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EPIDEMIOLOGY, BIOLOGICAL MECHANISMS, THERAPEUTIC SUGGESTIONS, AND FUTURE RESEARCH ON DIABETES AND CARDIOVASCULAR DISEASE

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ABSTRACT

Diabetes mellitus (DM) is on the increase and has fast become one of the most common and expensive chronic illnesses in the world. Diabetes and cardiovascular disease (CVD), the leading cause of morbidity and death in diabetic individuals, have a strong relationship. Obesity, hypertension, and dyslipidemia are frequent CV risk factors in diabetes patients, putting them at greater risk for cardiac events. Furthermore, several investigations have shown molecular processes connected with diabetes that independently enhance the risk of CVD in diabetic individuals. Targeting CV risk factors in diabetic individuals is therefore crucial for reducing the disease's long-term CV consequences. This study highlights the association between diabetes and CVD and investigates potential disease causes.

KEYWORDS: Diabetes mellitus, Cardiovascular disease, Mechanism, Treatment.

Core tip: The relationship between diabetes and cardiovascular disease (CVD) is summarised and addressed in depth, with an emphasis on rising prevalence, disease progression mechanisms, and current CVD therapy in diabetic patients. Future research directions are also considered.

INTRODUCTION

Diabetes mellitus (DM) is becoming more common over the world. The worldwide burden of diabetes has risen from 30 million in 1985 to 382 million in 2014, with current trends predicting that these rates will only continue to rise.[1] According to the International Diabetes Federation's most recent projections, 592 million (1 in 10) people worldwide will have diabetes by 2035.[2] While both type 1 diabetes (T1DM) and type 2 diabetes (T2DM) are on the rise, T2DM contributes proportionally more to the global rise in DM prevalence than T1DM[1]. One of the consequences of rising diabetes incidence is a significant fiscal burden on both the patient and the healthcare system. Gender, comorbidities, income, diabetes history, and employment status were statistically significant drivers of overall cost in India. According to the study, the median annual direct and indirect costs increased rapidly from 15,460 and 3572 in 1999 to 34,100 and 4200 in 2021. The economic impact of diabetes is significant, both in terms of direct medical care expenditures and indirect costs of lost productivity due to diabetes-related morbidity and mortality.[4] The direct expenses of diabetes are mostly due to macrovascular and microvascular consequences such as coronary artery disease, myocardial infarction, hypertension, peripheral vascular disease, retinopathy, end-stage renal disease, and neuropathy.[3,4]

Diabetes and cardiovascular disease (CVD) are inextricably linked. CVD is the leading cause of death and morbidity in diabetic populations.[5] According to the World Health Organisation, India accounts for one-fifth of these fatalities globally, particularly among the young. According to the findings of the Global Burden of Disease research, India has an age-standardized CVD mortality rate of 272 per 100,000 people, which is much higher than the global average of 235.

Both men and women have an elevated risk of CVD mortality when they are diabetes. In individuals with diabetes, the relative risk for CVD morbidity and death varies from 1 to 3 in men and 2 to 5 in women compared to those without diabetes.[7]

Diabetes management and treatment are crucial as the disease's incidence and economic impact continue to rise. Because CVD is the leading cause of death and morbidity in diabetic patients, one of the key goals of diabetes therapy should be to reduce diabetic patients' cardiovascular (CV) risk. One issue in managing diabetes and lowering CV events is the complicated and multidimensional nature of the interaction between diabetes and CVD. Obesity, hypertension, and

dyslipidemia are frequent in diabetic individuals, particularly those with type 2 diabetes. Furthermore, studies have found that various variables, such as increased oxidative stress, increased coagulability, endothelial dysfunction, and autonomic neuropathy, are frequently present in DM patients and may directly contribute to the development of CVD.[5] The high prevalence of CV risk factors, as well as the direct biological effects of diabetes on the CV system, place diabetic individuals at an elevated risk of developing CVD, and contribute to the increased incidence of MI, revascularization, stroke, and CHF.[5,8] Because of the complexities and various processes that link diabetes to CVD, it is critical to target treatment to what will have the most clinical impact on improving CV outcomes. This study investigates the factors that relate diabetes to CVD, as well as current treatment guidelines and future diabetes research.

