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REVIEW

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Diabetes and cardiovascular disease: inter-relation of risk factors and treatment

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Abstract

Background: The diabetes mellitus prevalence is still advancing and increasingly becoming one of the globally most severe and expensive chronic illnesses. The strong correlation between diabetes as well as the most prominent reason for diabetes and death in diabetic patients is cardiovascular disorders. Health conditions like dyslipidemia, hypertension, obesity, and other factors of risk like the risk of cardiovascular are frequent in diabetic persons and raise the likelihood of heart attacks.

Main text: In particular, several researchers have found diabetes mellitus-related biochemical pathways that raise the likelihood of cardiovascular disorder in people with diabetes individually. This review describes diabetes-cardiovascular disorder relationships, explores potential therapeutic mechanisms, addresses existing treatment, care, and describes the directions for the future for study.

Conclusion: Thus, in individuals with diabetes, it is important to concentrate on cardiovascular threat variables to reduce the illness's lasting cardiovascular complications. Further work to enhance knowledge of the disease state and its impact on cardiovascular function is required to boost medical treatment and cardiovascular disorders result in people with diabetes.

Keywords: Diabetes, Treatment, Mechanism, Risk factors, Cardiovascular disorders

Background

Globally, there is significantly higher diabetes mellitus (DM) prevalence. The worldwide incidence of DM has grown significantly in the past 30 years and projections suggest that such numbers are only growing significantly [1]. The new global projections of DM are 591 million (1 out of 10 persons) by 2035 as calculated by the Federation of International Diabetes [2]. Type 2-DM has a comparatively larger international impact on the increased incidence of DM than type 1-DM [1].

As a result of the rising incidence of DM, the individual, and the medical system is faced with substantial economic burdens. In the western world, mean DM costs $2108/patient annually, about double as much as non-diabetic subjects [3]. DM has a significant burden on the economy, in both relations to the actual costs of health care treatment as well as to the expense of reduced production (indirectly) due to the mortality and morbidity linked with diabetes [4]. The costing of DM is mostly due to complications of the vascular system (micro and macro) like neuropathy, disease of the renal system, retinopathy, hypertension, infraction of myocardia, and disease of the coronary artery [3, 4].

There is a strong association between DM and CVD (disorders of cardiovascular). Among the patients of diabetes, CVD is mostly responsible for mortality. Throughout the USA, the CVD mortality rate for diabetic adults (with age more than 18), showed a rise in the risk of a heart attack and infraction of myocardia which is 1.8 percent larger than for those who have no DM identified

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[5, 6]. For both males and females, this elevated risk of CVD death is seen in diabetic people. The overall risk in diabetic patients for CVD mortality rates varies from 1-3 in males and 2-5 in females as in those lacking DM [7].

Controlling DM properly and managing it is important because the progression of the disease incidence and financial burden is continuing to increase. Since CVD is the more common cause of death and morbidity in DM patients, the main purpose of care for diabetic must be the enhancement of diabetic patients' cardiovascular risks. But the complicated and ongoing strength of the association between DM and CVD is a problem linked with the treatment of DM and incidents of CV (cardiovascular). In DM patients, especially those with type 2 DM, the factors of risk of CV include dyslipidemia, hypertension, and obesity which are frequent. Furthermore, findings have shown that multiple causes, like neuropathy, dysfunction of endothelial, coagulation enhancement, and increase in stress of oxidation are frequently present in patients with diabetes which contributes to CVD development [5]. Taken together, elevated factors of risk of the cardiovascular system and clear physiological activities of diabetes mostly on the system of CV put patients with diabetes at greater risk for the presence of chronic heart failure, stroke, revascularization, increased risk of myocardial infarction, and other disorders of the cardiovascular system [8]. Due to the complexities of the DM-CVD and its processes, care needs to be optimized to maximize the CV results. This article discusses how DM can be associated with CVD and the latest strategies for treatment and possible work on the management of diabetes.

Main text

Possible risk factors of diabetes

Obesity

Obesity or overweight is related to adipose tissue accumulation that to an extent has a deleterious effect on both the physical and psychological health [9]. Obesity is associated with many chronic diseases including hypertension, diabetes mellitus, dyslipidemia, osteoarticular disease, sleep apnea, and cerebrovascular and cardio diseases. Obesity is a major concern of health worldwide due to the current lifestyle of people and their connection with other chronic diseases [10]. The data of WHO (World Health Organization) indicated that the obesity prevalence around the globe was 10 percent in males and 14 percent in females. According to the information from NHANES (National Health and Nutrition Examination Survey), it was found that the obesity prevalence and overweight amplified from 55.9% to 64.5% from 1988-1994 and 22.9% to 30.5% from 1999-2000 [10]. Body mass index is found to have a strong connection with the resistance of insulin and diabetes. The substances such as glycerol, non-esterified fatty acids, cytokines (interleukin (IL)-6, IL-1, leptin, fibrinogen, tumor necrosis factor-alpha (TNF), PAI-1, resistin MCP-1, angiotensin), hormones, proinflammatory markers which are involved in the growth of resistance of insulin, increase in obese patients. The pathogenesis of diabetes involves the impairment of beta-islet cells of the pancreas or resistance of insulin or both in severe diabetes [11]. The mechanisms of obesity being a factor of risk for diabetes are shown in Table 1. The mechanism behind both diabetes mellitus and obesity is the resistance of insulin.

The sensitivity of insulin fluctuates throughout the life cycle naturally as noticed during pregnancy, puberty, and the aging process [11]. Additionally, lifestyle changes such as enhanced uptake of carbohydrates and raised physical exercise are also factors causing the sensitivity of insulin fluctuations [18]. The main and foremost substance affecting insulin resistance is a non-esterified fatty acid (NEFA). The increased level of NEFA is linked with the resistance of insulin both in diabetes 2 and obesity [17]. Insulin sensitivity is also affected by body fat distribution. There has always been entirely different insulin sensitivity in lean individuals as compared to those who are not lean due to body fat distribution differences. The more peripheral fat distribution, the more is the insulin sensitivity [11]. The adipose tissue distribution differences also explain the difference in metabolic effects of intra-abdominal fat and subcutaneous fats. It has been found that intra-abdominal fats have genes that are responsible for the secretion of specific types of proteins that are responsible for energy generation. The secretion of adiponectin is done by omental adipocyte and it has been observed that this secretion has a negative co-association with increase in bodyweight. Thus, the NEFAs release may be influenced by the presence in different tissues [17]. Fat of intra-abdominal is more crucial in the resistance of insulin as it is more lipolytic and does not easily react to insulin activity of antilipolytic [19, 20]. CVD is also interlinked with diabetes and obesity due to the association of inflammation (low grade) as shown in Fig. 1. The overexpression of cytokines like IL-6, IL-1, leptin, PAI-1, resistin MCP-1, angiotensin, and TNF fibrinogen causes inflammation to increase and lipid to accumulate that in turn have a disastrous impact on vessels of blood and can ultimately cause endothelial dysfunction, cardiomyopathy, and myocardial infarction [12–16, 21]. These cytokines overexpression links the association of resistance of insulin and DM.

