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CARDIOVASCULAR DISEASES: A REVIEW ON COMPLICATION OF DIABETES MELLITUS

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ABSTRACT

Diabetes is a chronic disease. Insulin is hormone that controls blood sugar level. Uncontrolled diabetes mostly results in hyperglycemia. Thirst, polyuria, weight loss, and obscure vision are some symptoms. There are two major types of diabetes. i.e. type 1 and type 2. Type 1 presents following a pre-clinical phase, while type 2 has more insidious onset; patients may remain asymptomatic for years. Type 2 begins more slowly and the patients may not exhibit symptoms for years. Obesity, hypertension, and dyslipidemia are frequent CV risk factors in people with diabetes, especially those with type 2 diabetes. There are 3 main mechanisms which are hyperglycaemia, glucose fluctuations and insulin resistance. Selection of appropriate intervention which can improve endothelial function is clinically important for prevention of cardiovascular events in diabetic patients. There are two main methods of treatment. Insulin treatment is widely used for patients of diabetes mellitus type 2. In hypoglycemic drugs, sulfonyl ureas, metformin and Glucagon-like peptide 1 receptor (GLP-1R) agonists are also used which improves the control of level of postprandial blood glucose and sodium-glucose cotransporter 2 (SGLT2) inhibitors are used which deccrease blood glucose levels by increasing glucose excretion into urine by inhibition of reabsorption of renal glucose. Other treatments like treatment of other modifiable risk factors in patients with diabetes, it is recommended to select an intervention which improves endothelial function. The basic diabetes treatment is diet and exercise therapy. In case of calories, it is recommended to take calories based on the formula of appropriate daily energy amount (kcal) = standard weight (kg) × physical activity amount. Nanoparticles is also one of the latest method of treatment used for cure of diabetic CVD.

KEYWORDS: Diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, Insulin treatment, hypoglycemic Drugs.

INTRODUCTION

Diabetes is a chronic illness that develops when the body either cannot use the insulin that the pancreas creates effectively or does not create enough of it. The hormone that controls blood sugar is insulin. Uncontrolled diabetes frequently results in hyperglycemia, also known as elevated blood glucose or elevated blood sugar, which over time seriously damages numerous body's systems, including the blood vessels and neurons.[1] Diabetes results from either insufficient Insuline production by the Pancreas or from the body's cells losing their sensitivity to the hormone's effects.[2] In 2014, 8.5% of persons who were 18 years of age or older had diabetes. 2019 had 1.5 million deaths directly related to diabetes, with 48% of these deaths happening before the age of 70. Diabetes contributed to an additional 460000 deaths from kidney disease, and elevated blood glucose is responsible for 20% of fatalities from cardiovascular disease.[3] Diabetes caused an increase in age-standardized death rates of 3% between 2000 and 2019. Diabetes caused a 13% rise in mortality in lower-middle income countries. In contrast, between 2000 and 2019, there was a 22% global decline in the likelihood of dying from any of the four major non communicable diseases (cardiovascular diseases, cancer, chronic respiratory diseases or diabetes)between the ages of 30 and 70.[1] An estimated 1.5 million fatalities annually are related to untreated or inadequately controlled diabetes.[4] Thirst, polyuria, weight loss, and obscure vision are some classic symptoms. The illness can cause problems with the cardiovascular system, kidney, eyes and nerves, among other health issues, if treatment is not received.[5] The usual signs of uncontrolled diabetes include thirst, weight loss, and polyuria. There may also be a number of additional non-specific symptoms and indicators, such as tiredness,