CV RISK FACTORS AND CVD

Obesity

Obesity is widespread in diabetic patients, particularly T2DM, and is linked to an increased risk of CVD. Low-grade inflammation is one proposed pathway connecting diabetes and obesity to CVD[9]. Diabetes and insulin resistance are linked to adipose tissue upregulation of several cytokines, including tumour necrosis factor-, interleukin (IL)-1, IL-6, leptin, resistin MCP-1, PAI-1, fibrinogen, and angiotensin.[10] Overexpression of these cytokines contributes to increased inflammation and lipid buildup, both of which are harmful to blood vessels and can lead to endothelial dysfunction, MI, and cardiomyopathy (CMP).[5,11-14] Diabetics have higher levels of C-reactive protein (CRP), which may lead to endothelial dysfunction. Many studies have shown that CRP reduces endothelial production of nitric oxide (NO) and prostacyclin, both of which are essential for vascular compliance. CRP has also been demonstrated to enhance oxidised low-density lipoprotein (LDL) absorption in coronary vasculature walls, which can lead to endothelial dysfunction and the formation of atherosclerotic plaques.[14] Diabetes patients also have lower adiponectin production, which may result in reduced endothelial function.[10] Adiponectin reduces endothelial dysfunction by boosting NO generation and decreasing adhesion molecule expression. Adiponectin also protects against atherosclerosis by blocking LDL oxidation.[15] Diabetic people are at a higher risk of MI due to an increase in atherosclerotic plaque. Increased levels of the inflammatory cytokine IL-1, as found in diabetic individuals, can lead to atheromatous plaque destabilisation and consequent MI.[11] Insulin resistance is also related with an increase in plasma free fatty acids, which leads to increases in muscle triglyceride storage, hepatic glucose synthesis, and insulin production in T2DM patients.[16] Diabetes-related CMP has also been connected to insulin resistance via cardiomyocyte hypertrophy and contractile dysfunction.[16,17]

Hypertension

With incidence rates of 30% and 60%, respectively, among individuals with T1DM and T2DM, hypertension is highly common.[5] Diabetes-related hypertension is linked to the development of diabetic nephropathy (DN).[18] Hyperglycemia stimulates renal cells in DN, resulting in the release of humoral mediators, cytokines, and growth factors. These factors are frequently responsible for structural changes seen in diabetic patients' glomeruli, such as hyaline arteriolosclerosis (primarily of the efferent arteriole), increased collagen deposition of the extracellular matrix, and increased permeability of the glomerular basement membrane.[19] These structural alterations raise filtration pressure, which frequently results in microalbuminemia and compensatory activation of the renin-angiotensin system (RAAS). Chronic RAAS activation frequently leads to hypertension, putting more strain on the glomeruli and causing further damage to diabetes patients' nephrons. If untreated, DN can proceed to a nephrotic syndrome, which is characterised by proteinuria, hypercoagulability (due to ATIII loss), and hyperlipidemia, all of which may contribute to the elevated risk of CVD found in diabetic individuals with renal dysfunction.[20,21]

Dyslipidemia

Diabetic people are more likely to develop dyslipidemia.[22] Increased free fatty acid release in insulin-resistant fat cells is one mechanism behind this link. Triglyceride formation is stimulated by high amounts of free fatty acids, which in turn enhances the secretion of apolipoprotein B (ApoB) and very low density lipoprotein (VLDL) cholesterol. High ApoB and VLDL levels have both been linked to an increased risk of CVD.[23-26] In addition to elevated ApoB and VLDL levels, hyperinsulinemia is related with low HDL cholesterol levels.[27] Hyperglycemia may also have a deleterious influence on lipoproteins (especially LDL and VLDL) by increasing glycosylation and oxidation, lowering vascular compliance and accelerating the development of aggressive atherosclerosis.[28] High circulating FFAs and triglycerides, elevated ApoB and VLDL cholesterol stimulation, reduced HDL levels, and lipoprotein modification have all been seen in diabetes patients, possibly contributing to the high prevalence of CVD in diabetic individuals.

Diabetic cardiomyopathy

DM appears to contribute to the development of CMP directly, rather than only through coronary atherosclerosis and hypertension.[29] This diabetic CMP has been characterised in several noninvasive investigations and encompasses alterations in diabetes LV shape and cardiac performance. Diabetics, in particular, have larger cardiac mass, particularly LV mass, than non-diabetics.[30,31] This might be due to increased adipocyte secretion of cytokines including leptin and resistin, both of which have hypertrophic effects on cardiomyocytes.[12,13] Even after controlling for confounders, one research of a multi-ethnic population discovered that the risk of having LV mass that

exceeds the 75th percentile is higher in individuals with T2DM.[32] Diabetes patients also have somewhat worse diastolic function than nondiabetics.[33-35] One probable explanation is that increased triglyceride production in diabetic individuals leads to higher cardiac triglyceride content.[36] Increased myocardial triglyceride accumulation has been linked to lipotoxicity and altered calcium hemostasis in the myocardium, both of which have a deleterious influence on diastolic function.[37-39] This might help explain why 40%-75% of people with diabetes and no indications of overt coronary artery disease (CAD) have diastolic dysfunction.[34,35] Subtle changes in systolic function have also been found in diabetic individuals utilising tissue Doppler imaging and peak systolic velocity Doppler strain analysis.[40-44] This systolic dysfunction might be linked to decreased cardiac sympathetic innervation and contractile reserve.[45] Furthermore, interstitial fibrosis with higher collagen deposition has been seen in diabetics, which may contribute to the decreased heart function seen in diabetics.[46] Many of the factors that contribute to diabetes individuals' reduced systolic and diastolic performance are expected to also put them at risk of heart failure (HF).[47,48] Diabetic individuals have a greater prevalence of HF, particularly heart failure and maintained ejection fraction, than the overall population (4%-6%).[49] While established CV risk factors may explain for some of the variance, diabetes may independently change heart structure and function by increasing hypertrophy and fibrosis.[50]

Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN) is frequent in diabetic individuals and is associated with an elevated 5-year CVD death rate.[51] Resting tachycardia, postural hypotension, exercise intolerance, aberrant coronary vasomotor regulation, elevated QT interval, and perioperative instability are clinical symptoms of CAN. Clinical signs of CAN are associated with a higher risk of renal failure, stroke, CVD, and sudden death.[52] The development and progression of CAN is most likely linked to autonomic nervous system (ANS) dysfunction, as seen by increased sympathetic activity and higher inflammatory markers. Because the ANS regulates sinus node activity, end diastolic volume, end systolic volume, and systemic vascular resistance, ANS failure can result in arterial stiffness, left ventricular hypertrophy, and ventricular diastolic dysfunction.[53] The prevalence of CAN rises with age and poor glycemic control, putting individuals with diabetes at a greater risk of acquiring both CAN and CVD.[54]

Myocardial infarction and DM

Diabetes is a key risk factor for the development of CAD, with individuals with DM having a greater incidence of MI than those without.[55,56] Furthermore, diabetes individuals had greater rates of morbidity, death, and re-infarction after a MI than non-diabetics, with one-year mortality rates of approximately 50%.[57] Although the specific pathophysiology of CAD development in diabetic people has not been defined, current research suggest that the underlying atherosclerotic process is identical in those with and without diabetes. The greater incidence of myocardial infarction in diabetic individuals is assumed to be due to increased coagulability.[58] Many studies have indicated that diabetics have higher levels of glycoprotein IIB/IIIA receptors and vWF, both of which are involved in platelet activation.[59,60]

Diabetes patients also have higher levels of plasminogen activator inhibitor type 1, which may reduce fibrinolysis, increase thrombus formation, and accelerate plaque development.[61] Finally, diabetic patients have lower levels of circulating anti-coagulants such as protein C and antithrombin III, which is attributable in part to the proteinuria associated with DN.[62] These characteristics, taken together, put diabetes individuals in a prothrombotic and procoagulant condition, which may explain for the increased incidence of MI found in diabetic patients.

Diabetic individuals may have greater incidence of MI due to silent myocardial ischemia. Ischemia and consequent angina are frequently used to alert individuals who are developing obstructive CAD.[63] Silent ischemia, on the other hand, is frequently asymptomatic and detected later in the course of CAD, which is associated with increased rates of MI-related mortality and morbidity.[64] Silent ischemia is significantly more common in diabetic individuals (10%-20%) than in non-diabetics (1%-4%). This mismatch might explain why, in several angiographic investigations, CAD was frequently more progressed at the time of diagnosis in diabetic patients.[65,66] Diabetic neuropathy is one reason that might explain the higher prevalence of silent ischemia in diabetic patients.[67,68]

TREATMENT

Because CVD is the leading cause of death and morbidity in diabetics, efficient therapy is crucial to lowering the risk of CV events, notably MI, CAD, stroke, and CHF. Diabetes patients are at a higher risk of CV problems due to suboptimal glycemic management, obesity, hypertension, dyslipidemia, and autonomic dysfunction. Therapy aimed at modifying these risk factors can improve CV results, although it can be difficult to achieve. The guidelines for these risk factors often differ from those for non-diabetic individuals, and the recommendations frequently alter or differ depending on which organisation releases them. Furthermore, studies on how these many risk variables impact the CV risk profile of diabetics can be ambiguous and, at times, conflicting. The goal of this part is to present the most recent guidelines for treating glycemic control, hypertension, dyslipidemia, and autonomic dysfunction in diabetic patients, as well as to summarise the research that applies to each of these areas.

GLYCEMIC CONTROL

Because several studies have connected poor glycemic control to worse CV outcomes, current treatment

recommendations for DM patients include a strong emphasis on regularly monitoring and regulating glycemic levels in an effort to enhance cardiac outcomes. The precise glycemic level that should be addressed for diabetics, on the other hand, is debatable and varies depending on which organisation is developing the guidelines. The American Association of Clinical Endocrinologists Guidelines, for example, recommends a haemoglobin A1c (HbA1c) goal of less than or equal to 6.5%, and encourages providers to treat patients with an A1c value greater than 6.5% with a combination of lifestyle modification, weight loss, and pharmacological agents.[69] In order to lower the risk of microvascular or macrovascular consequences, the ACC/AHA recommends a somewhat more flexible A1c objective of fewer than 7% for non-pregnant individuals with T1DM or T2DM. Furthermore, the ACC/AHA qualifies their recommendation by stating that an A1c goal of greater than 7 may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or long-standing diabetes. The suggestion also notes that an A1c target less than 7.0% may be helpful for some diabetic patient groups, such as those with a short history of diabetes, a long life expectancy, and no CVD.[70] For diabetic individuals, the VA/DoD recommendations adopt a more individualised methodology to determine an appropriate A1c goal. The goal A1c ranges from 7 to 9 according to the patient's present health status, comorbid diseases, life expectancy, risk of hypoglycemia, and duration of diabetes status.[71]

