Chapter 5

Cardiovascular Disease and Diabetes: Two Sides of the Same Coin!

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Abstract

Cardiovascular disease (CVD) and type 2 diabetes (T2DM) are rapidly rising around the globe. Empirical researches demonstrated rapid increase in mortality and morbidity related to CVD and T2DM. Much of the diabetes-associated morbidity and mortality predominantly reflects its deleterious effect on macrovascular and microvascular diseases. The microvascular complications of T2DM include retinopathy, neuropathy and nephropathy and the macrovascular complications include ischemic heart disease, cerebrovascular disease and peripheral vascular diseases. Research indicates that coronary heart disease (CHD) is the major cause of mortality in people with T2DM. Herein, this chapter reviews relationship between CVD and T2DM, associated complications and effectiveness of relevant treatment modalities to treat/prevent diabetic macrovasculopthy. Macrovascular disease occur due to underlying obstructive atherosclerotic changes of major arteries which cause functional and structural abnormalities of blood vessels. The long-term complications can be controlled and prevented by controlling glycemia, maintaining normal lipid profiles, adopting a healthy lifestyle and using pharmacological interventions. Clinical trials have shown that lifestyle interventions help in prevention and reduction of CVD risk, but evidence for long-term CVD outcomes is lacking. A multidisciplinary approach involving patients, health professionals and researchers and governments should be undertaken to reduce the incidence and prevalence of diabetes-related cardiovascular complications.

Keywords: cardiovascular diseases, type 2 diabetes, vasculopathy, macrovascular diseases, atherosclerosis, pathophysiology, pathogenesis

1. Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in people with type 2 diabetes (T2DM) [1, 2], and coronary heart disease (CHD) is the most common cause of death among people with T2DM. It is estimated that up to 80% of the 200 million people suffering with T2DM globally die of CVD every year [3, 4]. In recent years, the pandemic of T2DM has emerged as a major and growing health problem. The cardiovascular (CV) complications associated with T2DM cause a considerable amount of disability, premature mortality, loss of productivity and tremendously increase burden on health care systems and economies worldwide [5–7]. Among the major complications, the development of CVD is two to four times higher in people with T2DM as compared with people without the condition [8, 9]. Thus, CVD and T2DM have become inseparable which need to be addressed by the global health initiatives.

T2DM acts as an independent risk factor for several forms of CVD (micro- and macrovascular diseases), and people with T2DM are more likely to develop CVD due to a variety of risk factors [10]. Preclinical manifestations of macrovascular diseases are developed much earlier in newly diagnosed, never-treated T2DM patients [11], and such macrovascular changes are also observed even in normoglycemic and normotensive offspring of parents with T2DM [12, 13]. Furthermore, early manifestations of preclinical vasculopathy and development of macrovascular disease were potentially found to be at increased risk with impaired glucose tolerance (IGT) [13]. The CV complications of T2DM have a significant impact on individuals, families, health systems, and economic development worldwide [14]. According to the International Federation of Diabetes, $673 billion was spent on diabetes in 2015 which is 12% of global health expenditure [15]. It is imperative to control the initiators of vasculopathy that ultimately develop into long-term CV complications by adopting a healthy lifestyle and using pharmacological interventions. This chapter reviews relationship between CVD and T2DM, associated complications and relevant treatment modalities to treat/prevent diabetic macrovasculopthy.

2. Cardiovascular disease risk in diabetes

CVD are the number one cause of death globally – more people die annually from CVD than from any other cause. Individuals at risk of CVD may demonstrate hypertension, hyperglycemia, and hyperlipidemia as well as overweight and obesity. According to World Health Organization [16]:

- Approximately 17.5 million people died worldwide from CVDs in 2012, representing 31% of all deaths.
- Of all CVD deaths, an estimated 7.4 million were due to CHD and 6.7 million were due to stroke.
- An estimated 75% of CVD deaths take place in low- and middle-income countries.
- Of the 16 million deaths (≤70 years of age) as a result of non-communicable diseases 37% are caused by CVDs.