impaired vision, and itching in the genitalia brought on by a Candida infection. About half of affected individuals may also be asymptomatic.[6] About half of affected individuals may also be asymptomatic.[6] Type 2 begins more slowly; patients may not exhibit any symptoms for years. Type 1 manifests suddenly after a pre-clinical stage.[7] Diabetic ketoacidosis is a medical emergency that primarily affects type 1 diabetes, although it can also affect type 2 if the condition has been present for a long time or if the patient has substantial β-cell malfunction. A reduced level of consciousness in extreme cases, deep breathing known as Kussmaul breathing Kussmaul breathing, nausea, vomiting, abdominal pain, and the smell of acetone in the breath are all indicators of excessive ketone body production.[8] Another emergency is a hyperosmolar hyperglycemic state, which is characterized by severe hyperglycemia-induced dehydration and hypernatremia, which can cause altered mental state and possibly even coma.[9] Hypoglycaemia is a recognised complication of insulin treatment used in diabetes. Acute presentations can range from minor symptoms like palpitations, sweating, and trembling to more significant ones like impaired cognition,, disorientation, convulsions, coma, and in rare cases, death. Frequent episodes of hypoglycemia may reduce the glycaemic threshold at which symptoms arise, thus moderate symptoms might not show up until cognitive decline starts.[1] Diabetes is classified into six categories type 1 diabetes, type 2 diabetes hybrid forms of diabetes (include slowly evolving, immune-mediated diabetes of adults and ketosis-prone type 2 diabetes) hyperglycemia first detected during pregnancy, "other specific types", and "unclassified diabetes".[10] Contrary to popular belief, diabetes can manifest in a variety of ways in a person.[11]

Table 1: Comparison of type 1 and 2 diabetes.

Features	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body size	Thin or normal[12]	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Heritability	0.69 to 0.88 [13,14,15]	0.47 to 0.77[16]
Prevalence (age standardized)	<2 per 1,000[17]	~6% (men), ~5% (women)[18]

Type 1 diabetes can occur at any age, and a significant proportion is diagnosed during adulthood. When type 1 diabetes strikes an adult, the condition is diagnosed as Latent autoimmune diabetes of adults of adults (LADA); it manifests later in life than it does in children. Because of this distinction, some people refer to this illness as "type 1.5 diabetes" informally. Based more on age than a cause, adults with LADA are often misdiagnosed as having type 2 diabetes at first.[19] Adults with LADA produce more insulin than those with type 1 diabetes, but not enough to maintain normal blood sugar levels.[20, 21] Insulin resistance, which may be coupled with comparatively decreased insulin production, is the hallmark of type 2 diabetes.[2] It is thought that the insulin receptor has a role in the bodily tissues' impaired ability to respond to insulin. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. 95% of cases of diabetes are type 2 diabetes, which is the most prevalent form of the disease. Many people with type 2 diabetes have evidence of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes.[22] Changes in lifestyle or drugs that increase insulin sensitivity or decrease the liver's synthesis of glucose can decelerate or even reverse the progression of prediabetes to over type 2 diabetes.[23] Diabetes mellitus (DM) and cardiovascular disease (CVD) are closely related. The leading cause of death and morbidity in diabetes populations is cardiovascular disease (CVD).[24] Adults (over the age of 18) with diabetes mellitus (DM) had 1.7 times the mortality rate from CVD in the US compared to those without the diagnosis. This is mostly because to an increased risk of stroke and myocardial infarction (MI).Reference.[25] Men and women with diabetes have an increased risk of dying from cardiovascular disease (CVD). Compared to adults without diabetes, individuals with diabetes have a relative risk of 1 to 3 for men and 2 to 5 for women for CVD morbidity and mortality.[26] The incidence and financial cost of diabetes mellitus are rising, making proper management and treatment of the disease essential. Improving the cardiovascular (CV) risk of diabetic patients should be the main objective of diabetes treatment, since CVD is the most common cause of death and morbidity in DM patients. However, the intricate and nuanced association between DM and CVD presents a barrier for managing DM and lowering CV occurrences. Obesity, hypertension, and dyslipidemia are frequent CV risk factors in people with diabetes mellitus, especially those with type 2 diabetes. Furthermore, research has shown that a number of variables, such as elevated oxidative stress, elevated coagulability, endothelial dysfunction, and autonomic neuropathy, are frequently observed in DM patients and may have a direct role in

the development of CVD. All things taken into account diabetic people are more likely to acquire CVD due to the high rates of CV risk factors and the direct biological effects of diabetes on the CV system. They also have a higher chance of getting MI, revascularization, stroke, and CHF.[24]