CV OUTCOMES

Many research have been conducted to explore the influence of severe hyperglycemia therapy on CV outcomes in diabetic individuals. The UKPDS experiment was one of the first multi-center, randomised control trials to look at the effects of strict glycemic control in patients with newly diagnosed T2DM. Patients were randomly assigned to either "conventional" or "intensive" glycemic-lowering treatment and tracked for ten years. Over ten years, the intensive glycemic group lowered HbA1c by 11% (median 7.0%) compared to the usual treatment group, which did not show a significant reduction in HbA1c (median 7.9%). The principal benefit of tighter glycemic control was a 12% reduction in all diabetes-related endpoints and a 25% reduction in microvascular disease (mostly through reduced retinopathy). Furthermore, although not statistically significant, the intensive therapy group showed a tendency towards a reduction in macrovascular disease.[72] The VADT trial was another big research that looked at the effect of strict glycemic control in people with T2DM. This study's cohort was largely older (mean age 60.4 years) adult men with poorly managed T2DM (average HbA1c of 9.4%) and a disease duration of 11.5 years. The individuals were randomly assigned to either "intensive" or "conventional" glycemic control treatment and were tracked for 5.6 years. The group with tighter glycemic control had a considerably higher decline in A1c levels over the course of the research (6.9% vs 8.4%), but there was no significant difference in MI or all cause mortality between the "intensive" and "conventional" treatment groups.[73]

The ADVANCE study focused on the vascular consequences of aggressive glycemic treatment in persons with type 2 diabetes. T2DM patients with a history of severe macrovascular or microvascular illness were recruited from 215 participating centres in 20 countries for this big multi-center randomised control experiment. The subjects were randomly assigned to either a "intensive" or a "standard" glycemic-lowering regimen and were tracked for 5 years. The intense glycemic therapy group received treatment until their HbA1c was less than or equal to 6.5%. The group randomised to the stricter glycemic control showed a 23% reduction in microvascular events (mainly nephropathy) and a considerably larger drop in HbA1c (6.5% vs 7.3%). However, there was no difference in MI or all-cause mortality across the groups, and the group receiving 'intensive' therapy had higher incidence of severe hypoglycemia hospitalization.[74] The ACCORD experiment, which ran concurrently with the ADVANCE trial, examined whether stringent glycemic management lowered the risk of CV events. This multi-center randomised controlled study looked to see if very tight glycemic control (HbA1c less than or equal to 6%) resulted in reduced incidence of nonfatal MI, nonfatal stroke, and CV mortality in older persons than conventional glycemic control (HbA1c 7%-7.9%). The participants were tracked for an average of 3.4 years, and the group with stricter glycemic control had considerably lower HbA1c than the control group (7.3% vs 6.5%). The intensive glycemic control group had somewhat reduced rates of nonfatal MI, but the study was terminated early after 3.7 years because the intensive treatment group had higher rates of all-cause and CV death. As demonstrated in the ADVANCE trial[75], the group with strict glycemic control also had significant weight gain and a higher risk of hypoglycemia.

DCCT and the long-term follow-up experiment EDIC looked examined how rigorous glycemic control combined with intense treatment affected CV outcomes in T1DM patients. These studies assigned young (13-39 year old) T1DM patients to either "intensive" or "conventional" glycemic therapy, with a HbA1c target of 7% in the "intensive" treatment group. The key finding of the DCCT study was that after ten years of follow-up, the group with stringent glycemic control showed a 70% reduction in the number of microvascular sequelae, specifically retinal. Furthermore, the EDIC long-term follow-up research discovered a 42% reduction in CV events in the intensive glycemic treatment group compared to the standard glycemic therapy group.[18,76]

While it appears that there is a relationship between glycemic control and CV outcomes in diabetes individuals, the research on the effect of strict glycemic

control on CVD is inconsistent. Current research does not suggest that intensive glycemic control (HbA1c 6.5%) offers a substantial CV advantage over routine glycemic control objectives (HbA1c 7%-7.9%) in T2DM patients. While stricter glycemic management may reduce the frequency of microvascular events in T2D patients, there does not appear to be a significant advantage in rates of all-cause and CV-specific mortality. Furthermore, as demonstrated in the ACCORD study, very tight glycemic control (HbA1c 6%) may put patients at increased risk of hypoglycemia, weight gain, and all-cause mortality.[75] Tighter glycemic control appears to be advantageous in T1DM patients. According to the DCCT and EDIC studies, rigorous glycemic treatment (target HbA1c 7%) can help lower rates of microvascular and macrovascular disease in T1D.[18,76]

