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Review Article

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NON-INSULIN-DEPENDENT (TYPE II) DIABETES MELLITUS AND CARDIOVASCULAR DISEASES

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ABSTRACT

Type 2 Diabetes mellitus, a disease that has now affected a very large population of the world, is considered to be a pandemic. It results in hyperglycaemia and resistance to insulin, which follows serious life threatening conditions such as hypertension, cardiac failure, anaemia, etc. Though medications such antihyperglycemics are given to diabetic patients, but, there is a major role of diet, physical activity and self-care in the management of diabetes. This review presents the pathophysiology of diabetes, relation of diabetes with cardiac failure and associated heart disease, and management techniques to control this disease. It also presents the current use of antihyperglycemics and evidences from various research articles, as to comment upon the efficacy of the drug.

KEYWORDS: Diabetes, Hyperglycemia, Cardiac Failure, Insulin, RAAS.

INTRODUCTION

Type 2 diabetes mellitus is a metabolic syndrome, also known as non-insulin-dependent diabetes mellitus, which is marked by hyperglycemia, insulin resistance, and hence its deficiency.[1] Most of the diabetic patients on average are seen to be obese and more resistant to insulin, which further leads to more increase in body weight after the onset of the disease.[2] Studies suggest that diabetes is more common among populations between 40 and 59 years of age and is a major cause of mortality in today's population because of many serious life-threatening conditions that follow the onset of the disease, such as, stroke, retinopathy, neuropathy, nephropathy, and ischaemic heart disease.[1,3,4] It is associated with people who generally have a family history of diabetes, obesity, impaired glucose metabolism, or those who lead a sedentary lifestyle.[4] The pathophysiology of the disease includes a decrease in insulin production, resulting in the failure of the β-cells in the pancreas that eventually results in a decline in the transport of glucose in the liver, muscle, and fat cells.[1] The impaired function of the hormones regulating blood glucose levels, such as somatostatin, GLP-1, adrenaline, glucagon, and cortisol often leads to the occurrence of prediabetes, followed by insulin resistance and type 2 diabetes mellitus.[5] If left untreated, it can result in various complications that may include failure of heart, kidney, and brain as well.[4]

Pathophysiology of Type II Diabetes Mellitus and Heart Failure

Non-insulin-dependent diabetes mellitus (NIDDM) is associated with hyperinsulinemia, hyperglycemia, and insulin resistance. It is accompanied by inflammation and vascular smooth muscle cells proliferation which leads to atherosclerosis. The level of low-density lipoprotein increases, dyslipidemia, and there is endothelial dysfunction which leads to ischemic cardiomyopathy.[6] There is an increase in the amount of free fatty acids which can cause the accumulation of lipids in cardiac myocytes and disturb the handling of calcium ions. There is impairment in contraction and relaxation of muscle due to disturbance in the handling of calcium ions. It is also associated with the rise in levels of advanced glycation end-products (AGEs) that results in microvascular remodeling. There is overproduction of angiotensin II due to the activation of the renin-angiotensin-aldosterone system (RAAS). Chances of left ventricular hypertrophy also increase. They will favor fibrosis and diabetic cardiomyopathy. It will lead to heart failure.[7]