Pathophysiology

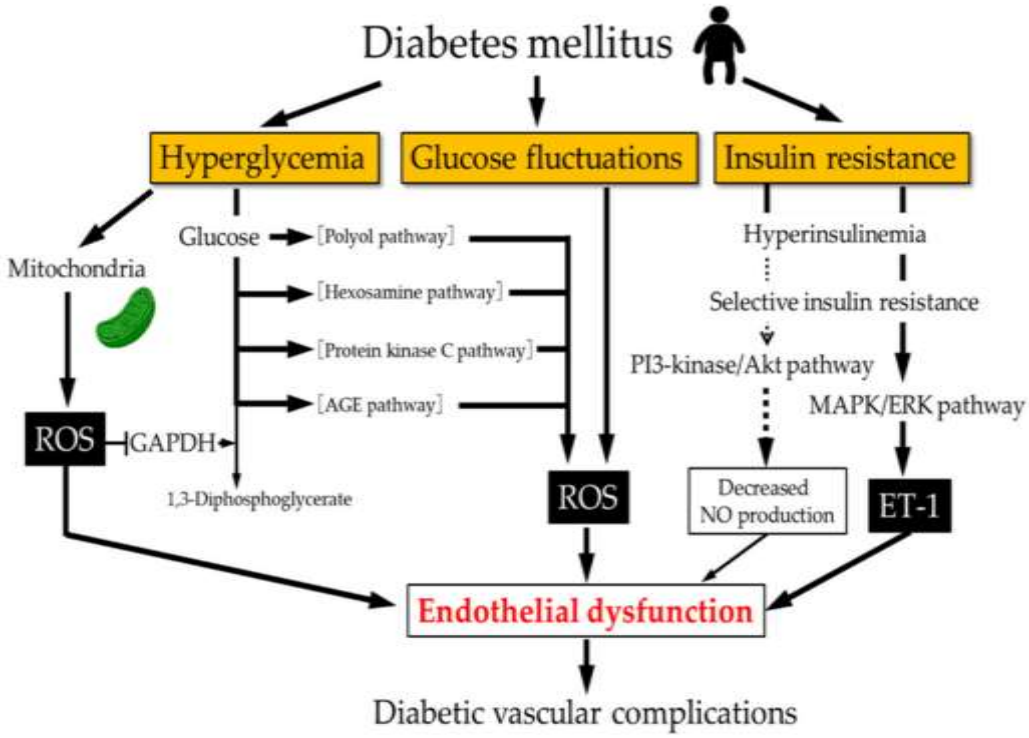

Fig 1: Pathophysiology of Diabetic CVD.[27]

1. Oxidative stress

Molecular oxygen is the source of reactive oxygen species (ROS). The term "oxidative stress" describes a state in which ROS outweigh antioxidant system function. Harmful effects of ROS, such as blockage of signal transduction pathways or normal cellular activities through damage to cellular lipids, proteins, or DNA, become apparent when the antioxidant system's counteracting action is insufficient. Various enzymatic sources, including xanthine dehydrogenase/oxidase, nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases, the mitochondrial electron transport chain, uncoupled endothelial NO(nitric oxide) synthase (eNOS), cyclooxygenase, lipoxygenase, and glucose oxidase, produce reactive oxygen species (ROS) in human cells. ROS comprise of non-radical species such singlet molecular oxygen, hydrogen peroxide, organic hydroperoxides, hypochlorous acid, and ozone, and free radical species like superoxide anion radical (O_2), peroxyl radical, alkoxyl radical, and hydroxyl radical.[28] There is an interaction between endothelial function and oxidative stress.[29]