One possible interpretation of the research thus far is that the concurrent CV risk factors present in diabetics may outweigh any benefit that aggressive hyperglycemia therapy might bring in terms of risk reduction. Thus, in terms of CV outcomes, diabetic patients who attain tighter glycemic control earlier in their disease course and prior to the development of other CV risk factors may benefit the most from more intense therapy. As a result, many of the new guidelines seek to customise A1c targets to the individual patient rather than establishing a set A1c threshold for all diabetes patients. For example, the ACC/AHA and VA/DoD change their glycemic objectives based on criteria such as age, years with the condition, and CV risk.[70,71] While further research is needed to identify the optimum glycemic treatment goal for these distinct patient categories, diabetic individuals may benefit from modifying the target A1c based on their present degree of CVD risk.

Obesity

Obesity is a prevalent comorbidity of diabetes, particularly T2DM, and is associated with increased CV morbidity and death. As a result, current treatment guidelines advocate weight loss in overweight and obese diabetic patients in order to enhance their CV risk profile and lower their risk of CVD. In diabetes individuals who are overweight or obese, a 5% weight decrease over four years is recommended. A "moderate" amount of data shows that in diabetes patients, 5% weight loss by lifestyle intervention is related with an increase in HDL-c, a drop in triglycerides, and a decrease in newly prescription lipid-lowering drugs. Furthermore, there is "high" evidence that orlistat leads in 2-3 kg of weight loss in overweight and obese diabetic individuals after 1 and 2 years, as well as larger decreases in fasting blood glucose and HbA1c. On the basis of scientific technique, scientific strength, and consistency of results, these suggestions were rated as high, moderate, or low.[77]

Because obesity is a prominent risk factor for both CVD and T2DM, several studies have been conducted to evaluate the effectiveness of weight loss in lowering the onset and severity of DM. Some research have concentrated on reducing body weight in pre-diabetic individuals in order to reduce the risk of developing diabetes later in life. The diabetes prevention programme (DPP) and Finnish diabetes prevention research, in particular, looked into the influence of behaviour change on weight reduction and the risk of acquiring diabetes in pre-diabetic persons. Both trials found that individuals assigned to the lifestyle intervention group lost considerably more weight and had a lower chance of acquiring diabetes than those assigned to the control group.[78,79] Other research have looked at approaches for losing weight and reducing the CV risk profile of diabetes people. A range of approaches, including intensive lifestyle intervention, weight loss drugs, and bariatric surgery, were helpful in achieving weight reduction and lowering diabetes patients' CV risk profile through better glycemic management, blood pressure, and cholesterol levels.[80-82]

Although several studies have demonstrated that diabetic people may lose weight, there is conflicting data as to whether weight loss in these patients lowers eventual CV morbidity and death. There has been conflicting research on whether modest weight loss in diabetic persons reduces their CV risk. While the SCOUT trial revealed that moderate weight reduction might reduce 5-year CV death rates in diabetic individuals, the Look AHEAD study found no impact on CV mortality, MI, stroke, or angina hospitalisation after 9.6 years of follow-up.[83,84]

The current advice for overweight and obese diabetic individuals is a 5% weight loss goal.[77] So far, studies have shown that this aim may be achieved in both pre-diabetic and diabetic patients using a range of treatments including as rigorous behavioural modification therapy, pharmacological medications, and bariatric surgery. Furthermore, all of these weight loss techniques tend to either reduce the incidence of onset diabetes in pre-diabetic individuals or improve the CV risk profile of diabetic patients.[78-82] However, whether moderate weight loss in diabetes individuals leads to a reduction in CVD is unknown.[83,84]

It is likely that the CV risk profile in older persons with diabetes is too high for moderate weight loss to generate a substantial improvement in CV outcomes. It may be more beneficial to concentrate obesity treatment efforts on pre-diabetics before they acquire DM. Weight reduction programmes, such as the DPP, have shown that it can reduce the risk of incident diabetes, but further study is needed to evaluate if moderate weight loss in pre-diabetic individuals results in better CV morbidity and mortality.[78] It is also plausible that, while moderate weight reduction appears to enhance the CV risk profile of diabetic individuals, significantly greater weight loss is required to show more definitive benefits in CV event rates. Further research into the effects of higher than 5% weight reduction on CVD in diabetes people may assist determine the presence of a dosage effect with weight loss and CV health.