Hypertension

Hypertension is very common among diabetics and one of the highly prevalent diseases around the world. Sixty percent of diabetes 2 patients have hypertension in

Table 1 Obesity as a factor of risk for diabetes

S. no.	Proposed mechanisms of obesity being a risk factor for diabetes	Result
1	Overexpression of cytokines by adipose tissues [12]	-Increased inflammation -Lipid accumulation [13–16]
2	An increased amount of C-reactive protein [16]	-Impairs nitric oxide production and prostacyclin -Increased uptake of LDL (low-density lipoprotein) [16]
3	Decreased adiponectin production	Increased NEFA [17]
4	Fat mass distribution	The more peripheral fat distribution, the more is the insulin sensitivity [11]

adjunct [22, 23]. The two conditions when coexists increase the chances of both complications, i.e., microvascular and macrovascular. Complications of macrovascular include infarction of myocardial and stroke whereas complication of microvascular includes retinopathy and nephropathy [24].

The onset of hypertension in diabetics relies on diabetes type. In diabetes (type 1), hypertension onset appears after years of diagnosis and majorly have diabetic nephropathy [23]. Hypertension can be present before the glucose level increases in the body in diabetes 2 patients [25]. The development of diabetic nephropathy is closely related to patients with diabetes and hypertension [26]. Hyperglycemia stimulates the renal cells and as a result cytokines, humoral mediators, and growth factors are produced. This production causes an alteration in the structure of glomeruli of a diabetic patient, an increase in the matrix of extracellular collagen deposition, and a rise in glomerular basement membrane permeability [27]. The structural changes result in microalbuminuria and chronic generation of RAAS (renin-angiotensin system) which progresses into hypertension [28].

Dm is involved with various mechanisms pathophysiologically as shown in Fig. 2. Diabetes and hypertension have interlinked pathways like the stress of oxidation, renin-angiotensin-aldosterone system (RAAS), resistance of insulin, (SNS) sympathetic nervous system, PPARs, and adipokines. These pathways are interconnected and interact with each other and may even result in a vicious cycle [29, 30]. The development of proteinuria in diabetic patients leads to hyperlipidemia which increases the chances of CVD in these patients.

Dyslipidemia

Diabetic patients are at an increased prevalence of dyslipidemia development [31]. The proposed underlying pattern observed in the development of dyslipidemia in diabetic patients is an increased level of triglycerides, LDL (low-density lipoprotein), and reduced level of HDL-C (high-density lipoprotein cholesterol) [32]. One of the prominent features of dyslipidemia in diabetes is an elevated number of LDL particles from either LDL-P or ApoB. There is also an associated high risk of nephropathy as LDL particles tend to be more atherogenic

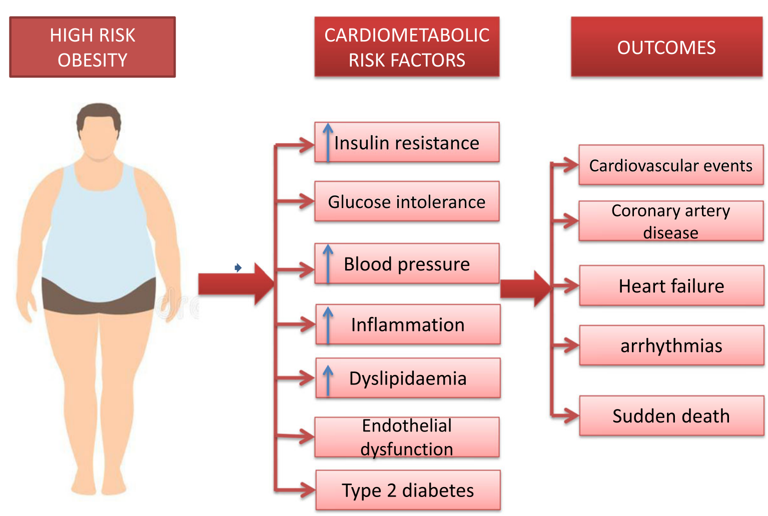

Fig. 1 Relationships between high-risk obesity, intermediate cardiometabolic risk factors, and cardiovascular outcomes (obesity phenotypes, diabetes, and cardiovascular diseases)

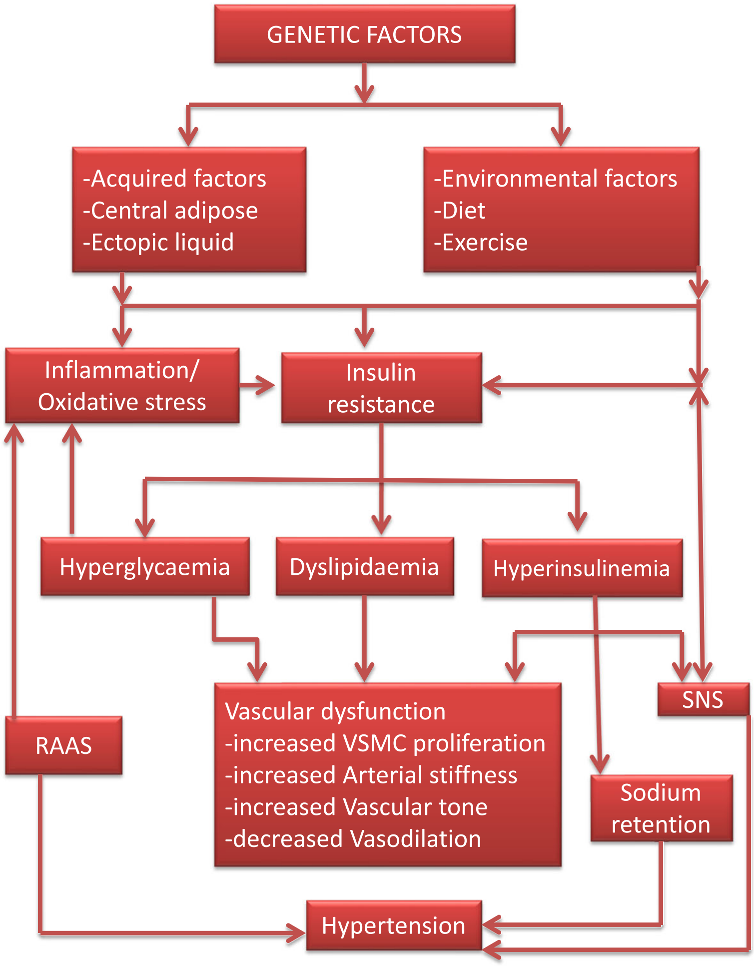

Fig. 2 Summary of pathophysiologic mechanisms in the development of hypertension in diabetes mellitus (VSMC—vascular smooth muscle cell)

[33]. Lipid abnormalities in diabetic patients are shown in Table 2.