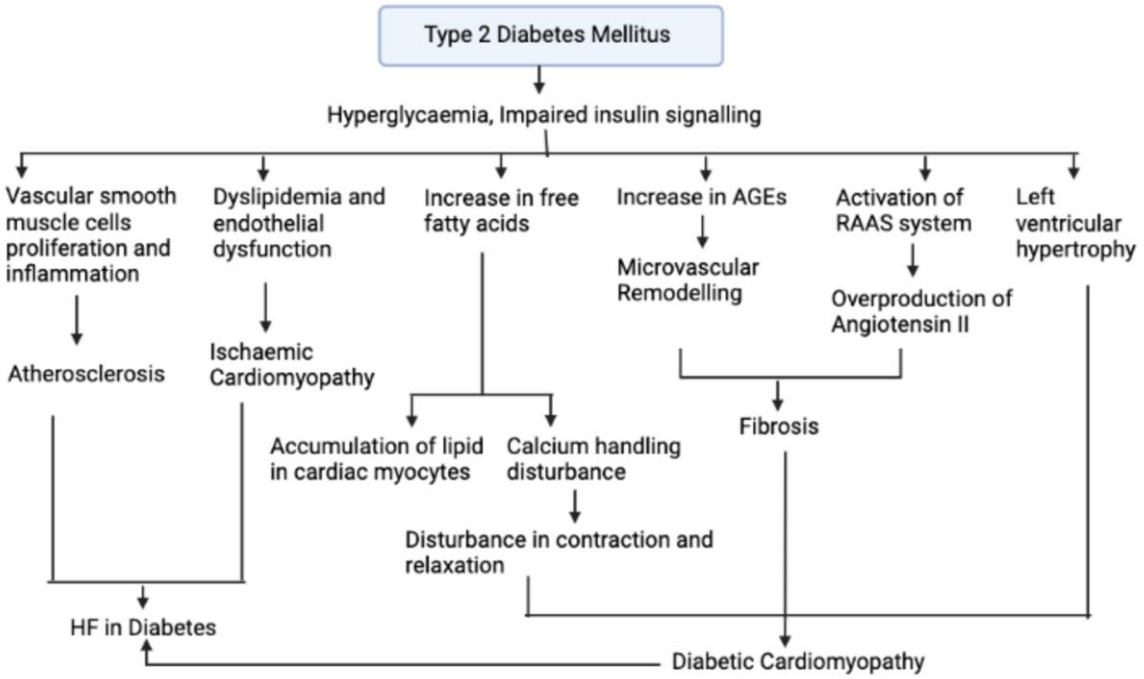

Fig 1.1: Pathophysiology of Type II Diabetes mellitus and Heart Failure.

DIABETES AND CARDIOVASCULAR DISEASES

Diabetic Cardiomyopathy

Diabetic Cardiomyopathy is characterized by the presence of aberrate cardiac structure and execution without even a trace of cardiovascular disorders, such as myocardial ischemia, coronary artery disease, hypertension, and significant valvular disease, in people suffering from diabetes mellitus.[8] As Diabetic Cardiomyopathy advances, ventricular remodeling occurs which is usually not detected in the early stage.[9] It is characterized by structural and functional aberrations which comprise of left ventricular (LV) hypertrophy, perivascular and interstitial fibrosis, leading to hardening of cardiac muscle, cell signaling abnormalities, heart failure with preserved and reduced ejection fraction and there is more probability of cardiac failure.[10] Left ventricular hypertrophy is a condition in which the left ventricle becomes thick and enlarged due to which it is not able to pump the blood efficiently. Major abnormalities in diabetes mellitus like hyperglycemia, altered energy metabolism, insulin resistance, inflammation, activation of the renin-angiotensin-aldosterone system (RAAS), and impaired cardiac insulin metabolic signaling are also associated with diabetic cardiomyopathy. Cellular mechanisms that are included in contractile dysfunction in diabetes are diastolic dysfunction, systolic dysfunction, and reduced contractile reserve. Diastolic dysfunction is due to cardiac steatosis and altered calcium homeostasis. Systolic dysfunction is due to insulin resistance and reduced contractile reserve is associated with mitochondrial dysfunction and altered calcium homeostasis.[11]

Diabetes and Atherosclerosis

Atherosclerosis is a disease that occurs due to the agglomeration of cholesterol and fibrous elements inside arteries. It causes hardening and narrowing of arteries over time. The outset of lesions in atherosclerosis comprises of subendothelial agglomeration of cholesterol-engorged macrophages, called foam cells. These lesions are usually found in the first, second, and third decade of life in the aorta, coronary arteries, and cerebral arteries respectively.[12] The inner surface of the artery bulges in the lumen and narrows the passage of the artery. Blood supply will be reduced to the organs. Alteration of lipid metabolism and hypercholesterolemia are related to atherosclerosis.[13] Atherosclerosis is speed-up by diabetes and is the major cause of other cardiovascular diseases.[14] Dyslipidemia, Insulin Resistance, and Hyperglycemia are related to Diabetes Mellitus. These pathological pathways link atherosclerosis and diabetes mellitus. An increase in very-low-density lipoprotein, low-density lipoprotein, and a decrease in high-density lipoprotein cholesterol are the characteristic features of Dyslipidemia. Fragments of native LDL are not responsible for atherogenicity. LDL fragments undergo various alterations which are responsible for their atherogenicity. When the LDL fragments remain in the subendothelial spaces for a long time, it results in the formation of foam cells. Hyperglycemia also plays a role in heart diseases. When the blood sugar level is high, advanced glycation end-products (AGE) are formed and accumulate in the diabetic individual. This leads to the development of atherosclerosis.[14,15] Endothelial dysfunction and chronic inflammation are known features that are associated with both diabetes mellitus and atherosclerosis. The patients

can be treated by controlling the glycemic level and other known factors responsible for diabetes mellitus and atherosclerosis.[15,16]

