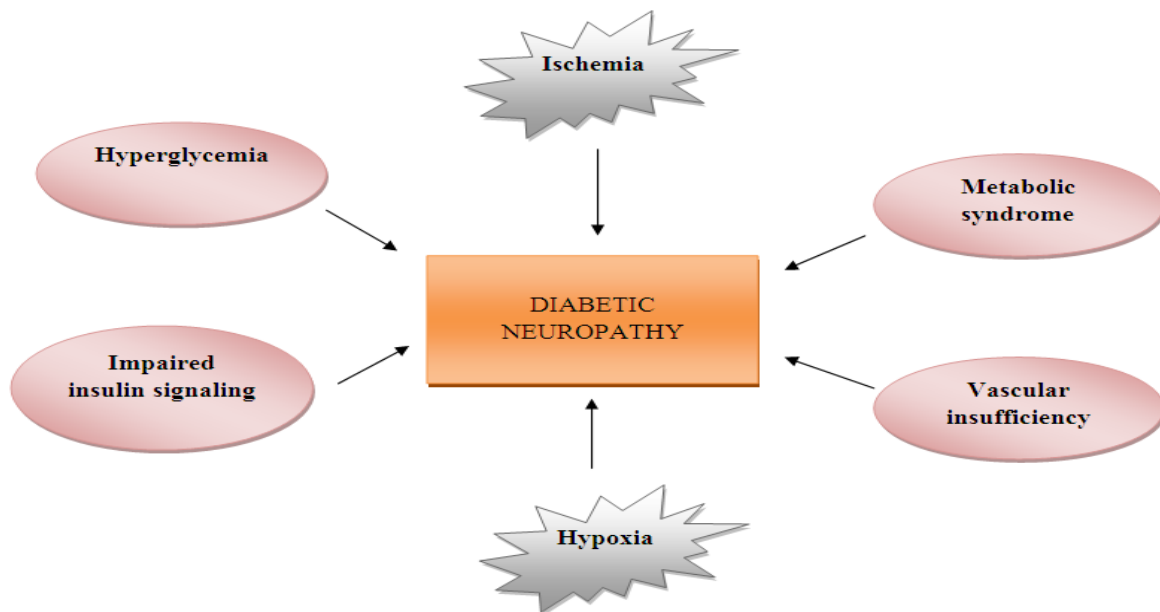
Proliferative retinopathy



Diabetic neuropathy

Diabetic neuropathy is the condition, where various nerves are affected and is characterized by metabolic disorders. The pain experienced is due to alterations in

blood supply to peripheral nerves, changes in Na-Cl channel and more.^[18] Hypertension, dyslipidemia, obesity and severe ketoacidosis increase the risk of diabetic neuropathy.^[19]



Peripheral neuropathy

Diabetes is the leading cause of peripheral neuropathy which is characterized by stabbing, burning and tingling pain. Peripheral neuropathy is the most common type of

neuropathy and the pain is located in feet, legs, arms and hand.^[20]

Autonomic neuropathy

Autonomic neuropathy is a condition results from the damage of nerve supplied to internal organs. It is least understood complication of diabetes having greater negative impact on patient's quality of life. Silent myocardial ischemia is one of the major manifestations of this autonomic neuropathy.^[21]

Diabetic nephropathy

Diabetic nephropathy is a condition in which nephrons get damaged by metabolic and hemodynamic pathway

Diabetic retinopathy and its stages^[25]

Stage	Designation	GFR	Albumin excretion mg/day
I	Hyperfiltration	>150ml/min	<30
II	Microalbuminuria	High normal	30 – 300
III	Overt proteinuria	Normal	30 –300
IV	Progressive nephropathy	Decreasing	>300
V	End stage renal failure	<15ml/min	1000

Macrovascular complications

Cardio vascular disease is the leading cause of mortality in people with type 2 diabetes mellitus^[26] and it accounts for about 70% of mortality in diabetes patient. Hyperglycemic condition accounts for damage of myocardial structures causing ischemic events^[27] and increase the risk of coronary diseases two times in men and four times in women.^[28] Atherosclerotic plaque

interactions which are induced by hyperglycemic condition. It has emerged as major reason for chronic renal failure.^[22] Microalbuminuria is the feature of nephropathy which may then progress to proteinuria. The risk of nephropathy is relatively high in nonwhite people than white people. Patient with diabetic nephropathy have more insulin resistance and poor glycemic control causes left ventricular hypertrophy.^[23] Initially imbalance of efferent and afferent arteriolar resistance causes hyperfiltration by glomerulus followed by decreased rate of glomerular filtration in diabetic nephropathy.^[24]

triggers the cardiovascular complications resulting in inhibition of achieving efficient therapeutic outcome.^[29] In contrast diabetes worsens plaque deposit by accelerating the inflammation in blood vessels which lead to plaque formation.^[30] Hypertension, diabetic cardiomyopathy and myocardial infraction are most common cardiovascular disease accompanying diabetes mellitus.^[31]