The main underlying mechanism for the development of dyslipidemia in diabetic patients is insulin resistance as shown in Fig. 3 [38]. Adipose tissue release of free fatty acids increases in the case of peripheral insulin resistance, which are further entrapped by the liver, in turn, leads to the elevated synthesis of TG (triglycerides) by the hepatic cells. There is an elevation in ApoB secretion and synthesis of triglyceride-rich VLDL (very low-density lipoprotein) due to the hepatic stimulation caused by triglyceride synthesis [39]. The highly loaded VLDL with triglycerides enriches HDL and LDL and makes them richer in cholesterol through the work of cholesterol ester transfer protein [40]. The triglyceride-rich LDL molecules aid in the synthesis of small dense LDL as it gets hydrolyzed by lipoprotein lipase or hepatic lipase. This underlying pathophysiology of dyslipidemia increases the CVD

Table 2 Lipid abnormalities in diabetic patients

S. no.	Type of diabetes	Lipid profile
1	Type 1 diabetes mellitus	Similar to the general population if glycemic control is good [34]
2	Type 2 diabetes mellitus	Apolipoprotein B, particle number of LDL, LDL (small dense) increase with LDL-C. HDL-C decreases. Non-HDL-C, IDL, VLDL, triglycerides increase [35–37]
3	Poor glycemic control	Particle number and LDL (small dense) increase. HDL-C decreases and IDL, VLDL, and triglycerides increase [36]

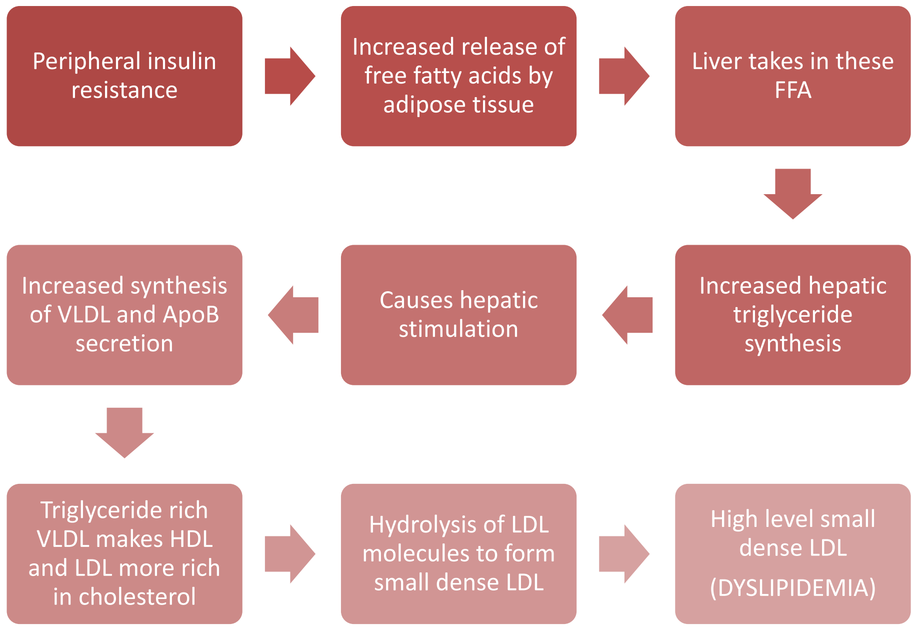

Fig. 3 Mechanism of dyslipidemia in a diabetic patient

prevalence in patients of diabetes. Modern therapy of diabetic patients necessitates lipids to be treated to decrease the risk of cardiovascular diseases.

Cardiomyopathy

The development of cardiomyopathy is a direct consequence of DM. The pathophysiological pathways of cardiomyopathy of diabetes are shown in Fig. 4. The diabetic cardiomyopathy shows heart changes functionally and the left ventricle changes structurally [41]. The diabetic patient shows to have increased left ventricle mass as compared to non-diabetics [42, 43]. It may be proposed that the increased cardiac mass in diabetics is due to the increased release of cytokines having hypertrophic effects on cardiac cells like resistin and leptin from the adipocytes [44, 45]. Patients with diabetes mellitus are also found to have slightly decreased diastolic function in comparison to non-diabetic [46–48]. Mechanisms contributing to diabetic dysfunction of the cardiac system are shown in Table 3. One proposed mechanism for the same could be the increased triglyceride content in the cardiomyocytes due to the elevated synthesis of

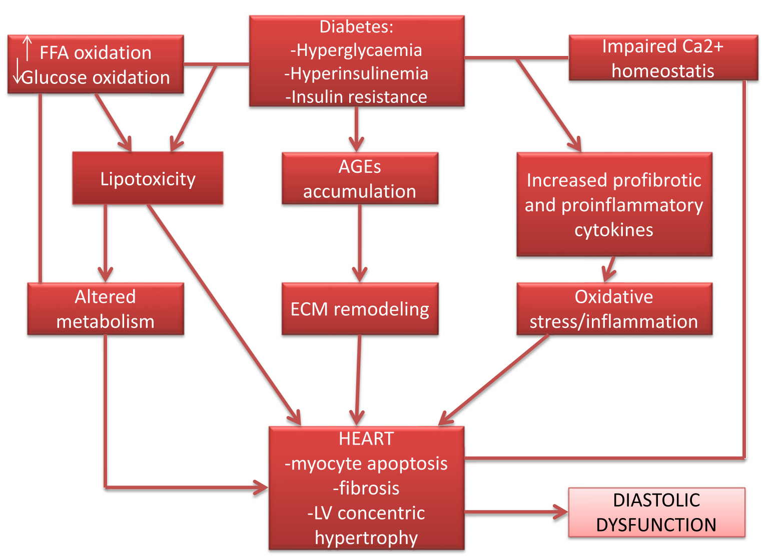

Fig. 4 Mechanism of the pathophysiology of cardiomyopathy of diabetes

Table 3 Mechanisms contributing to diabetic dysfunction of the cardiac system

S. no.	Dysfunction of the cardiac system		
	Diastolic dysfunction	Systolic dysfunction	Contractile reserve
1	Cardiac steatosis	AGE formation	Mitochondrial dysfunction
2	Homeostasis of calcium is altered	Resistance of Insulin	Homeostasis of calcium is altered