Diabetes, The Renin Angiotensin Aldosterone System (RAAS) and Cardiac Failure

Juxtaglomerular (JG) cells of the kidney synthesize Renin. Autoregulatory control of blood pressure takes place through Renin Angiotensin Aldosterone System. It is produced due to a variety of stimuli, like low blood pressure and sympathetic activation.[17] Renin converts Angiotensinogen into Angiotensin I. The latter is converted into Angiotensin II with the help of Angiotensin-Converting Enzymes (ACE). Angiotensinogen acts mainly through the AT_1 receptor. Its effects are arterial vasoconstriction, vascular smooth muscle constriction, sodium and water retention, which will increase the blood volume, and release of Aldosterone from adrenal glands.[18] In diabetic cardiomyopathy complications like atherosclerosis, myocardial fibrosis, cardiac failure, and loss of cardiomyocytes, RAAS has a significant role.[19] Noninsulin-dependent diabetes mellitus (NIDDM) has a major role in activating RAAS.[10] Miller and associates showed that during the beginning phases of NIDDM, there was an increment in renin activity, resistance offered by blood vessels to renal blood flow, and mean arterial pressure.[20] Various mechanisms are involved by which diabetes promotes the activity of Angiotensin II. Tissue response to Angiotensin II can be enhanced by the high glucose concentration in diabetes.[21] As cardiac failure progresses, RAAS has a deleterious role which increases the workload on the heart.[22] In addition to Angiotensin II, Aldosterone is also responsible for congestive cardiac failure.[23] Therefore, RAAS inhibitors like Angiotensin-Converting Enzyme (ACE) inhibitor, Angiotensin Receptor Blocker (ARB), and Direct Renin Inhibitor are applicable in diabetic patients with hypertension.[24]

Diabetes, Hyperglycemia and Cardiac Failure

Hyperglycemia or high blood sugar is a condition in which blood glucose level is more than 125mg/dL. Postprandial hyperglycemia is a condition in which there is a rise in blood sugar level after having a meal. When HbA_{1c} is below 7.3%, postprandial hyperglycemia accounts for most of the HbA_{1c}.[25] Oxidative stress is increased and protein kinase C is disrupted due to hyperglycemia. Furthermore, there is an increase in advanced glycation end products, and the receptors of the same are activated. Thereby, the synthesis of nitric oxide (NO) is reduced. Consequently, vascular endothelial cell function is impaired. Vasodilation is decreased due to disturbance in protein kinase C signalling.[26] Both duration of diabetes and severity of hyperglycemia is associated with the heart diseases risk.[27] Hyperglycemia can lead to atherosclerosis, increment in oxidative stress, and various proteins undergo glycosylation and peroxidation in the body.[28] Advanced glycosylation end products formation occurs with the passage of time.[29] Hence, treatment of hyperglycemia might be a possible treatment for cardiovascular diseases.[30]

Diabetes, Obesity and Cardiac Failure

Obesity, a consequence of high body fat, is now considered an epidemic as it imposes a serious threat to the population by increasing the occurrence of diabetes, heart disease, hypertension, and cancer.[31] Diabetes occurs due to increased fat cell size because of the excess fat stored by the body, which may lead to cardiovascular risk because of increased visceral adiposity.[31,32] Obesity is often linked with hypertension and dyslipidemia and hence patients with obesity are at a higher risk of developing cardiovascular diseases (CVD) and heart failure.[32–34] However, on contrary, patients with higher Body Mass Index (BMI) or obese patients have a better survival rate compared to lean patients with established Heart Failure.[34,35] Although, it is expected to worsen the situation of the population with Diabetes Mellitus and established Heart Failure, thereby increasing the death rate in the world.[34,36,37] Heart failure is a major cause of mortality in patients with diabetes and in fact, prediabetes is an underlying cause of heart failure in patients with higher BMI and altered glucose levels. The alteration in metabolic pathways such as TCA cycle, glycolysis, glucose oxidation, the electron transport chain, and fatty acid β oxidation, leads to switching of myocardial energy preference that is a consequence of obesity, diabetes, and an early stage of heart failure, and can also induce cardiac inefficiency and cardiac dysfunction due to accelerated β oxidation.[37,38]