Hypertension

Because hypertension is a prevalent comorbidity of diabetic patients and a major risk factor for CVD, current treatment guidelines strongly encourage clinicians to control blood pressure in hypertensive diabetics. Many studies have been conducted to explore the effect of decreasing blood pressure in diabetic individuals on CV outcomes. The UKPDS 38 study investigated the effect of tight blood pressure management (150/85) with less strict control (180/105) on macrovascular and microvascular problems in T2DM patients. After 9 years of follow-up, the patients in the carefully managed BP group had considerably lower mean blood pressure (144/82 mmHg) than the patients in the less tightly controlled group (154/87 mmHg). Furthermore, compared to the less tightly controlled BP group, the group with tighter BP control had a 34% reduction in macrovascular disease risk (myocardial infarction, sudden death, stroke, and peripheral vascular disease) and a 37% reduction in microvascular disease risk (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure).[85]

While many studies have shown that lowering BP in diabetics improves CV outcomes, the ACCORD-BP trial compared the risk of fatal or nonfatal major CV events in patients with T2DM to intensive BP control (systolic BP 120 mmHg) versus standard BP control (systolic BP 140 mmHg). After 4.7 years of follow-up, the intensive BP control group did not have a lower rate of fatal and nonfatal major CV events than the normal BP control group (1.87% vs 2.09% per year). Furthermore, the intense BP group saw an increase in adverse events such as hypotension, syncope, bradycardia or arrhythmia, hyperkalemia, angioedema, and renal failure.[86]

Based on the findings of these studies, new treatment guidelines recommend that diabetic people between the ages of 18 and 60 begin pharmacologic therapy when their SBP exceeds 140 mmHg or their DBP exceeds 90 mmHg. The treatment threshold for adults over the age of 60 is an SBP of 150 mmHg or a DBP of 90 mmHg. The sort of pharmaceutical therapy that should be employed differs between the nonblack and black populations. Treatment for nonblack people with diabetes and hypertension should begin with a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB). The first line of therapy for black people with diabetes and hypertension should be a thiazide-type diuretic or a CCB. Furthermore, hypertensive individuals with diabetes and kidney disease should be treated with an ACE inhibitor or an ARB to enhance renal outcomes[87]. While the metabolic effects of various antihypertensive agents used to treat hypertension vary, many studies, including the ALLHAT trial, found no significant difference in the risk of coronary heart disease, nonfatal myocardial infarction, total mortality, or other clinical complications attributable to the initial antihypertensive drug therapy used to treat diabetic patients.[88,89] This would imply that metabolic variations between antihypertensive medications do not have a significant effect in the development of CVD in DM patients. It should be noted that these recommendations have been controversial, with several authors arguing that the guideline is too lax in treating certain at-risk groups, such as African Americans, women, and the elderly, based on previous studies evaluating blood pressure control and subsequent CVD in these populations.[90] There is most likely a therapeutic blood pressure range that not only lowers diabetes patients' CV risk but also protects them from side effects associated with hypotension. It remains to be seen whether the revised guidelines, notably with the raised systolic BP threshold in persons over 60, match this therapeutic BP range. There is very no information as to what the appropriate treatment range for different age groups should be. Furthermore, hypertension may have distinct consequences on CV health in various ethnic populations. More study is needed to determine the appropriate blood pressure range for individuals of all ages and races.

Dyslipidemia

Dyslipidemia is frequent in diabetic individuals and is related with an increased risk of CVD.[91,92] Health care practitioners are advised to detect and actively treat dyslipidemic individuals in order to reduce their risk of further CV events. The current advice for treating dyslipidemia in diabetic patients varies by age and is consistent with the awareness that therapy with fixed-dose statins, rather than LDL target levels, is the clinically validated method. As a result, diabetic individuals under the age of 40 who have clinical evidence of atherosclerotic CVD or an LDL-c more than 189 mg/dL are advised to use a high-intensity statin. Statin treatment is recommended for all diabetes individuals over the age of 40. Patients over 40 with an estimated 10-year ASCVD risk higher than 7.5% are given a high-intensity statin, whereas those with an estimated 10-year ASCVD risk less than 7.5% are given a moderate-intensity statin.[93]

Many studies have been undertaken to investigate the effect of treating dyslipidemia in diabetic individuals as a way to reduce CV risk. The CARDS study was the first multicenter randomised controlled trial to examine statin treatment in T2DM patients prospectively. Adults with T2DM were randomly assigned to either a placebo or 10 mg/d atorvastatin. The median follow-up duration was 3.9 years, and the atorvastatin group experienced a 26% reduction in total cholesterol and a 40% drop in LDL-c. Furthermore, as compared to the placebo group, the statin treatment group experienced a 37% reduction in CV events, a 27% reduction in all-cause mortality, and a 48% reduction in stroke. The CARDS study was terminated early due to the strong improvement seen by statin therapy.[94]

Following the discovery that statin medication conferred a substantial CV benefit in diabetic patients in the CARDS trial, the TNT study investigated the effect of high-dose statins on CAD mortality, nonfatal MI, and fatal or nonfatal stroke in diabetes patients with T2DM. Adults with T2DM were randomly assigned to either a high dosage (80 mg/d) or a low dose (10 mg/d) statin and were monitored for an average of 4.9 years. When compared to the lower dosage group, the high dose group showed a larger reduction in LDL-c (77 mg/dL vs 101 mg/dL) and a better reduction in combined CAD mortality, nonfatal MI, or fatal or nonfatal stroke (8.7% vs 10.9%). The higher dosage group did, however, have a greater risk of adverse events (myalgia, sustained rise in alanine aminotransferase, aspartate aminotransferase, or rhabdomyolysis).[95]