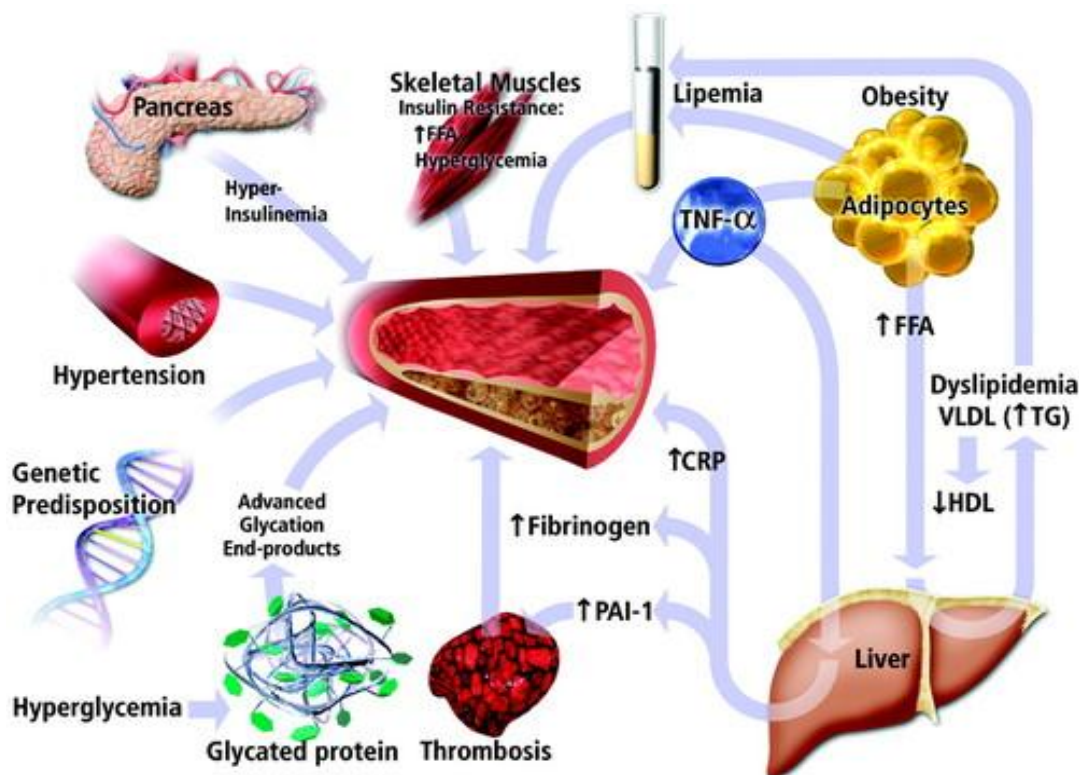


Fig. 1 Pathophysiology of macrovascular complication.^[32]

Hypertension affects about 60% of diabetic population and is the major comorbid condition.^[33] It occurs due to vascular remodeling that is characterized in mid stage

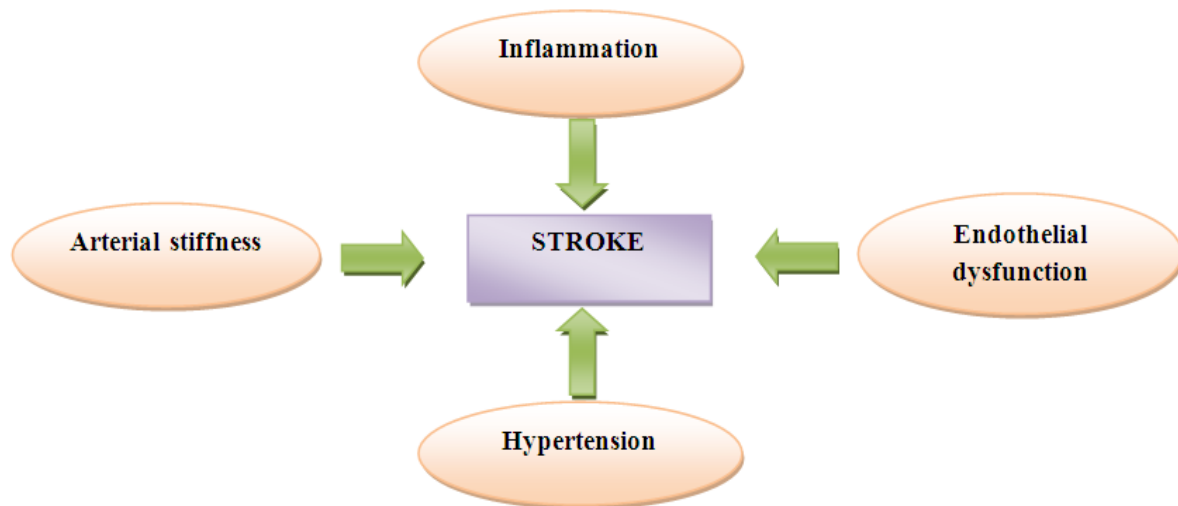
diabetes. Remodeling that occurs in afferent artery increases the glomerular pressure which affects RAAS pathways causing hypertension.^[34] As a result, excess