A study conducted by Despa et al on failing hearts from obese, type 2 diabetic, and non-diabetic patients, concluded that failing hearts from obese patients with type 2 diabetes mellitus had a significant amount of amylin accumulated in their hearts, indicating that these patients are at a higher risk of developing heart failure, whereas it was not the case in normal hearts.[39] Conversely, few studies also state that obesity may be associated with an improved health condition in patients with CVD.[32]

Patients who have higher BMI and diabetes mellitus, with the associated risk of heart failure are generally given β-blockers, Iva brads, diuretics and are asked to maintain a physically active lifestyle for a better survival rate.[38,40]

Diabetes, Hypertension and Cardiac Failure

Hypertension, an asymptomatic disease, affecting populations all over the globe, also increases the risk of other related acute conditions such as heart failure, stroke, acute myocardial infarction, and renal disease.[41] It has been reported that diabetes, heart failure, and hypertension are all age-related conditions and with an increase in age the overall longevity and chances of developing hypertension, diabetes and congestive heart failure also increase, since, the complex interactions

between the autonomic tone and organ responsiveness are affected more in elderly.[42,43]

An increase in BMI is also associated with an increased risk of diabetes and hypertension. A study conducted by Bays et al on 200,000 households concluded that the prevalence of diabetes mellitus and hypertension was higher in participants with a higher BMI, which also concludes that obese patients are more likely to develop these metabolic diseases.[44] The probability of incidence of heart failure is higher in patients with diabetes and also have been diagnosed with hypertension when compared to patients who are normotensive with normal glucose levels.[43] In such patients, there is an increased risk of systolic and diastolic left ventricular dysfunction that often leads to heart failure, yet the evidence that diabetes mellitus directly leads to heart failure is still under consideration.[45,46] Hence, the underlying cause of diabetic cardiomyopathy is myocardial damage in diabetic patients, especially when the systolic function is affected much before the diastolic function.[47] Generally, β-blockers such as atenolol, metoprolol are used as a pharmacological treatment for hypertension and heart failure.[41]

Diabetes, Anaemia and Cardiac Failure

Anaemia, a condition in which there is a reduced quantity of circulating red blood cells, is a common component in diabetic nephropathy patients and may have a serious negative impact on the health of diabetic patients.[48,49] Cardiovascular complications lead to an increased risk of death in diabetic patients coupled with anaemia, which may lead to renal failure in diabetic nephropathic patients.[50] It has been found that around 20-40% of all patients with cardiac failure have diabetes which can be a result of severe anaemia.[51] It is a consequence of erythropoietin- deficiency in diabetic patients that is a result of decreased red blood cell production which leads to an increase in mortality rate and reduced quality of life in patients.[50]

Diabetic patients are rarely tested for anaemia because of its low incidence, although it may have a serious implication on the health of the patients.[52] It has been reported by Vlagopoulos et al that anaemia in diabetic patients caused a risk for adverse cardiovascular disease and can cause mortality in patients with chronic kidney disease.[53]

Diabetes, Coagulation and Cardiac Failure

Atherothrombotic events are the same in diabetic as well as non-diabetic patients who have a history of Ischaemic Heart Disease.[54] Cardiovascular disease is completely associated with the onset of a thrombotic event, which is a common cause of mortality in diabetic patients due to increased complications.[55] The mechanism of action of thrombosis in diabetic patients involves an increased propensity of thrombosis as a result of platelet hyperactivity and an increase in the propensity of prothrombotic coagulation factors with decreased fibrinolysis.[54] Plasminogen activator inhibitor (PAI) is linked with hyperinsulinemia and an increased level of PAI has been seen in diabetic patients, but fibrinolysis cannot be explained alone by this and should be evaluated by thrombus formation and fibrinolysis balance.[55]