triglycerides in diabetics [49]. As a response to triglyceride accumulation in the myocardium, there is a chance of lipotoxicity and the calcium hemostasis also is altered. Both of these factors harm the diastolic function [50–52]. It has also been stated that 40-70% of diabetics with no indication of overt CAD (coronary artery disease) are diagnosed with diastolic function. Subtle alterations have also been found in systolic functioning in diabetic patients using Doppler strain analysis of systolic velocity and tissue Doppler imaging [53–57]. The systolic dysfunction can be due to the impaired contractile reserve and impaired sympathetic innervation of the myocardium [58]. Interstitial fibrosis accompanying elevated collagen deposition is also seen in diabetic patients and has a negative impact on cardiac function [59]. The mechanisms following the diminished systolic and diastolic functions of the heart also increase the risk of having heart failures in diabetic patients [60, 61]. The chances of heart failure in a diabetic are very much that is 16-31% as compared to the general population that accounts for only 4-6% [62].

Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) has been commonly noticed in diabetic patients [63]. It is one of the most overlooked complications in diabetic patients [64–66]. CAN involves the harm to fibers of the autonomic nerve. These autonomic fibers innervate the vessels of blood and the heart and the result is abnormalities in vascular dynamics and heart rate control [67]. The chances for a diabetic patient to have CAN persist from 2.5 to 90% and the risk raises with diabetes duration, age, and improper glycemic control [68]. An inter-link among inflammation, imbalance of autonomic, and CVD has been demonstrated in recent studies as increased inflammatory markers (IL 1 and CRP) are involved in dysregulation of ANS (autonomic nervous system) with elevated activity of the sympathetic system [69, 70]. As the ANS is involved in activity modulation of the sinus node (heart rate), end-diastolic and systolic volume, the resistance of systemic vascular, the dysregulation of the autonomic nervous system may result in left ventricular hypertrophy, arterial stiffness, and dysfunction of diastolic of the ventricle [71]. Clinical manifestations of CAN be named as follows: postural hypotension, abnormal coronary vasomotor regulation, tachycardia, the elevation of QT interval, increased danger of renal disease, exercise intolerance, death, and stroke [72]. CAN tends to be a robust presence of cardiovascular disease in both type 1 and type 2 diabetes. Diabetics with CAN have a mortality rate of 5 years ranging from 16-53% and entirely depend on the severity [73]. According to a study conducted, a complex interaction between duration of the disease, neuronal death relating to age, a diastolic and systolic pressure of blood, and control of glycemic results in diabetes-related CAN [66]. The main culprit is thought to be hyperglycemia that is involved in the stimulation of a cascade of multiple complex pathways and mechanisms which result in oxidative stress induction and production of toxic glycosylation substances that ultimately lead to neuronal abnormalities and death. With age, the diabetics increase the chance of development of CVD and CAN [74].

Glycation

Advanced glycation—a biochemical process that tends to accelerate in diabetes due to elevated oxidative stress and chronic hyperglycemia and is found to play a central role in diabetes. Generation of the advanced glycated end products (AGEs) that are a heterogeneous group of chemical moieties takes place due to advanced glycation. This production of AGEs is a result of a non-enzymatic reaction involving vital intermediates such as methylglyoxal and a reaction with the glucose that interacts with lipids, nucleic acids, and proteins. AGEs produce deleterious results in diabetic patients. AGEs can alter the structure and function of the vasculature as it promotes vascular stiffness by directly inducing the cross-linking of proteins such as collagen that are long lived. AGEs also enhance the oxidative stress and release of key pro-sclerotic and proinflammatory cytokines by interacting with certain receptors such as RAGE (receptor for AGE).

AGEs are heterogeneous complex moieties that are formed via a non-enzymatic reaction between glucose and other reducing sugars with amine residues on proteins, nucleic acids, or lipids. N (carboxymethyl) lysine and pentosidine are some of the prominent AGEs found in humans [75, 76]. AGEs can be produced by exogenous sources also apart from endogenous production. Exogenous sources include tobacco smoke and diet [77–80]. Prolonged heating can accelerate the production of glycol oxidation and lipo-oxidation compounds. A major part of the ingested AGEs is absorbed with food. AGEs often concentrate intracellularly as they are generated from dicarbonyl precursors derived from glucose [81]. The intracellular AGEs act as stimuli for intracellular signaling pathways activation as well as are also involved in the modification of intracellular protein function [82].

Accumulation of AGEs in organs damaged due to diabetes increases as a result of hyperglycemia. AGEs cause the crosslinking of intermolecular collagen that leads to diminished myocardial and arterial function. It also increases vascular stiffness. All these phenomena can be used to partly explain the elevation in systolic hypertension and diastolic dysfunction noted in diabetic patients. Some of the diabetic damaged sites of accumulation of AGEs are retina, kidney, and atherosclerosis plaques as shown in Table 4 [91, 95, 96].

Role of genetics between CVS disorders and DM

The close association of DM and CVD and their factors give rise to the theory that both the conditions follow common genetic, epigenetic, and environmental factors. Many SNP (single nucleotide polymorphism) are found to be associated with CVD and DM [97]. Postulates proposed by "stern" also shows that both the disease occur independently but share a common soil [98]. Recently, many noncoding RNA appeared as indispensable factors involved in the pathophysiology of both the conditions which underlie common epigenetic links between these two [99, 100].

Monogenic factors CVD and DM are polygenic but Mendelian forms have been described for both the conditions where a single gene mutation initiates the disease [101, 102]. However, all gene mutation does not predispose to both the disease. A recent study shows the protective role of Apo B gene mutation in DM which is the most commonly studied gene in familial hypercholesterolemia [103].

Genetic polymorphism Many loci are associated with both conditions. Genome-wide association studies (GWAS) in combination with large cohort studies support to find of the common loci's. As of now, at least 83 loci are found to be associated with DM and more than 30 loci with CVD [104, 105]. Some genes are shown in Tables 5 and 6 whose variants are involved in both the disease.