The main contributing factor in the increasing prevalence of CVD deaths is the increase in the cases of diabetes at very alarming rate, in particular, due to increasing prevalence of obesity, lifestyle choices, urbanization, aging, and genetic factors [17]. According to the International Diabetic Federation [15]:

- In 2015, 415 million people had diabetes, and in 2040, 642 million people will develop diabetes worldwide.
- At present, 3/4 of people with diabetes live in low and middle income countries.
- In 2015, 1 in 11 adults had diabetes, and in 2040, 1 in 10 adults will have diabetes.
- One in two adults with diabetes remains undiagnosed.
- Every 6 s 1 person dies from diabetes.
- Five million deaths occurred in 2015 as a result of diabetes.

3. Diabetes and macrovasculopthy: double trouble!

The alterations in vascular homeostasis that include anatomic, structural, and functional changes in blood vessels lead to multi-organ dysfunction and increase CV risk burden [18]. Diabetic microvascular and macrovascular complications have similar pathogenetic mechanisms and characteristics. The microvascular complications include retinopathy, neuropathy and nephropathy and the macrovascular complications include ischemic heart disease, cerebrovascular disease and peripheral vascular diseases [19–21].

The relationship between diabetes and CVD is complex and multifactorial [22]. Studies demonstrated the following macrovascular complications in T2DM patients:

- In diabetic men, CV mortality increased three-fold [23, 24] and in diabetic women, two to fivefold [25, 26].
- Patients with diabetes who develop clinical CVD have higher mortality than those CVD patients with no diabetes [26, 27].
- T2DM is considered to be one of the six major controllable risk factors for CVD [28].
- T2DM and IGT are related to increased risk of CV problems [28].
- People with T2DM also have high rates of hypertension, lipid abnormality, and obesity, which contribute to their high rates of CVD [28].
- T2DM is associated with increased risks of stroke, myocardial infarction, hypertension and intermittent claudication [29–31].
- Approximately 7% of people with T2DM have had a stroke at time of diagnosis and, indeed, stroke is the second major cause of death in T2DM [31].
- Risk of fatal stroke is increased 2–3-fold compared with non-diabetics [29], accounting for 15% of all deaths in T2DM [32].

- It was also demonstrated that 18% of diabetic patients have evidence of coronary heart disease at diagnosis, and the risk of a fatal myocardial infarction is increased 2–4 times in people with T2DM [29].
- Fatal cardiovascular events were 70 times more common than deaths from microvascular complications [33].
- Peripheral vascular disease (PVD) is estimated to be the most costly complication of diabetes in relation to inpatient care.
- PVD greatly increases the risk of intermittent claudication, foot ulcers, gangrene, infection and amputation [32].
- Lower extremity amputations are at least 10 times more common in people with diabetes than in non-diabetic individuals in developed countries and more than half of all non-traumatic lower limb amputations are due to T2DM [34].

4. Pathophysiology of diabetic macrovasculopathy

Atherosclerotic vascular disease mainly occurs due to endothelial dysfunction [35, 36], which is the failure of the vascular endothelium to subserve its normal role in vasodilatation and/or vascular homeostasis. The physiological impairment that causes diabetic vasculopathy includes endothelial dysfunction, platelet hyper-reactivity, smooth muscle cell (SMC) dysfunction, impaired fibrinolysis coupled with a tendency for thrombosis and coagulation, and increased inflammation [37, 38]. Endothelial dysfunction links each of these pathological manifestations to develop macrovasculopathy [39]. The main regulatory function of endothelium stimulation includes vasodilatation; other mechanisms include vasoconstriction, and antiplatelet and anticoagulant effects [40]. Endothelial dysfunction lead to morphologic and structural vascular changes [41]. Capillary endothelium rapidly disappears [42], intercellular junctions weaken causing increased vascular permeability [43], protein synthesis is dysregulated and expression of adhesion glycoproteins on endothelial cells is altered [42–45], thereby triggering adherence of monocytes and leucocytes and their increased transendothelial migration [43].