It has been reported by Goldberg in his study that coagulation, inflammation, and endothelial dysfunction are important to identify the patients who are at risk of developing diabetes and cardiovascular disease.[56] The risk of cardiovascular disease in diabetic patients could be contributed by a hypercoagulable state due to elevation on clotting factors in plasma that leads to an imbalance and hence a procoagulant state is observed that increases the risk of vascular disease.[57] Researches show that there is an increase in the concentration of FVIII and its carrier von Willebrand factor (vWF) in diabetic patients which is a reason for the increased risk of heart attacks in this population.[58]

MANAGEMENT OF CARDIOVASCULAR DISEASES ASSOCIATED WITH DIABETES PHARMACOLOGICAL MANAGEMENT

Insulin

Insulin is generally given to diabetic patients though it is considered as a last resort for the management of diabetes.[59] There is the abnormal secretion of insulin in diabetic patients and hence insulin is given orally or intravenously to these patients.[60] Though more than 50% of diabetic patients receive insulin today, its acceptance and patient compliance is the major area of concern, as other therapeutic agents are better tolerated than insulin.[59,61] It has also shown major effects on the heart as it has both pro-atherogenic and anti-atherogenic effects, as well as shows cell proliferating property indicating that it may convert normal cells to malignant cells.[61]

Skeletal muscles play a major role in insulin resistance as it is the site of glucose disposal.[62] The goal of giving insulin externally is to mimic the action of normal insulin secretion to control the glucose levels in the body.[63] Insulin increases the transport of glucose by Glut-4 whose function is impaired in diabetic patients.[62] Hence, including insulin therapy has shown better glycaemic control as the insulin action is improved and there is a decrease in hepatic glucose production, thereby improving β-cell function.[64]

In type 2 diabetes patients insulin is generally given in combination with other oral drugs.[61] Insulin is given to diabetic patients as intermediate- or long-acting preparation, as intermediate-acting with short-acting or rapid-acting preparation, or as an intensive insulin therapy.[63] There were certain barriers to insulin therapy such as patient's perceptions about pain, weight gain, and risk of hypoglycaemia.[65] Studies conducted by Scognamiglio et al show that insulin plays no role in diabetic patients who have a myocardial dysfunction as it

plays no role in controlling heart rates and myocardial contractility.[66] Hence, nowadays more acceptable drugs such as DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists are favoured over insulin therapy.[65]

Anticoagulants

Since diabetes shows a risk of stroke in patients with atrial fibrillation, generally anticoagulants are recommended to prevent the associated embolic events and risk of cardiovascular events.[67,68] The risk of cardiovascular events in diabetic patients is the major cause of death and so oral anticoagulants and oral antiplatelets are given to them as a preventive measure.[68] A study conducted by Bhatt et al concluded that the risk of CVD in diabetic patients was largely reduced by the administration of aspirin plus low-dose rivaroxaban than aspirin alone and also caused a total reduction in mortality rate.[69] Hence, atrial fibrillation is a common event in type 2 diabetic patients than without diabetes and the rate of oral anticoagulants given are higher in diabetic patients than without diabetes.[67]

Warfarin, a Vitamin K agonist was used for a long as an anticoagulant but was discontinued due to its poor absorption and non-linear kinetics, so now non-vitamin K antagonists have opted for diabetic patients for their better safety and efficacy.[70,71] Vitamin K antagonists are known to inhibit the process of carboxylation of glutamate residues of factors VII, X, XI, prothrombin, and protein C.[71] Anticoagulants, especially those given orally shows an increased risk of gastrointestinal bleeding, with low patient compliance compared to traditional treatment given to patients.[72]

GLP-1 Agonist

Glucagon-like peptide 1 (GLP-1) are the peptides produced in the intestinal L-cells and help in stimulating insulin secretion, whenever blood glucose levels increase.[73] GLP-1 receptor agonists provide a potential treatment of diabetes by regulating the blood glucose and also preserving the β-cell function.[74] It works by reducing the state of hyperglycemia by stimulating the GLP-1 receptor affinity and is fast-acting.[73]