Treatment

Since CVD is perhaps the common cause of death and disease among diabetic patients, it is vital to have adequate therapy to minimize the chances for events of the cardiovascular system in patients with diabetes, especially with CHF (chronic heart failure), stroke, and infarction of myocardia. The enhanced chance of cardiovascular complications in patients is due to the factors like dysfunction of the autonomous system, dyslipidemia, hypertension, and obesity. Treatment aimed at improving these health risks can boost CV results, though this can be difficult to accomplish. Investigation on how the CV risk level of people with diabetes is affected by these various risk factors may be vague and often conflicting. This section aims to include the current recommendations on several treatment strategies for the same. Treatment

Table 4 Effect of AGEs accumulation on target organs

Complication	Target organ	AGEs role in preclinical studies
Diabetic nephropathy	Kidney	-Glomerular membrane thickening -Mesangial expansion -Glomerulerosis -Tubulointerstitial fibrosis [83, 84]
Diabetic ocular diseases	Eyes-retinal blood vessels [85, 86]	-Basement membrane thickening -Breakdown of inner blood-retinal barrier [87, 88]
Diabetic peripheral neuropathy	Peripheral nerves	-Link microangiopathy and neuropathy -Localization of RAGE, IL-6, CML, and NF-kappaB to endoneurial vessels, perineurium, and epineurial vessels -Reduce sensorimotor conduction velocity -Decrease blood flow to peripheral nerves [89]
Atherosclerotic disease		-Elevates endothelial dysfunction -Increase vascular LDL levels by decreasing LDL uptake -Promote plaque destabilization -Dysfunctioning of vascular repair in response to injury [90] -Quench nitric oxide and impair LDL removal -Elevated localization of AGE—LDL in vessels and elevated generation of foam cells thus accelerate atheroma formation [91]
Diabetic cardiomyopathy and peripheral arterial disease (PAD)	Cardiovascular system	-Crosslinking of collagen [92] -Carotid intima-media wall thickening -Arterial stiffness [93, 94] -Increased levels of malondialdehyde and pentosidine

Table 5 Genes whose variants increase the risk of DM and CVD

Gene	Protein function
TCF7L2	Transcription factor 7 like 2 [106, 107]
PHACTR1	Phosphatase and actin regulator 1. It involves the reorganization of the actin [108]
HMGA1	High-mobility group A1. Involved in glucose metabolism and cell growth differentiation [109, 110]
Paraoxonase	Protects from lipid oxidation [111, 112]
Adiponectin	Adipokine with anti-atherogenic and anti-inflammatory effects [113]
CDKN2A/2B	Cyclin-dependent kinase inhibitor. Cell cycle regulation [108]

approaches can be divided into lifestyle modifications and pharmacological interventions.

Pharmacological interventions

Obesity Obesity is one of the major factors of risk which raises the prevalence of CVD-related mortality and morbidity in DM patients. So many clinical guidelines suggest reducing the weight of DM patients to reduce CVD risk profiles. The syndrome of metabolic and resistance of insulin is found to play a prominent role in cardiovascular mortality and morbidity [114, 115]. Type 2 DM along with visceral adiposity and an excess of ectopic fat clearly show high risks of cardiovascular morbidity and mortality [116]. Individuals with high visceral adipose tissue—this is the condition where fat deposition occurs at lean tissues like the liver, the skeletal muscle, and the heart are at high risk. The simultaneous presence of obesity and DM should further increase the risk of cardiovascular outcomes [117].

According to the trial of SCOUT, the modest loss of weight can enhance rates of mortality of CV in DM patients. Look AHEAD trial did not find any reduction in the chances of CV events like MI, stroke after weight loss in DM patients after 9.6 years of follow up [118, 119].

Various pharmacological drugs are found to be effective in weight loss which reduces the CVD risk [120–124]. Some drugs which are prescribed to control glucose level in DM patients are also effective in weight loss; GLP-1 (glucagon-like peptide-1) receptor agonists and SGLT2 (sodium-glucose co-transporter 2) inhibitors indicated efficacy towards weight loss in diabetes patients [125, 126].

A meta-analysis stated that the inhibitors of SGLT 2 decreased the chance of hospitalization in heart attack and cardiovascular death by 23% in patients with or without a history of heart attack and in patients with or without atherosclerotic CVD [127]. Another meta-analysis showed a 13% risk reduction in cardiovascular deaths in DM patients using GLP-1 receptor agonists [128].

Surgical interventions are more effective for sustained weight loss than standard approaches [129, 130]. The STAMPEDE clinical trial (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently), demonstrated that weight loss surgeries are more effective than intensive medical therapy in terms of weight reduction, glycemic control and in reducing the dose of lipid-lowering medications and improving the quality of life during the 5 years follow-up study.

Two main mechanisms are involved in weight loss surgeries:

1. Restrictive surgeries
2. Mal-absorptive surgeries

Restrictive surgeries restrict the intake of food by reducing the size of the stomach and mal-absorption surgeries reduce the amount of absorption by bypassing the different parts of the small intestine. Sleeve gastrectomy is the most famous restrictive type which reduces weight by reduced meal volume and reduced appetite. Both types of surgeries restrictive and bypass reduce visceral fat and reduce more subcutaneous fat levels [131–133].

In a study of Swedish obese patients, weight loss surgery leads to a 30% reduction in cardiovascular events and a 50% reduction in cardiovascular deaths in obese patients in comparison to those who received standard care after 15 years of follow-up [134]. A retrospective study on 20,235 surgical and non-surgical treated patients demonstrated a reduction in incidences of coronary artery disease in patients who are treated with weight-loss surgeries [135]. In one more retrospective study, 14 patients with heart failure and reduced ejection capability treated with weight loss surgeries, and a significant reduction in BMI and improvement in left

Table 6 Genes whose variants decrease the risk of DM and CVD

Gene	Protein function
PCSK9	Proprotein convertase subtilisin/Kexin type 9. Metabolism of plasma cholesterol [108]
CELSR2-PSRC1-SORT1	CELSR2 belongs to the cadherin superfamily; carry out contact mediated-communication [108]

ventricular ejection was seen at 6 months [136]. Similarly, another retrospective study on 12 patients with a heart attack and low ventricular ejection who underwent weight-loss surgery showed significant improvement in ventricular ejection following surgery [137].

Treatment of obesity and maintenance of BMI could significantly improve the condition and could reduce the cardiovascular risk factors in DM patients.

Hypertension Around 50-80% of type 2 diabetes mellitus patients suffer from coexisting hypertension. The existence of hypertension in diabetic patients worsens the clinical outcomes of both macrovascular and microvascular diabetes. Their coexistence is the leading factor for atherosclerosis and linked complications [138]. The pharmacological treatment for hypertension management is utilization of inhibitors of ACE (angiotensin-converting enzyme), blockers of the receptor of the angiotensin receptor, diuretics, blockers of the channel of calcium which reduces blood pressure by blocking various receptors and channels that contribute to elevated blood pressure [139–142].