The characteristic feature of diabetic complications includes the progression of atherosclerotic lesion or alteration of vasculature, which is a major cause of CVD development [46]. It was shown that diabetes accelerates these processes by stimulating the atherogenic activity of vascular SMC and these considered as the integral part in the development of atherosclerosis [35]. The process begins as a response to chronic minimal injury to the endothelium leading to it being dysfunctional. Fewer vascular SMCs are also found in patients with diabetes with advanced atherosclerotic lesions [47]. Diabetes alters vascular smooth muscle function in ways that promote atherosclerotic lesion formation, plaque instability and clinical events. Platelet aggregation and adhesion are seen in diabetic patients [48–51]. The process involves an increase in intrinsic platelet activation and decrease endogenous inhibitors of platelet activity [35]. Platelets exhibit enhanced platelet aggregation activity in the early disease state that may precede the development of CVD [48–54]. T2DM also brings about some changes in

coagulation of blood. A procoagulant state has been shown in people having diabetes [55–57]. It was demonstrated that there is an increase in plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), fibrinogen, factor VII and thrombin–antithrombin complexes in macrovascular diseases and poor glycemic control [55–61].

5. Pathogenesis of vasculopathy

It is now well-established that metabolic, humoral and hemodynamic factors contribute to the characteristic dysfunction in diabetic vasculopathy. Prolonged hyperglycemia is considered as a major factor in the pathogenesis of diabetic vasculopathy [62–64]. Hyperglycemia together with several other factors accelerates the progression of atherosclerosis. In particular, hypoglycemia increases oxidative stress [65]; enhances leucocyte–endothelial interaction [66], and glycation of protein, lipoproteins, apolipoproteins and clotting factors, which cumulatively enhance vasomotor tone, vascular permeability, growth and remodeling [42–45]. Moreover, hyperglycemia delays endothelial cell replication, increases cell death [42, 45, 67–70] and potentially accelerates the atherosclerotic process. Glucose-induced damage occurs through advanced glycation, activation of protein kinase C (PKC), and sorbitol accumulation [71, 72]. Early glycated products on collagen, intestinal tissues and blood vessels undergo a series of chemical rearrangement to form irreversible AGE. AGE product promotes atherosclerotic effect by receptor-mediated biological activities e.g. monocyte emigration, release of cytokines and growth factors from macrophages and increase in endothelial permeability and procoagulant activity [73].

Dysregulation of Lipid metabolism underlies pathogenesis of macrovascular diseases of diabetes origin [74]. Diabetic dyslipidemia causes increase in total cholesterol and low-density lipoprotein (LDL) and -decrease in high-density lipoprotein (HDL) and high triglyceride levels [74, 75]. LDL and other lipoproteins enter the endothelial cells by vascular transport and may get modified by oxidation, glycation, aggregation, association with proteoglycans or incorporation to immune-complexes [76–78].

Insulin resistance is a common feature associated with T2DM and development of CVDs. Insulin resistance precedes the development of overt T2DM and leads to endothelial dysfunction and increases blood plasma levels of endothelin and vWF [79]. Furthermore, insulin resistance may cause increase in arterial blood pressure by triggering several mechanisms, such as, activation of sympathetic nervous system, increase in renal sodium retention, alteration in transmembrane cation transport, augmentation of growth-promoting actions of SMCs and vascular hyperactivity [80–82].

Increased expression and action of various cytokines and growth factors in T2DM may induce macrovascular injury via activation of proliferative cytokines epidermal growth factor [83] and platelet-derived growth factor (PDGF) [84]. Metabolic and hemodynamic factors interact to stimulate the expression of cytokines and growth factors in the various vascular trees, which contribute to the characteristic dysfunction observed in diabetic vasculopathy [20].

Intracellular hyperglycemia has been implicated in the pathogenesis of diabetic complications through the activation of PKC, an intracellular second messenger system [85, 86]. PKC appears to be activated in a range of diabetic tissues including heart and aorta [20]. The beta isoform of PKC is involved in abnormalities of endothelial-dependent vasodilatation in diabetes by promoting superoxide ions (O_2^-) to react with nitric oxide to produce peroxynitrate ($ONOO^-$), which damages tissues and activates monocyte macrophages [87]. Diabetic vasculopathy is characterized by early migration of monocytes into the arterial wall [88]. Monocytes differentiate into macrophages to form foam cells which secrete growth factors and metalloproteinases. The growth factors stimulate cell proliferation and matrix production, and the metalloproteinases cause matrix degeneration [78].