GLP-1 shows better safety and efficacy as it also decreases gluconeogenesis and improves insulin sensitivity.[74] It also decreases the body weight, though a plateau is seen over time and is observed to improve the body metabolism.[75] Few adverse effects are also reported by the use of GLP-1 agonist including thyroid cell tumors, pancreatitis, and should be used with full caution in patients with gastroparesis or severe gastroesophageal reflux disease.[76]

Metformin

Metformin, 1,1-Dimethylbiguanide, is a drug that is a biguanide derivative. It has found application in non-insulin-dependent diabetes mellitus (NIDDM) as it has a positive effect in microvascular complications (stroke, atherosclerotic cardiac disease, and acute myocardial infarction) and macrovascular complications (renal disease and peripheral nerve disease).[77] Metformin is responsible for repressing the synthesis of glucose by the hepatic cells and uptake of glucose by insulin is also increased. Metformin obstructs the respiratory chain due to which peripheral glucose utilization is enhanced. Activation of AMP-dependent protein kinase (AMPK) is due to metformin which has an effect on reducing energy sources. All of these actions result in the lowering of blood glucose concentration.[78,79] When metformin and sulfonylurea are given in combination, they have a synergistic effect and they aid in the reduction of $HbA1_c$ level. Glycemic control is improved when metformin is given along with insulin. The usage of metformin is limited in pregnancy as it can cross the placental barrier and is known to have side effects on the mother and fetus.[80] The route of administration of metformin is oral and has a low bioavailability. It is not metabolized but removed from the body unchanged with the help of the kidney. In the case of renal failure, it gets accumulated and increases the risk of lactic acidosis.[81] Earlier it was believed that patients suffering from heart failure should not be given metformin as it can cause lactic acidosis but various studies revealed that the drug reduces the blood glucose level in patients suffering from cardiovascular diseases.[79] It has a cardiovascular protective effect and reduces the risk of various cardiovascular diseases.[82]

Beta-blockers

Beta-blockers are the drugs that inhibit the actions mediated through beta receptors. There are three types of β receptors: β_1, β_2, and β_3. β_1 receptors are mostly present in the heart and juxtaglomerular cells of the kidney, β_2 receptors are located in the smooth muscles of bronchi and blood vessels, and β_3 receptors are present in the adipose tissue. β receptors are G protein-coupled receptors. There is an increase in the level of cAMP, the second messenger, due to the activation of adenyl cyclase. Furthermore, there is an increase in the level of calcium in cytosol because of the opening of a specific type of calcium channel due to the production of cAMP.[83] Beta-blockers inhibit this action and there is a decrease in the level of cAMP and calcium due to which it decreases heart rate, the force of contraction, and cardiac output, hence the risk of ischemia is lowered.[84] Beta blocking drugs are well absorbed orally but they have high first-pass metabolism due to which their bioavailability is less.[83] The risk of developing atherosclerosis is less with nebivolol as endothelial proliferation is inhibited. Carvedilol and nebivolol are used in patients having type II diabetes mellitus because they do not increase insulin resistance. Both of them have vasodilated property which is beneficial in cardiovascular diseases.[85]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitor

SGLT-2 inhibitors, Dapagliflozin, lowers the blood glucose level and causes weight loss in patients suffering from diabetes mellitus type 2.[86] SGLT-2 is present in the segment of the proximal convoluted tubule (PCT).

These drugs lower the blood glucose level by promoting glucose excretion and preventing its reabsorption by inhibiting the SGLT2 in proximal convoluted tubules (PCT). The actions of insulin don't affect the mechanism of SGLT-2 inhibitors.[87] These drugs have two types of action: natriuretic action and glucosuric action. Due to the natriuretic effect, there is a decrease in atrial stiffness and plasma volume which leads to lowering of blood pressure, decrease in ventricular arrhythmias, and decrease in acute decompensated heart failure. Due to the glucosuric effect, there is a decrease in HbA_{1c} and an increase in excretion of uric acid which lowers the risk of atherosclerosis. Furthermore, there is an increase in the insulin/glucagon ratio which leads to an increase in ketone bodies and improves cardiac metabolism.[88] Hence, inhibition of SGLT-2 results in blood pressure lowering, an increase in diuretic effect, lowers hyperuricemia, and a decrease in oxidative stress.[89] Due to the above reasons, it is given in patients suffering from non-insulin-dependent diabetes and cardiovascular diseases.[90]