One electron is taken out of molecular oxygen to create O_2, one of the free radical species.O_2 immediately and highly affinitively inactivates NO, reducing its bioavailability. Furthermore, the direct interaction between NO and O_2 results in the production of peroxynitrite.[18] Strong oxidants like peroxynitrite can damage DNA, lipid peroxidation, protein tyrosine nitration, and even induce cell death.[30] Reduced availability of tetrahydrobiopterin (BH4), an important eNOS cofactor, results from peroxynitrite's oxidation of BH4 to the physiologically inactive form. When there is insufficient BH4, uncoupled eNOS produces O_2 rather than NO.[31] Therefore O_2 is strongly linked to the emergence of endothelial dysfunction. Endothelial function is further compromised by a vicious loop of elevated O_2 and reduced NO bioavailability after an oxidative state is established. Endothelial dysfunction in diabetes mellitus is thought to be primarily caused by insulin resistance, abrupt glucose swings, and persistent hyperglycemia.[27]

2. Hyperglycemia and oxidative stress

Intracellular O_2 is generally produced by mitochondria.[32] Pyruvate is produced in the cytosol by glycolysis and utilized by the mitochondria for oxidative phosphorylation, which produces ATP. The tricarboxylic acid cycle (TCA cycle) oxidizes pyruvate after it has been transported into the mitochondria, producing H2O, CO_2, nicotinamide adenine dinucleotide (NADH), and 1,5-dihydro-flavin adenine dinucleotide (FADH2).[21] The electron-transport chain located at the inner membrane of the mitochondria uses electrons from mitochondrial NADH and FADH2 as energy to

synthesize ATP. Proton pumping from the mitochondrial matrix into the inter membrane space is accompanied by the transfer of electrons from NADH and FADH2 via the electron-transport chain of the mitochondria. Proton pumping creates a proton gradient across the inner membrane of mitochondria, which supplies the energy needed to energize ATP synthase. Enhanced TCA cycle synthesis of NADH and FADH2 results in enhanced transfer of NADH and FADH2 to the electron-transport chain in a hyperglycemic condition. Since FADH2 and NADH act as electron donors, there is a greater proton gradient across the inner mitochondrial membrane and concurrent enhancement of electron transfer and proton pumping across the electron-transport chain. Consequently, there is a decrease in both proton pumping and electron transfer, which leads to an increase in electron leakage from the electron-transport chain and an increase in O_2 production in mitochondria.[33] The glycolytic enzyme required to keep glycolysis going is called GAPDH. The excess generation of mitochondrial O_2 caused by hyperglycemia partially limits GAPDH activity. Consequently, the buildup of glycolytic metabolites upstream of GAPDH and the increased flux of upstream metabolites into pathways of glucose overutilization are caused by the inhibition of GAPDH action by mitochondrial O_2.[33] An increase in the flux of glucose into the polyol pathway results in a rise in NADPH consumption. Reduced glutathione cannot regenerate without NADPH. Consequently, increased NADPH consumption brought on by an increase in glucose flux into the polyol pathway results in decreasing intracellular concentrations of reduced glutathione. Endothelial dysfunction results from increased intracellular oxidative stress, which is exacerbated by diminished glutathione, a primary intracellular antioxidant. The hexosamine pathway may see an increase in glucose flux, which could lead to endothelial dysfunction. The hexosamine pathway converts fructose-6-phosphate to glucosamine-6-phosphate, which raises UDP-N-acetylglucosamine levels. This is necessary for reactions including the production of proteoglycans and the creation of O-linked glycoproteins. O-linked N-acetylglucosamine modifies transcriptional factors, nuclear proteins, and cytoplasmic proteins as a result of elevated UDP-N-acetylglucosamine, changing both gene and protein activities in numerous ways. For example, O-acetylglucosaminylation of the eNOS protein at the Akt location inhibits eNOS activity, which reduces NO generation and subsequently causes endothelial dysfunction. A multitude of pathogenic effects, including decreased eNOS expression, increased ET-1 expression, increased plasminogen activator inhibitor-1 expression, increased transforming growth factor-β expression, NF-kB activation, and NADPH oxidase activation, are brought on by hyperglycemia-induced activation of protein kinase C (PKC) through an increase in diacylglycerol. Modifications to extracellular matrix and plasma proteins, as well as functional changes to intracellular proteins, result from increased intracellular production of precursors to advanced glycation end products (AGEs). Endothelial dysfunction is caused by activation of the receptor on the surface of endothelial cells, which results in generation and NF-kB activation. Consequently, endothelial dysfunction results from the overproduction of mitochondrial O_2 generated by hyperglycemia and the diversion of glycolytic flow from the usual glycolytic pathway to other metabolic pathways since mitochondrial O_2 inhibits GAPDH activity.[27]