Because several studies had shown that statins, particularly high-dose statins, had a CV benefit in diabetic patients, the 4D research investigated the effect of statins in diabetic patients receiving hemodialysis. Diabetic patients on hemodialysis were randomly allocated to either 20 mg of atorvastatin per day or a placebo in the 4D experiment. The study's goal was to see if a low-dose statin reduced the risks of mortality from cardiac causes, nonfatal myocardial infarction, and stroke in diabetic individuals with end-stage renal disease compared to the placebo group. The statin treatment group had a considerable reduction in LDL-c compared to the placebo group (-42.0% vs -1.3%), however there was no meaningful difference in CV outcomes after 3.96 years of follow-up. Furthermore, there were substantially higher incidences of fatal stroke in the statin medication group than in the placebo group.[96]

Other study groups have explored the effect of non-statin lipid-lowering medications on CVD in diabetic patients, while prior studies concentrated on decreasing cholesterol in diabetic patients with statin therapy. The FIELD study, for example, looked at whether decreasing cholesterol with fenofibrate medication may improve CV outcomes in people with diabetes. In the FIELD study, diabetic individuals (mean age 62 years; 63% males) were randomly assigned to either fenofibrate (200 mg/d) or a placebo and subsequently their rates of fatal coronary heart disease (CHD) or nonfatal MIs were examined. While the fenofibrate group did lower their cholesterol compared to the placebo group at 4 months (total cholesterol, LDL-cholesterol, and triglycerides by 11%, 12%, and 29%, respectively), the differences between the groups decreased as the trial progressed, owing in large part to patients beginning additional cholesterol-lowering therapies outside of the study. After a median of 5 years, the fenofibrate group had a combined 11% decrease in fatal CHD or nonfatal MIs, although this difference was not statistically significant. However, as compared to the placebo group, the fenofibrate group had a statistically significant reduction (24%) in nonfatal MIs.[97] Furthermore, because HDL has been linked to enhanced CV health in several large prospective studies, some research groups have studied whether increasing HDL by pharmacological treatments decreases the incidence of CV events. The HATS study was the first to look at the effect of boosting HDL with Niacin therapy on CV outcomes in adult participants (16% of whom had diabetes). After 38 months of follow-up, the niacin-treated group showed a substantial rise in HDL, and patients with T2DM had a 13% drop in absolute risk of CV disease.[98] However, the AIM-HIGH study recently demonstrated no meaningful therapeutic benefit in individuals with atherosclerotic CVD when compared to a placebo. The trial was terminated after three years due to a lack of efficacy; the niacin-treated group (34% with DM) did not have a significant reduction in composite coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalisation for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (16.4% vs 16.2%), despite significant improvements in HDL (25% vs 11.8%). These findings were identical in diabetics and non-diabetics.

Dyslipidemia is common in diabetics and a major risk factor for CVD.[91,92] Current treatment guidelines encourage doctors to decrease cholesterol levels in diabetes patients, mostly through the use of statins, the dose of which is determined by the patient's level of risk. Some trials have also looked into whether combining a statin with other lipid-lowering medicines might provide further CV benefit in individuals with diabetes. The IMPROVE-IT study, for example, discovered that combining ezetimibe (a cholesterol absorption inhibitor) with simvastatin was better to simvastatin alone in lowering CV events in diabetic individuals with acute coronary syndrome.[100] So far, the data shows that statin medication is beneficial for CV health in individuals with diabetes, and that larger dosages, as well as combination lipid-lowering therapy, can give extra CV protection.[93] While several meta-analyses have revealed that statin medication may raise the risk of diabetes, the absolute benefit of the therapy in diabetic individuals much surpasses the risk.[101] Other lipid-lowering medications, such as fenofibrates, have not showed the same degree of effectiveness and CV event reductions as statins.[97] Pharmacological treatments that increase HDL appear to have little, if any, CV benefit.[98,99] More research is needed to better understand the function of HDL in CV health.

CAN

Diabetes complications such as CAN put diabetic individuals at a greater risk of CV morbidity and death. Autonomic dysfunction is related with an increased risk of cardiac arrhythmias and sudden death, as well as other significant CV sequelae such as silent myocardial ischemia, diabetic cardiomyopathy, stroke, and intraoperative and perioperative CV instability. Heart rate variability (variability in instantaneous beat-to-beat intervals), resting tachycardia, exercise intolerance,