Another major factor involved in the pathogenesis of vasculopathy is oxidative stress [89–91]. Increased oxidative stress in T2DM induces generation of free radicals that cause vascular tissue damage. In the pathogenesis of diabetic vasculopathy, white blood cells (WBCs) play a potential role. High WBC count predicts a decrease in insulin action and development of T2DM [92]. Inflammation is a primary risk factor for CVD [93], and proinflammatory cytokines and C-reactive protein are found to be linked to the development of diabetes. Increased WBC count, in particular, increase in activated neutrophils is a major contributing factor in development of CVD [94]. Activation of neutrophils leads to altered rheological properties of blood, increases blood corpuscular adhesion, and damages endothelium with cytotoxic reactive oxygen species and proteolytic enzymes [95]. These changes trigger activity of granulocytes and monocytes in endothelial injury site and result in atherogenesis. Besides, leucocyte adhesiveness/aggregation is found to be slightly increased in those who have had concomitant diabetes [96].

6. Diagnosis of vasculopathy

Increased arterial stiffness is a dysfunctional property of the arterial circulation that leads to CVD. The stiffening of aorta and other central arteries is a potential risk factor for increased CV morbidity and mortality [97]. Arterial stiffness can be measured by a number of methods. Some of these are more widely used in the clinical settings as these are simple, accurate and, reproducible and thus can easily be applied for the evaluation of CV risk. [98]. Most of them are complex or need sophisticated technical equipment, which limits their application in clinical practice. Among the non-invasive and simple methods of evaluating arteries, pulse wave velocity (PWV) [99] and augmentation index (AI) [100–103] measurement are widely used as indexes of large artery elasticity and stiffness.

Pulse wave velocity (PWV) is the oldest and probably the best clinical measure of stiffness over an arterial segment [104]. The technique of PWV is valid and reproducible, and has been widely applied in clinical and research setting [105]. PWV is determined by measurement of the time taken for the pulse wave to traverse the distance between two fixed measuring points [99]. PWV may be measured in various segments of the arterial circulation [106] and is therefore derived as (distance [m]/time [s]), in m/s, ranging from 5–20 m/s [104]. It is assessed either between carotid and femoral arteries (aortic PWV) or carotid and radial arteries known as brachial PWV [99].

The pulse wave analysis (PWA) is the generation of ascending aortic pressure wave [107]. The system is used to assess central aortic pressure which depends on accurate recording of the radial pulse wave [108, 109]. The radial pressure pulse contains all the basic information from which the ascending aortic pulse is generated [107]. It is calibrated against the brachial pressure, then generation of ascending aortic pressure waveform through the use of generalized transfer function in a computerized process [107]. It gives information to ventricular/vascular interaction from both pressure and time values, as calculated from the synthesized aortic waveform. Therefore, PWA used for deriving central arterial pressure waveforms, from which *augmentation index* (AI) and the timing of the reflected pressure wave can be determined as indices of arterial stiffness. Aortic AI is defined as the increment in pressure after the first systolic shoulder to the peak of the aortic pressure expressed as a percentage of aortic pulse pressure [110]. It is a surrogate measure of systemic arterial stiffness [111–113] which is calculated from the derived aortic waveforms using PWA and expressed as a percentage (%).

Pulse pressure is one of the simplest measures of arterial stiffness, varies with the rigidity of the arterial wall and easily practicable in the clinical setting. Pulse pressure is the difference between systolic and diastolic BP, depends on cardiac output, large artery stiffness and wave reflection. It can be easily measured by sphygmomanometer. However, pulse pressure alone is inadequate to assess arterial stiffness accurately. Brachial pulse pressure may not change despite increasing arterial stiffness when induced by circulating angiotensin II [114].

Pulse contour analysis estimates arterial stiffness non-invasively and measures both capacitive (storage) and cushioning (oscillatory) arterial functions. In this technique arterial pulse contour is used to assess large artery capacitance and the capacitance of smaller arteries that are the primary source of reflected waves or oscillations in the arterial system. This technique involves tonometry at the radial artery, but the compliance is derived differently, using a model of the circulation and an assessment of diastolic pressure decay. Pressure pulse contour analysis requires estimation of cardiac output from an algorithm.