3. Glucose fluctuations and oxidative stress

As a result, since mitochondrial O_2 inhibits GAPDH activity, endothelial dysfunction arises from the overproduction of mitochondrial O_2 caused by hyperglycemia and the diversion of glycolytic flow from the typical glycolytic pathway to other metabolic pathways.[27] Studies conducted in vitro have demonstrated that intermittent high glucose, which activates PKC and NADPH oxidase, induces more endothelial cell death than continuous high glucose.[34, 35] A measure of endothelial function and the marker of glucose variations had a negative correlation.[36] Consequently, to safeguard the endothelium from oxidative damage brought on by postprandial hyperglycemia, attention must be paid to postprandial glucose levels in addition to HbA1c and fasting plasma glucose levels.[27]

4. Insulin Resistance-Induced Endothelial Dysfunction

Insulin stimulates NO production in endothelial cells. When insulin binds to its corresponding receptor on endothelial cells, it phosphorylates insulin receptor substrate (IRS), which activates the phosphoinositide 3-kinase (PI3-kinase)/Akt pathway. Akt phosphorylates eNOS at Ser1177, which raises NO production.[37, 38] Additionally, insulin increases the production of ET-1 in endothelial cells by triggering the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway, which is independent of the PI3-kinase/Akt/eNOS pathway.[39] Insulin resistance causes a specific impairment of the PI3-kinase/Akt/eNOS pathway due to decreased IRS expression in endothelial cells. Conversely, the compensatory hyperinsulinemia causes the MAPK/ERK/ET-1 pathway to be preferentially activated, which in turn causes endothelial dysfunction.[40] This phenomenon is referred to as selective insulin resistance.[27]

5. Endothelial Dysfunction

Patients with type 1 diabetes have decreased antioxidant defense and higher oxidative stress.[41] Indicating that endothelial damage in type 1 diabetic individuals is related to oxidative stress. Clinical research has shown that in individuals with type 1 diabetes, both acute and chronic hyperglycemia are linked to endothelial dysfunction.[42,43] Furthermore, research on mice has suggested that the dysregulated immunological response associated with type 1 diabetes could exacerbate oxidative stress by activating NADPH oxidase, which in

turn could lead to endothelial dysfunction.[44] Due to a lack of clinical evidence, it is still unknown whether glucose variations in type 1 diabetes patients contribute to endothelial dysfunction.[27]

Treatment

Selection of appropriate intervention which can effectively improve endothelial function is clinically important for prevention of cardiovascular events in diabetic patients. Considering that endothelial function can be damaged by chronic hyperglycemia, acute glycemic variability, and insulin resistance through increased oxidative stress, behaviour modification and pharmacotherapies which is aimed at decreasing blood glucose levels without hypoglycemia, reducing glucose variability, and ameliorating insulin sensitivity are expected to improve endothelial function.[27]

1. Insulin Treatment

Increased glucose control with insulin has been shown to decrease in microvascular and macrovascular complications in patients with type 1 diabetes.[45] Insulin therapy can be advantageous for endothelial function in patients with type 1 diabetes who have a healthy energy balance without insulin resistance as there is little concern about selective insulin resistance. In comparison, the effect of insulin treatment on endothelial function may depend on the achieved level of metabolism control in patients with type 2 diabetes.[46] In overweight patients suffering from type 2 diabetes who have insulin resistance due to overnutrition and a positive energy balance, endothelial function is probably impaired by high-dose insulin therapy due to selective insulin resistance.[27]