DIET AND SELF-CARE

Diabetes can be managed in patients by self-care methods such as including physical activity, improving diet, self-monitoring of blood glucose, and maintaining good mental health.[81] Taking a high-calorie diet, a higher amount of carbohydrates, and sugar-sweetened beverages increases the risk of diabetes, as this results in an increase in blood glucose level and insulin demand.[91] Studies show that lack of physical activity, intake of soft drinks and high-calorie food raises the blood glucose level and BMI, which is not only related to the quantity of food intake but also on the quality of diet All this may lead to higher energy intake and low energy output resulting in obesity and increased insulin resistance.[91] Hence, good knowledge on dietary behaviours and calorie needs of the body is required to be given to the diabetic patients, so as to improve their quality of life.[92]

Meta-analysis revealed that dietary patterns also affect the control of glycemia, and weight loss by diet or physical activity reduced the risk of diabetes in susceptible population.[93] So, a diet that which contains low trans-fatty acids helps in reducing the risk of development of type 2 diabetes mellitus and also prevents weight gain.[94] Diabetes self-care involves people who are at risk of developing diabetes to manage the disease on their own by making many lifestyles and dietary changes.[95] Studies state that around 98% of diabetic patients are treated by self-care, as a patient's capability to organize and control his behaviour helps more in management of this diseases.[96] Genetics also play an important role in the development of diabetes and the population most prone to develop this disease is most required to maintain a good self-care routine so as to improve their quality of life.[95]

ROLE OF EXERCISE

Various complications, nephropathy, neuropathy, retinopathy, cardiovascular disease, and slow healing, are associated with type II diabetes mellitus. That's why treatment and prevention of it is really important. Physical exercise plays a very important role in improving the quality of life in patients suffering from type II diabetes mellitus. Oxygen consumption of the body increases during physical exercise. To meet the energy requirements of the body, skeletal muscle starts using stored glycogen, triglycerides, and free fatty acid. So, the level of glucose is well maintained during exercise.[97] There are various types of exercise like aerobic exercise, resistance training, and balance exercise. Aerobic exercise, cycling, walking, and swimming, relieves oxidative stress damage and control glucose level in an individual. Resistance (strength) training helps in improving insulin resistance in patients.[98] Physical exercise provides various benefits like increasing energy metabolism, inhibiting cardiomyopathy apoptosis, and improving microvascular disorders. Myocardial fibrosis is associated with intestinal fibrosis and collagen deposition. Regular exercises result in the improvement in an individual having myocardial fibrosis.[99] Hence, these trainings are considered to be very effective in patients suffering from type II diabetes mellitus and cardiovascular diseases.

CONCLUSION

From this review, we conclude that type 2 diabetes mellitus is a metabolic syndrome that has affected a large number of population and still continues to affect people all over the globe. This pandemic is a major result of lifestyle changes that include diet and physical activity. It has been found that apart from drugs, diabetes can only be treated and prevented by self-care. It should also be noted that no treatment should be done without the advice of a registered medical practitioner, as it may cause more harm than benefit. Studies also conclude that diabetes is a disease that should be treated on time as a prolonged decrease in insulin level may result in complications that include failure of the vital organs of our body. So, it can be concluded from the review that diabetes should not be left untreated as it is a major cause of mortality in today's population.

ABBREVIATIONS

AGEs - Advanced glycation end-products
NIDDM - Non-insulin-dependent diabetes mellitus
RAAS - Renin-Angiotensin-Aldosterone system
LV - Left Ventricular
LDL - Low density lipoprotein
JG - cells Juxtaglomerular cells
ACE - Angiotensin-Converting Enzymes
ARB - Angiotensin Receptor Blocker
CVD - Cardiovascular Diseases
BMI - Body Mass Index
TCA cycle - Tricarboxylic acid cycle
PAI - Plasminogen activator inhibitor
NO - Nitric Oxide

vWF - von Willebrand factor
GLUT-4 - Glucose transporter type 4
GLP-1 - Glucagon-like peptide 1
AMPK - AMP-dependent protein kinase
cAMP - Cyclic Adenosine Mono Phosphate
SGLT-2 -Sodium-glucose cotransporter-2
PCT- Proximal Convoluted Tubule
Hb – Hemoglobin

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