Photoplethysmography records the digital volume pulse [115]. This technique records the transmission of infrared light passing through the finger to measure the alteration in flow and produces a volume waveform. A stiffness index and a reflexion index that reflect systemic arterial stiffness are developed using this technique. The technique is relatively simple and easily portable [105]. However, problems include the damping of peripheral pulse, and temperature-dependant changes in the peripheral circulation.

Ultrasound and Doppler techniques are used to visualize wall thickness and vascular diameter on a monitor screen. Using an ultrasound transducer to perpendicularly project ultrasound beams to the artery, the optimal sound reflections from the wall are obtained and the reflected echoes from the wall and lumen are monitored. Simultaneously, blood pressure is also measured to adjust the change in arterial diameter to estimate arterial stiffness.

Magnetic resonance imaging (*MRI*) *technique* is used to measure vascular compliance and distensibility. The technique demonstrates the inverse relationship between aortic distensibility and age, i.e. aortic distensibility is reduced in hypertensive patients [116], and that arterial compliance is reduced in patients with CAD but increased in athletes [117].

Oscillometric BP measurement can be used to estimate the arterial stiffness. The pattern of oscillations depends on arterial stiffness. As the cuff is deflated, oscillations are increased, reaching a peak at mean arterial pressure. By coupling this to a computer algorithm, an index of arterial stiffness can be calculated.

7. Treatment modalities of diabetic vasculopathy

CVD is a major complication and the leading cause of early death among people with T2DM [118]. Much of the diabetes-associated morbidity and mortality predominantly reflects its deleterious effect on macrovascular and microvascular diseases [119, 120]. As T2DM is a complex metabolic disorder characterized by hyperglycemia, hypertension, hypercoagulability, and dyslipidemia, the diabetic patients with CVD require therapy for each of these metabolic abnormalities to reduce atherogenesis and prevent CV complications [121]. The main strategies for an effective therapy are to reverse insulin resistance, restore beta cell function, and control hepatic glucose output. The key treatment modalities include lifestyle modification and pharmacological interventions.

7.1. Lifestyle management

Lifestyle management is an essential part of management of T2DM and CVD in diabetic patients. Dietary restriction is recommended to achieve weight loss and reduce the risk factors for CVD in T2DM. Calorie restriction and weight loss bring down the blood pressure to normal limits and improves blood lipid profile, especially triglycerides and very low-density lipoprotein cholesterol. Exercise improves glycemic control, reduces certain CV risk factors, and increases psychological wellbeing [122]. In addition, physical training has been shown to reverse insulin resistance by increasing the number of skeletal muscle glucose transporters, which may reduce the need for hypoglycemic agents [123].

7.2. Pharmacotherapy

Patients with T2DM who do not show improvements in blood glucose levels with diet therapy are generally prescribed *oral hypoglycemic drugs*. These drugs control hyperglycemia by either increasing the release of insulin from the pancreatic beta cells or increasing the sensitivity of peripheral tissues to insulin [124–126]. The efficacy of these drugs depends on the endogenous capacity of insulin production in the T2DM patients. Among the main oral hypoglycemic drugs are biguanides and sulfonylureas. Other prominent groups include α-glucosidase inhibitors, meglitinides, thiazolidinediones, incretin mimetics, and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Sulfonylureas act by promoting insulin secretion from the pancreatic islet beta cells and may improve insulin resistance in muscle and liver by improving insulin sensitivity in these target tissues. Metformin is the most commonly used biguanide and is suggested as the first-line drug of choice. It reduces hepatic glucose output, primarily by decreasing gluconeogenesis, and to a lesser extent, by enhancing insulin sensitivity in hepatic and peripheral tissues. Alpha-glucosidase inhibitors such as acarbose, miglitol, and voglibose inhibit the α-glucosidase

enzyme which is essential for the release of glucose from more complex carbohydrates and is found in the brush border of enterocytes of small intestine. Thus, α-glucosidase inhibit the absorbance of carbohydrates in the gut and help in prevention of hyperglycemia [127]. Rosiglitazone and pioglitazone belong to the group of thiazolidinediones. The thiazolidinediones enhance insulin sensitivity in the peripheral target tissues such as muscle and adipose tissue, and inhibit hepatic glucose production to some extent, but have no effect on insulin secretion. When used in combination with other antidiabetic drugs, the thiazolidinediones achieve significant improvement in insulin resistance. Importantly, the thiazolidinediones have also been shown to improve the dyslipidemia in patients with T2DM.