2. Hypoglycemic Drugs

Sulfonylureas are insulin secretagogues. So, sulfonylureas, as well as high-dose insulin therapy, could have an adverse effect on endothelial function in overweight or obese diabetics because of the selective insulin resistance, which further results in endothelial dysfunction.[27] Glucagon-like peptide 1 receptor (GLP-1R) agonists improves the control of level of postprandial blood glucose . Hense, GLP-1R agonists improves endothelial function through decreasing glucose fluctuations in patients with diabetes mellitus. Also, GLP-1R agonists shows augment endothelial function in patients with diabetes.[47] Metformin, which is an insulin sensitizer, which remediate endothelial function with a significant cooperation between endothelial function and insulin resistance following treatment in patients of type 2 diabetes mellitus.[48] Also, metformin improves endothelial function in patients without diabetes who have insulin resistance.[49] Sodium-glucose cotransporter 2 (SGLT2) inhibitors deccrease blood glucose levels by increasing glucose excretion into urine by inhibition of reabsorption of renal glucose reabsorption.[50] The glucose-lowering effect of SGLT2 inhibitors does not dependent of insulin. So, there is little concern that treatment with SGLT2 inhibitors in overweight or obese diabetics with insulin resistance will later decline endothelial function through the mechanism of selective insulin resistance in endothelial cells. SGLT2 inhibitors decrease postprandial glucose levels and further decrease overall glucose variability in patients suffering from diabetes mellitus.[51,52]

3. Other Treatments

Dyslipidemia and hypertension are significantly corelated with endothelial dysfunction and are also highly prevalent in patients suffering from type 2 diabetes.[53,54] Therefore, a multiple-risk-factor intervention approach should be performed to improves endothelial function and also prevent future cardiovascular events. The risk of microvascular complications and cardiovascular events significantly get reduced by an intensified, target-driven and multifactorial intervention involving a combination of focused behavior modification and medications which are aimed at subsequent cardiovascular risk factors than by a conventional strategy.[55,56] In the treatment of other modifiable risk factors in patients with diabetes, it is recommended to select an intervention which improves endothelial function, such as administration of statin, administration of blockers of the renin-angiotensin system and behavior modifications such as body weight reduction, aerobic exercise and smoking discontinuation.[57,58,59] As oxidative stress is considered as a major cause of endothelial dysfunction in patients with diabetes, an intervention targeting direct reduction in oxidative stress is attractive and expected to improve endothelial function and cardiovascular outcomes in patients suffering from diabetes. Also, endothelial function is increased by concomitant intra-arterial infusion of vitamin C in patients suffering from diabetes.[60,61] On other hand, oral administration of antioxidants, including vitamin C, vitamin E and N-acetylcysteine, has failed to show a protective effect of antioxidants on diabetic vascular complications in patients having diabetes.[62] Although, the accurate reasons for the ineffectiveness of oral administration of antioxidants remain unclear, Ineffectiveness can be due to the lack of pharmacokinetic evaluation; plasma levels of the supplemented antioxidants were'nt monitored and the drug safety range and efficacy was'nt determined. So, administration of antioxidants for the prevention of diabetic vascular complications is'nt clinically recommended in patients having diabetes.[27] The basic diabetes treatment is diet and exercise therapy and if hypertension or heart failure is complicated, salt intake should be decreased. In case of calories, it is recommended to take calories based on the formula of appropriate daily energy amount (kcal) = standard weight (kg) × physical activity amount.