There have been many studies that evaluated high blood pressure (BP) role in DM patients on CV outcomes. The UKPDS 38 trial evaluated the significance of BP in DM patients on macrovascular and microvascular complications. The patients were randomized into a more tightly controlled BP group (< 150/85) and a less tightly controlled BP group (< 180/105). After 9 years of the follow-up period, there was a significant reduction found in BP of the tightly controlled group (144/82 mmHg versus 154/87 mmHg) in comparison to a less tightly controlled group. Also, a 34% reduction in macrovascular complications was seen in the tightly controlled BP group and a 37% reduction in microvascular disease in comparison to the less tightly controlled group [143].

Most of the studies showed that lowering BP could improve CV complications in DM patients, the ACCORD-BP trial investigated the effect of tight BP control (systolic BP < 120 mmHg) to the standard BP control (systolic BP < 140 mmHg) on the risk of fatal or non-fatal major CV events in DM patients. After 4.7 years of the follow-up period, the tight BP control group does not show any significant reduction in risks of fatal and non-fatal major CV outcomes in comparison to the standard BP control group. Also, the tight BP control group showed more chances of adverse events [144].

Dyslipidemia Dyslipidemia is very prevalent in DM patients and an important risk factor for CVD [145]. Improvement in the profile of lipid, glycemic control, and resistance of insulin is observed in patients with a 5% reduction in their body weight [146]. Weight loss improves blood pressure, reduces the level of triglycerides, and elevates HDL-C levels [147]. Although the loss of weight has indicated to enhance factors of multiple risks like blood pressure and hemoglobin A1C, it did not show any significant improvement in events of cardiovascular in the Look AHEAD study [119], indicating a necessity for pharmacotherapy with simultaneous lifestyle modification for the treatment of diabetic dyslipidemia [148].

Many pharmacological therapies are currently available including statins, niacin, fatty acids of omega-3, sequestrants of bile acid, inhibitors of absorption of cholesterol, and fibrates [149]. These drugs adopting different mechanisms of action have a crucial part in the treatment of diabetic dyslipidemia.

The Collaborative Atorvastatin Diabetes Study (CARDS) study was carried out in T2 diabetes mellitus patients to evaluate the effect of statin therapy. Patients were treated with 10 mg/d atorvastatin and the controlled group received a placebo. After 3.9 years of the follow-up period, a 26% reduction in total cholesterol level, and a 40% reduction in LDL-c was found. Also, a 37% reduction in CV events and a 48% reduction in stroke were found in patients treated with statin therapy in comparison to the controlled groups. The CARDS study was stopped in between due to the significant results demonstrated in favor of statin therapy [150].

After significant results of the CARDS study, the TNT trial was carried out, high dose versus low dose statin therapy in T2 DM patients to examine non-fatal MI, CAD mortality, and fatal non-fatal stroke risk. Patients were randomized to receive high dose (80 mg/d) and low dose (10 mg/d) statin therapy. After a follow-up period of 4.9 years, high dose statin group received a greater reduction in LDL-c (77 mg/dl vs 101 mg/dl) and a greater reduction in non-fatal MI, CAD mortality, and fatal nonfatal stroke risk (8.7% vs 10.9%) in comparison to low dose statin group but it was observed that high dose statin group also shows high chances of adverse events [151].

The HDL Atherosclerosis Treatment Study (HATS) trial is one of the first trials which examined the increased level of HDL cholesterol by niacin therapy and its effect on CV outcomes. Adults were randomized to niacin therapy (16% with DM) and after a follow-up period of 38 months, a significant increase in HDL level was found in niacin therapy patients and patients with T2 DM had 13% fewer chances of CV outcomes [152].

CAN Patients with diabetes mellitus and CAN are at an elevated risk of cardiovascular associated mortality and morbidity as it is a very common complication of diabetes. The autonomic dysfunction that occurs in diabetic patients is linked with an elevated risk of cardiac arrhythmia and sudden deaths. Other serious CV problems include myocardial ischemia, perioperative, and intraoperative CV instability, stroke, diabetic cardiomyopathy. Common manifestations of CAN include hypotension, tachycardia, heart rate variability, and irregular blood pressure [73].

The complications and the pathogenesis of CAN can be reduced by the treatment of autonomic dysfunction [73]. According to many studies, it has been observed that strict glycemic control can be beneficial in reducing the occurrence of CAN in a diabetic patient. An example of the mentioned statement is that reports by DCCT mentioning that patients measured for Hba1c and found to have enhanced glycemic control are safer and have a lower risk to develop autonomic dysfunction as measured by CAN index [153]. Apart from glycemic control, many studies including the Steno-2 study states that by improving glucose control and cardiovascular risk factors, the incidence of CAN can be reduced in diabetic patients [154]. Pharmacotherapy agents include angiotensin receptor blockers, ACE inhibitors, and aldose reductase inhibitors that help in decelerating the progression of cardiovascular autonomic neuropathy [155]. The best pharmacological treatment is yet to be found by conducting various studies and researches.

Diabetic cardiomyopathy In cardiac myopathy, heart muscles become enlarged, thick, and rigid [156]. The prevalence of cardiac myopathy also increases along with the severity of DM. Diabetic cardiomyopathy represents various conditions such as dysfunction of diastolic, remodeling dysfunctionally, and myocardial fibrosis [41]. Some treatment therapies are shown in Table 7 [157].

Adjuvant pharmacological interventions Phytoconstituents also play a significant role in the treatment of various chronic diseases such as CVD, DM, and certain types of cancer. Overproduction of oxygen free radicals in the human body and an increase in oxidative stress is involved in the pathogenesis of many chronic diseases. Chronic inflammation is also a significant factor that is involved in the pathogenesis of CVD and DM and cancers [158–160]. So, the protective role of phytoconstituents is due to their antioxidant and anti-inflammatory properties. Phytoconstituents like curcumin, anthocyanins show anti-inflammatory properties by reducing the production of prostaglandins and by inhibiting nuclear factor κ-B activity [161, 162].

Obesity is one of the significant risk factors in CVD and DM could be treated by phytoconstituents. Antioxidant defenses (endogenous antioxidant) activity is low in obese parts in comparison to their normal-weight counterparts [163]. Fruits and plants which have a high saturation of antioxidant phytoconstituents show anti-obesity action. Due to the high level of flavanones, citrus fruits show inhibitory activity on pancreatic lipase and α-glucosidase in vitro [164]. Phytochemicals like proanthocyanidins and anthocyanins present in *Aristotelia chilensis* and *Vaccinium floribundum* limit the adipogenesis and inflammatory pathways in vitro [165].