orthostatic hypotension, and poor blood pressure control are among of the most prevalent clinical symptoms of CAN.[102] Autonomic dysfunction can be treated early to delay the aetiology and consequences of CAN.[102] According to several research, strict glycemic management may have an essential role in lowering the occurrence of CAN in DM patients. The DCCT, for example, found that individuals with better glycemic control, as evaluated by Hba1c, had a considerably decreased probability of developing autonomic dysfunction, as measured by a CAN index.[103] While the effect of glycemic management on CAN in T2DM patients has been less definitive, certain trials, notably the Steno-2 research, revealed that increasing glucose control and other CV risk factors lowered the occurrence of CAN.[104] Lifestyle therapies that promote weight reduction and enhance exercise endurance have also benefited autonomic dysfunction. Pharmacological treatment, such as ACE inhibitors, angiotensin-converting enzyme inhibitors, and aldose reductase inhibitors, appears to help delay the course of CAN.[54] Furthermore, IGF-1, ACE inhibitors, and beta-blockers appear to benefit diabetic cardiomyopathy therapy by decreasing ventricular hypertrophy and normalising calcium homeostasis in diabetic cardiomyocytes.[105-109] However, further research is needed to determine the optimum pharmacological therapy for diabetic individuals with CAN.

FUTURE DIRECTIONS IN THE TREATMENT OF DM

While several studies have contributed to a better knowledge of diabetes and CVD, further research is needed to accurately identify and quantify CV risk in diabetic individuals. Another area where further study is needed is determining how glycemic management links to CVD. There is limited evidence that better glycemic management improves CV outcomes in diabetic individuals.[72,73] One research also discovered that HbA1c is an independent predictor of coronary artery disease and its severity in non-diabetic individuals, implying that glycemic management is crucial to controlling CV health in all patient populations.[110] While this observational trial suggests that glycemic levels may have an independent association with CVD, large randomised control trials such as ADVANCE and ACCORD have shown that the effect of tight glycemic control on subsequent CVD is modest and largely attributable to coexisting traditional risk factors.[73-75,110]

Poor assessment tools may be one cause for the contradictory data concerning the link between glycemic control and CVD. Fasting plasma glucose (FPG) is commonly employed as a marker of glycemia, however studies have indicated a day-to-day within-person range of 12%-15% in diabetes patients' FPG levels.[111] While the within-person variability for HbA1c is much lower (2%), there is evidence that HbA1c does not adequately reflect glycemic management due to biological variances and changes in RBC survival across patients.[111-113] If glycemic management is important, adequately measuring it and linking it to CV risk is critical in order to create clinically useful targets for diabetic patients.

Improved glycemic control's length and initiation may potentially contribute to the development and severity of CVD. The UKPDS found that tight glycemic control was linked with lower CV outcomes in middle-aged people (median 54 years) newly diagnosed with DM.[72] In contrast, the ADVANCE and ACCORD studies found that tight glycemic control did not reduce eventual CVD and may even be hazardous in patients who were somewhat older and had diabetes for a longer period of time.[74,75] This might mean that treating hyperglycemia aggressively in high-risk individuals with long-standing diabetes is too late to have a clinically significant impact, and that treating hyperglycemia aggressively in patients immediately after DM diagnosis is more helpful. More research is needed to better understand the association between glycemic control and the development of CVD, as well as to evaluate if the initiation and duration of therapy affect the decrease of CV events in DM patients.

More study is also needed to find the best therapy to reduce the risk and severity of cardiomyopathy and CAN in diabetic people. Many investigations have shown that autonomic dysfunction and diabetic cardiomyopathy are disease processes that are not only frequent in DM patients, but also put them at a higher risk of future CV complications.[102] Lifestyle changes, stricter glycemic management, and pharmacological treatments appear to help reduce the course of CAN and diabetic cardiomyopathy.[54,102-109] However, few research have been conducted to determine which specific therapies are most helpful in treating these illnesses, as well as what may be done to avoid the onset of these disease processes entirely.

More study is also required to better understand how classic CV risk factors, such as dyslipidemia, obesity, and blood pressure, should be evaluated and controlled in diabetes individuals. Contrary to current recommendations, which mostly focus on statin monotherapy, combination treatment may be the best strategy to manage dyslipidemia. More trials like IMPROVE-IT might aid in determining the best efficient medication for managing dyslipidemia in diabetes patients.[100] Furthermore, the function of HDL in CV health is complex, and further research is needed to identify whether pharmacological treatments aimed to raise HDL might give therapeutic benefit in diabetes individuals. It is also uncertain if and how much weight loss is required in people with diabetes to obtain clinically significant changes in CV outcomes. For diabetic individuals with additional CV risk factors and comorbidities, a 5% weight loss may not be enough. More research is needed to understand the amount of weight reduction required to achieve CV benefit and the optimum treatment technique to achieve that weight loss target. Finally, follow-up on the new blood pressure

standards will need to be thoroughly monitored in the future, particularly in those over 60 who now fall within the higher systolic BP threshold.

CONCLUSION

As the prevalence of diabetes rises, so will the prevalence of CVD - through both classic CV risk factors and the direct impact of diabetes on CVD. As a result, adequate DM control and treatment, as well as proactive treatment of related CV risk factors, are critical to reducing the rising prevalence and progression of DM and CVD. More study is needed to better understand the illness process and its implications on CV health in diabetes individuals in order to enhance medical care and CV outcomes.

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