angiotensinogen in circulation elevates blood pressure. Obesity and adiposity are key factors for coexistence of hypertension diabetes mellitus. Oxidative stress causing cell injury results in endothelial dysfunction. This play a major role in insulin resistance^[35] leading to worsening the condition.

Diabetic cardiomyopathy refers to heart muscle disorder characterized by abnormal structure and functioning of myocardial cells without coronary artery disease^[36] occurring due to hyperglycemic condition even in absence of hypertension or coronary artery disease.^[37] Impairment of metabolic signaling due to systemic

insulin resistance is considered as a reason for development of diabetic cardiomyopathy.^[38] Perivascular fibrosis resulting in increased collagen deposits and left ventricle hypertrophy and these changes occurs in association with diabetic cardiomyopathy.^[39]

Stroke risk is more in population with diabetes. The risk of developing stroke is 3 times more in diabetic people.^[40] This is associated with inflammation of blood vessels in cerebral region. Structural changes of capillaries and endothelial dysfunction may also contribute to stroke.^[41]



Management of complications

Retinopathy usually occurs in population of age above 50 years. Laser surgery is the choice of treatment for diabetic retinopathy.^[42] Vascular endothelial growth factor (ranimizumab) and corticosteroids are useful for non-proliferative retinopathy.^[43] Lipid lowering agent is found to be effective in decreasing the progress of diabetic retinopathy.^[44] Pregabalin and Gabapentin which are anticonvulsants are used in the management of neuropathic pain.^[45]

Angiotensin converting enzyme inhibitors (captopril, enalapril) and angiotensin receptor blockers (telmisarton, olmesarton) are used as first line therapy for management of hypertension in diabetic population.^[46]

Control of hypertension along with salt restriction and limited intake of protein is essential for management of nephropathy.^[47] ACE inhibitors are recommended for reduction of albuminuria to decrease the progress of proteinuria.^[48] Hyperlipidemic condition fastens the loss of kidney functioning hence lipid lowering agents result in reduction of proteinuria.^[49]

Low doses of aspirin is recommended for primary prevention of heart disease in diabetic population.^[50] Intake of Antioxidants reduces the oxidative stress and helpful in preventing severity of complications.^[51] Common drugs used in management of various complications are enlisted in the table given below.

CLASS	DRUG	DOSE	INDICATION
VEGF-A antagonist	Ranimizumab	0.5 mg q1month	Retinopathy
Anticonvulsant	Pregabalin	150-300mg/day	Neuropathy
Anticonvulsant	Gabapentin	900-3600mg/day	Neuropathy
ACE inhibitor	Captopril	250mg q8h	Hypertension Nephropathy
ACE inhibitor	Enalapril	2.5-5mg/day	Hypertension
Angiotensin II receptor antagonists	Telmisarton	80mg/day	Hypertension
Angiotensin II receptor antagonists	Olmesarton	20mg/day	Hypertension
Antiplatelet	Aspirin	80-325mg/day	CVD
Bile Acid Sequestrants	Colestyramine	4-8g/day	CVD

CONCLUSION

This article is an overview of common complications of diabetes mellitus with their brief pathophysiology and management. The uncontrolled sugar levels results in variety of acute and chronic effects which affecting patient's quality of life.^[52] People with type 1 diabetes have less chances of developing microvascular complications.^[53] The goal of therapy is maintenance of HbA1C below 7, total cholesterol below 200mg/dl^[54] and appropriate body weight to reduce the risk of development of complications. Regular screening for kidney functioning, lipid deposits along with life style modifications help in eliminating complication progress. Chance of diabetic cataract formation is higher due to stimulation of certain apoptosis growth factor by oxidative stress associate with diabetic retinopathy.^[55] Control of hypertension decreases the chances of retinopathy as well as nephropathy. Proper education to patient on disease, patient adherence to therapy and appropriate follow up of guidelines has great impact on positive outcome.

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