A recent advance in the management of T2DM has been the development and clinical use of incretin-based therapies, i.e., glucagon-like peptide-1 (GLP-1) receptor analogs (e.g., exenatide) and DPP-4 inhibitors (e.g., sitagliptin, vildagliptin, saxagliptin) [128–131]. GLP-1 receptor agonists mimic the action of GLP-1 and increase the incretin effect in patients with T2DM, stimulating the release of insulin. DPP-4 inhibitors prevent degradation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide, thereby helping in glycemic control [129].

Anti-hypertensive drugs i.e. diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin II receptor blockers, and calcium antagonists have been effectively used in the treatment of high blood pressure control. For the prevention of cardiovascular complications and treatment of hypertension these drugs have shown beneficial effects in T2DM patients. In such patients, thiazide diuretics have been found to be very effective either alone or in combination with other anti-hypertensive therapy [132]. ACE inhibitors have beneficial effects in reducing macrovascular complications, improving insulin sensitivity and glucose metabolism in T2DM patients [18, 133]. ACE inhibitors can be used alone, however, their effectiveness significantly increases when combined with a thiazide diuretic or other antihypertensive therapeutic drugs [132]. Calcium antagonists have been found to be beneficial in controlling hypertension when used as part of a combined regimen [132]. Anti-hypertensive therapy using a calcium channel blocker lowers the risks of developing complications associated with beta-blocker usage [134].

Lipid-lowering agents reduce the risk of major macrovascular events in patients with T2DM [135, 136]. Statins (HMG-CoA reductase inhibitors) are considered to be first-line therapy for the majority of T2DM patients [137] and has demonstrated benefit in both the primary and secondary prevention of CVD [135, 138, 139]. Several clinical studies have found beneficial effects associated with fibrate therapy [140–142]. Statins are effective in lowering plasma LDL-C, apolipoprotein B, and total cholesterol to HDL-C ratio, whereas fibrates are found to be beneficial in lowering triglycerides, shifting LDL particle size from smaller to larger, and raising HDL-C that results in lowering the total cholesterol to HDL-C ratio [18].

Anti-platelet drugs i.e. aspirin, clopidogrel, dipyridamole, and the glycoprotein IIb/IIIa receptor antagonists reduce CV risk in patients with T2DM [137] due to their antiplatelet effects. Aspirin irreversibly inhibits prostaglandin H synthase (cyclo-oxygenase-1) in platelets and megakaryocytes that prevents synthesis of thromboxane A2, which is a potent vasoconstrictor and platelet aggregant [143]. The thienopyridine derivatives, such as clopidogrel, ticlopidine, are converted to active metabolites in the liver which significantly decrease blood platelet activation via their action on the adenosine phosphate receptors on platelets. Dipyridamole

increases cAMP concentration in platelets by inhibiting phosphodiesterase enzyme, and the increased cAMP levels inhibit activation of cytoplasmic second messengers. Dipyridamole also promotes prostacyclin release and inhibits thromboxane A2 synthesis. Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway for platelet aggregation.

8. Clinical trials on prevention strategies and therapeutic approaches for diabetic vasculopathy

Growth of overweight and obese population due to diet and life-style changes worldwide correlates with the global T2DM epidemic [144]. However, majority of the studies focusing on diabetes prevention were not designed to assess CV outcomes [145]. There is a need for studies to explore the effect of exercise and diet on quality of life, morbidity, and mortality, with a special focus on CV outcomes.