In short-lived model organisms like yeast, nematodes and flies calorie restriction increases their lifespan. Studies in healthy humans have also improved health-related quality of life and decreases oxidative stress in a 2-year 15% calorie-restricted group compared to those in

a group without restriction.[63] Pioglitazone, a thiazolidinedione, increases the risk of development of heart failure and it is not used in patients suffering from heart failure. Also, pioglitazone does not decrease cardiac function. Pioglitazone causes Na + reabsorption and causes fluid retention by activation of sodium transporters in the proximal tubule and epithelial sodium channels in the collecting duct via peroxisome proliferator-activated receptor γ (PPARγ). In other ways, pioglitazone is used for secondary preventive purposes as it also has a strong protective effect on cardiovascular events. In this case, to prevent the onset of heart failure due to fluid retention, it is suggested to use it in combination with a mineralocorticoid receptor antagonist or thiazide diuretics.[64,65]

Cardiomyopathy and fibrosis are one of the main causes of heart failure in patients of diabetes mellitus. For therapeutic purposes, a delivery system is needed to increase in antidiabetic drug efficacy and specifically target profibrotic pathways in cardiomyocytes. Nanoparticles (NPs) have many advantages, like biocompatibility, bioavailability, targeting efficiency, and minimal toxicity, which make them ideal for antidiabetic treatment.[66]

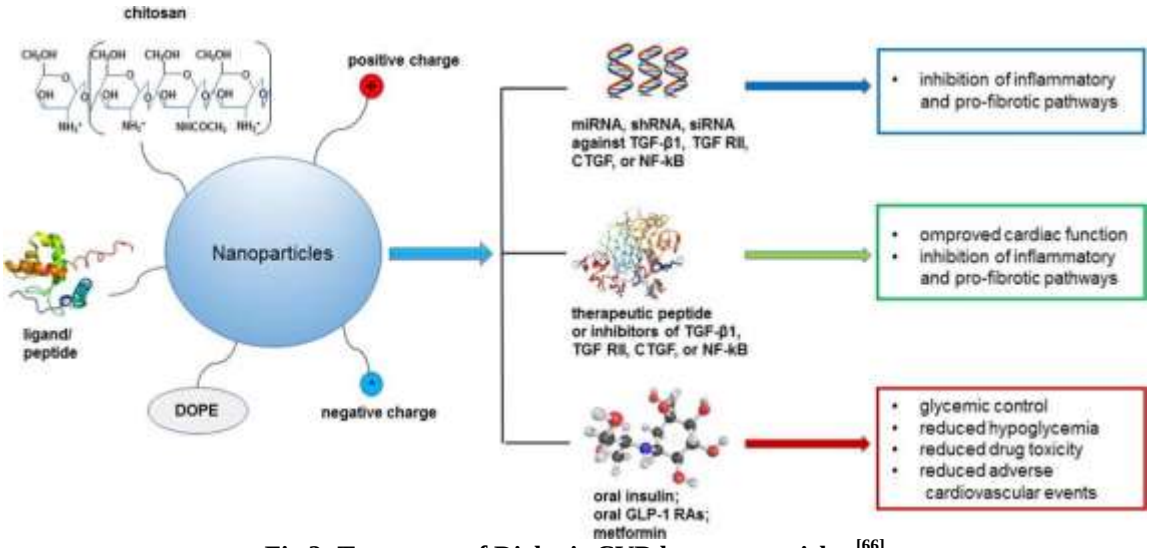

Fig 2: Treatment of Diabetic CVD by nanoparticles.[66]

CONCLUSION

Diabetes Mellitus affects the cardiovascular system by three main mechanisms i. e. hyperglycaemia, glucose fluctuations and insulin resistance. For the treatment of this, selection of appropriate drug is important as some drugs also have adverse effects on the body. Treatment of diabetic CVD is widely done by insulin treatment and hypoglycemic drugs. In hypoglycemic drugs, sulfonyl ureas, metformin and Glucagon-like peptide 1 receptor (GLP-1R) agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors are widely used drugs. But those drugs also have some adverse effects like diarrhea, nausea and, flatulence, chest discomfort, flushing, palpitation, headache , chills, dizziness, taste disorder, diaphoresis, nail disease, skin rash, vitamin B12 deficiency, etc. Hence, more researches are being done to find a novel drugs for the treatment of Diabetic CVD.

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