Antioxidant compounds including phenol carboxylic acids, ascorbic acid, flavonoids, iridoids which are present in *Plantago maxima* extract, could reverse diet-induced obesity. Grape products rich in polyphenols could reduce the obesity-mediated chronic inflammation

Table 7 Treatment strategies of diabetic cardiomyopathy

Conventional therapies	Inhibitors of angiotensin-converting enzyme
	Therapies of lowering lipid
	Blockers of calcium channel
	Beta-blockers
	Thiazolidinediones
	Incretin based therapy
	Glycemic control
Novel therapies	Dysregulated microRNAs
	Gene therapy
	Inhibition of mitogen activity of pathway of protein kinase
	Signaling of protein kinase C
	Signaling of cardiac phosphoinositide 3-kinase
	Exercise
	Supplementation of coenzyme Q10

through various mechanisms such as blocking proinflammatory cytokines, by activating transcription factors that antagonize chronic inflammation [166, 167]. Resveratrol shows in vitro anti-obesity action by inhibiting adipogenesis. Curcumin also reduced obesity and related adverse effects of obesity. Allicin also showed anti-adipogenesis activities [168, 169].

Lifestyle modifications

Apart from pharmacological interventions, complications of DM and CV disorders can be managed by modifications in the lifestyle.

Current treatment recommendations encourage obese DM patients to reduce their weight and in turn reduce risk factors for CVD. These recommendations are divided into “high,” “moderate,” and “low” based on the different methodologies of scientific and clinical practice. There is a “moderate” amount of shreds of evidence which suggest a 5% loss in weight by lifestyle intervention leads to a subsequent increase in HDL cholesterol, a decrease in triglyceride level, and reduces in the latest prescribed lipid slowing drugs [120–122]. The diabetes prevention program (DPP) and Finnish diabetes prevention data stated that lifestyle changes and weight loss prevents pre-diabetic patients from diabetes. As in general, lifestyle interventions (physical activity and diet) leads to excess loss of VAT and ectopic fat which subsequently decreases CV risk profile [123, 124, 170].

The lifestyle changes and management significantly assist in lowering blood pressure that is in controlling hypertension. The lifestyle modifications needed are caloric restrictions, reduction of sodium intake to a maximum of 2300 mg/day, increasing fruits and vegetable consumption, and restricting alcohol consumption. Other lifestyle changes needed to control hypertension includes increased physical activity, smoking cessation, and reducing sedentary time. Lifestyle changes have been found to show a role in lowering blood pressure enhances metabolism and vascular system and also plays a synergistic role with antihypertensive medications. The treatment options or the ways to control and reduce the complications of the coexisting diseases with hypertension are lifestyle management, sodium reduction, physical activity, weight loss, sleep apnea treatment as shown in Table 8.

For managing dyslipidemia, non-pharmacological therapy or lifestyle modifications consist of nutrition, physical exertion, and loss of weight. Intake of plant stanols/steroids, n-3 fatty acids, and viscous fiber (legumes, oats, citrus) should be increased and the consumption of saturated and trans-fatty acids should be decreased. Agents like peanuts, tree nuts, and grains should be consumed as they help in lowering cholesterol and blood pressure as they are a good source of unsaturated fat. Improvement in the profile of lipid, glycemic control, and resistance of insulin is observed in patients with a 5% reduction in their body weight. Weight loss improves blood pressure, reduces the level of triglycerides, and elevates HDL-C levels [148, 180, 181].

Interplay between lifestyle modifications and genetics Various investigations involving epidemiology have suggested that the effect of various T2DM linked loci can be reduced by upgrading lifestyle and dietary patterns. The variant of PPARγ that is Ala 12 is linked with enhancing the sensitivity of insulin. It has been found that the Ala 12 variant is more receptive to unsaturated fat than saturated fat. On the other hand, the Pro12 variant of PPARγ shows more sensitivity to the damaging effects of malformed homeostasis of glucose and saturated fat. There is evidence of a potential interaction between the TCF7L2 risk variant and lifestyle modifications such as MNT, physical activity, and

Table 8 Treatment options for hypertension associated with diabetes

S. no.	Treatment	Steps	Impact
1	Lifestyle management [138, 171]	-Caloric restrictions -Sodium intake restrictions (2300 mg/day) -Increase fruits and vegetable consumption -Restricting alcohol consumption -Reduce sedentary time -Smoking cessation -Increase physical activity [172–174]	-Lowers blood pressure -Synergistic for antihypertensive medications -Enhances metabolism and vascular system
2	Reduced sodium	-Reduction of sodium intake per day. in a clinical trial, the sodium intake was reduced from 4600 mg to 2300 mg [175]	-Reduced pressure of blood (systolic approx. 5 mmHg and 2-3 mmHg diastolic).
3	Physical activity	-30-45 min of brisk walking -Regular exercise -Type and intensity of exercise should be preferred according to patient functional statu s[176, 177].	Reduced blood pressure
4	Weight loss	Approximately 1 mmHg of reduction in blood pressure can be achieved by losing 1 kg of weight [178]	Reduced blood pressure
5	Sleep apnea	Treat obstructive sleep apnea [179]	Reduced blood pressure

dietary changes. The decline in insulin resistance and the reduced risk in the risk variant TCF7L2 can be attributed to lifestyle modification [182–184].

There lies a shared SNP in obesity-linked genes such as FTO rs9939609 and fat mass. The SNP is linked with the increased vulnerability to T2DM. An increase in physical activity assists in reducing the FTO rs9939609-induced obesity and the linked T2DM risk [185]. The allele GCKRrs780094 is an insulin raising allele, a result of SNP in glucokinase regulatory gene. The gene interaction with whole grain reduces the carrier fasting insulin levels [186]. The gene KCNQ1 belongs to the subfamily Q of potassium voltage-gated channel and is a susceptible gene to T2DM. Mutation in this gene results in a decline in insulin secretion. The reduced expression of the Kcnq1 gene noncoding RNA Kcnq1ot1 region leads to an increment in Cdkn1c (cyclin-dependent kinase inhibitor 1C) expression that ultimately results in the decline of insulin release and cell mass of pancreatic-beta cells. The concentration of C/EBPbeta in the beta cells of the pancreas elevates in the existence of a high-fat diet and thus potentiates the dysfunction of beta cells in the susceptible population [182].

Reduction in hyperglycemia is also witnessed when there is an increment in the T2DM related genes (SLC26A3, GABAAalpha1, SLC26A6, CIC1-7, CFTR, and Bestrophin-3) expression due to the presence of *Lactobacillus casei*—a gut microbe [187]. There is an urgent need to consider the possible interplay between multiple T2DM linked genes and lifestyle modifications as it can turn out to be an effective therapeutic intervention.

Medical nutrition therapy in the management and prevention of diabetes There lies a direct correlation between diabetes management and diet and therefore medical nutrition therapy (MNT) serves as a complement to the traditional pharmacological intervention. The American Diabetes Association (ADA) recommended personalized MNT to individuals who are diabetic or pre-diabetic for effective treatment by the registered dietician having proper knowledge of diabetes MNT [188]. The combination of MNT and medical treatment has the potential for effective diabetes treatment.

MNT can be defined as the nutritional diagnosis and treatment to manage a particular disease furnished by a nutritional professional or a registered dietician. It also provides proper counseling service to the patient. The nutrition counseling of MNT provides a supportive process with priorities in order and to establish goals. It also involves the creation of individualized action plans to foster and acknowledge self-care [189].

The effectiveness of MNT in the treatment of diabetes I and diabetes II has been demonstrated by research. In 18 studies reviewed by the American Dietetic Association in which the individuals were provided with the MNT by a registered dietician as a complement to the treatment demonstrated a positive effect of medical nutrition therapy on the management of diabetes by showing an improvement in the levels of A1C [190]. It has been postulated by the ADA that MNT has potential in effective diabetes management whether type I or II.

Several studies adapted from Pastors et al. in which MNT was included in the diabetes treatment intervention reported a 0.9 to 1.9% improvement in the A1C levels [191]. MNT has also successfully shown its role in preventing type 2 diabetes. It has also been postulated that the type 2 diabetes onset can also be delayed with lifestyle modification such as changes in diet. The diabetes prevention program, 2002, is a notable prevention study. A total of 1079 participants aged 25-84 received an intensive lifestyle intervention that comprised MNT showed a 58% decline in the incidence of diabetes over 3 years. The study was controlled and randomized. MNT shows a positive role in the management and prevention of type II diabetes in adults as shown in Table 9 but the same role of MNT is yet to be demonstrated for children and adolescents.

Chrono pharmacology and diabetes treatment The study of the drug effects variation with the biological timing of the endogenous periods is known as chronopharmacology. The main aim behind chronopharmacology lies in understanding the predictable and periodic changes in both the desired and undesired effects of a drug. Chronopharmacology may be divided into chronopharmacokinetics, chronotherapy, and chronotoxicity [198]. Chronopharmacological aspects have shown to have an important role in the treatment and management of diabetes mellitus as the timing of medication and patient activities can have a major impact on the occurrence of troughs and peak in blood glucose levels [199].

Changes in the biological clock are associated with increased rates of myocardial infarction. The misalignment in circadian cycles and behavioral cycle results in adversarial cardiometabolic endpoints such as increased arterial blood pressure, insulin, glucose, catecholamines, and cortisol [200]. Circadian rhythm influences both the insulin release as well as the counterregulatory hormones such as glucagon, cortisol, growth hormone, and epinephrine that increase the blood glucose levels when needed. There is an increase in the level of growth hormone followed by a cortisol release surge and results in an overall elevated glucose production level by the liver in the middle of the night. In people not suffering from

Table 9 Goals of MNT in diabetes management

Goals of MNT in diabetes management	Result
A1C < 7%	Decline the risk of microvascular complications [192]
Blood pressure < 140/180 mmHg	Reduce risk for cardiovascular complications [193, 194]
LDL cholesterol < 100 mg/dL	Reduce risk for cardiovascular complications [193, 194]
Maintain body weight	Glycemic management
Address individual nutrition needs	Maintain energy balance
Maintain eating pleasure by educating about choices of food	Maintain energy balance and body weight
Day to day meal planning	Maintain energy balance and body weight [195–197]

diabetes, this increase in glucose is counteracted by the increased release of insulin in the pancreas and thus the glucose level remains constant. But, for people who suffer from type I diabetes and type II diabetes, the rise in blood glucose levels during sleep can have a significant effect on morning blood glucose levels. Blood glucose level rises between 4 am to 8 am and the event is known as the "dawn phenomenon." Circadian misalignment has been found to increase the resistance of insulin and decrease the function of the pancreas [201].

Daily rhythmicity is exhibited by both the pancreatic insulin secretion and the target organs of insulin. This daily rhythmicity may be associated with glucose metabolism homeostasis maintenance for an effective treatment of diabetes. It is necessary to correct these rhythms in diabetic patients. Several medications like glinides and long- and rapid-acting insulin analogs that are used to correct the impaired secretion of insulin have shown the chronotherapeutic approach. They are not only helpful in glycemic control but also reduce the risk of prolonged hypoglycemia and weight gain of the body. Lifestyle modifications affect the biological clock of humans. A therapeutic agent is required for the correction of the impaired biological clock as it is challenging to alter lifestyles in modern societies [202, 203].

Future prospects

While several studies led to the deeper comprehension of DM in the field of CVD, more work is needed to enhance the recognition and quantification of the threat of CV in DM patients. Further investigation is required to decide how glycemic regulation correlates to CVD. Some research indicates that better glycemic regulation potentially improves CV results for DM patients [73, 204]. Researchers need further analysis to help to understand the connection among glycemic control and CVD growth, and to decide whether beginning and length of therapy are relevant in reducing events of CV in DM patients. Additional studies are also required to figure out the best way of reducing cardiomyopathy and CAN risk and severity in DM patients. Several findings have also shown that autonomous dysfunction and cardiomyopathy of diabetes are disorder pathways that are normal in DM patients and raise the risk of potential CV problems. Modifying lifestyle, greater regulation and active compounds seem to be of help in reducing CAN and cardiomyopathy of diabetes development [205–208]. Nevertheless, fewer researchers have analyzed the most appropriate possible treatment for these problems and what could be done to avoid the creation of such systems. More work is required to better understand the regulation and management in people with diabetes of the typical risk factors of CVs, like blood pressure, obesity, and dyslipidemia. In comparison with the currently prescribed guidance based solely on statin prophylaxis, drug combination could be the best method of treating dyslipidemia. Further studies such as IMPROVE-IT will help to decide what treatment is best for treating diabetic dyslipidemia [208]. Additionally, HDL's function in CV healthcare is unclear and further work is required to evaluate whether pharmacologic drugs intended to boost HDL are clinically beneficial to people with diabetes.

It also is uncertain if losing weight in patients with diabetes is appropriate for the clinically important enhancement of CV production as well as how much dieting is needed. In people with diabetes with the other CV risk factors and co-morbidities, 5% losing weight may not even be appropriate. Eventually, follow-ups on the latest blood pressure recommendations will have to be monitored closely, especially in individuals above 60 years.

Conclusion

The related CVD could also be predicted to increase as the incidence of DM keeps growing, due to both the conventional factors of risk of DM and the direct impact on CVD. Appropriate treatment and management of DM together with successful therapy of related risk factors are therefore important for reducing DM and CVD's increasing prevalence and advancement. Further work to enhance knowledge of the disease state and its impact on CV function is required to boost medical treatment and CV results in people with diabetes.

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