Clinical trials examining the effect of *intensive glucose control* on CVD did not report consistency in beneficial effects of intensive glycemic control on CV events [146–149]. Although the risk of microvascular complications was reduced with strict glucose control in T2DM patients, its beneficial effects on CVD prevention or reduction remain ambiguous [150–152]. Data from UKPDS 34 (the United Kingdom Prospective Diabetes Study) suggested a protective effect of improved glucose control on CVD, CV mortality, and all-cause mortality [146]. However, a number of large randomized, controlled trials have reported conflicting results. ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) [147], VADT (Veterans Affairs Diabetes Trial) [153], and NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) [154] showed no effect of intensive glucose control on major CV events. However, ACCORD (Action to Control Cardiovascular Disease in Diabetes) [149] demonstrated an increased risk of death from CV causes and total mortality associated with intensive glucose control. In the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study [155], patients treated with pioglitazone had a significant 16% reduction in mortality, non-fatal myocardial infarction, and stroke. Further research is needed to examine effect of pharmacological approaches for the management of hyperglycemia on CVD.

Diabetic vasculopathy can be improved by *lowering blood pressure* with antihypertensive drugs which have antiatherogenic effects, e.g., ACE inhibitors, angiotensin II receptor blockers, beta-blockers, and calcium channel blockers. Randomized controlled trials like UKPDS [33, 127], HOT (Hypertension Optimal Treatment) [156], SHEP (the Systolic Hypertension in the Elderly Program) [157–159], Syst-EUR (Systolic Hypertension in Europe) [158–161], HOPE (Heart Outcomes Prevention Evaluation) [162], LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) [163], and ALLHAT (the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) [164] have found beneficial effects of adequately controlling blood pressure in improving CV outcomes, specifically, for stroke, when aggressive blood pressure targets are met [33, 156, 165, 166].

Dyslipidemia plays a significant role in CV complications in T2DM. Dyslipidemia comprises elevated total cholesterol and LDL cholesterol, decreased HDL cholesterol, and high

triglyceride levels [74, 75]. Lowering LDL cholesterol reduces the risk of major vascular events in T2DM patients [167]. Randomized clinical trials in T2DM have consistently shown that statins significantly reduce the risk of major primary and secondary CVD endpoints. Clinical trials of fibrate therapy have shown mixed results.

Clinical trials e.g. CARDS (the Collaborative Atorvastatin Diabetes Study) [168], LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) [169], 4S (Scandinavian Simvastatin Survival Study) [170] and HPS (the Heart Protection Study) [171], demonstrated that statin significantly reduced the incidence of stroke in diabetic patients.

Subgroup analysis of the Helsinki Heart Study [136], and VA-HIT (Veterans Affairs High-density lipoprotein Intervention Trial) [172, 173] provided evidence for the potential benefit of fibrate therapy in reducing CVD in T2DM. However, FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study [174] failed to show similar benefits. The lipid arm of the ACCORD study examined combination therapy of statin and fibrate and failed to support the effectiveness to reduce CV risk as compared with statin alone [175].

Antiplatelet drugs reduce the risk of CV events in T2DM patients. Currently, aspirin is widely recommended for primary prevention of CV events in T2DM patients and is the main drug under investigation to reduce the risk of CVD [176]. Aspirin reduces the risk of serious vascular events in high risk patients by about 25% and also prevents the recurrence of angina, heart attack and stroke. Aspirin is routinely given for primary prevention of CV events in T2DM patients as all major guidelines recommend such preventive use that is based on evidence gathered from clinical trials of high-risk patients [177, 178]. However, the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial [179] demonstrated that aspirin failed to prevent a first CV event or death in T2DM patients, which contradicts the recommendations by many guidelines. The POPADAD trial recommended that aspirin should be used for secondary prevention of CVD in patients with T2DM. The JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in T2DM patients and found that low-dose aspirin when used for primary prevention did not reduce the risk of CV events [180].

In a subgroup analysis of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study, patients with T2DM taking clopidogrel seem to derive enhanced benefit from clopidogrel compared with aspirin [181, 182]. The subgroup analysis of PRISMPLUS (Platelet Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) trial showed that triple therapy (aspirin, heparin, tirofiban) significantly reduced the incidence of myocardial infarction or death as compared with aspirin plus heparin [183].

9. Conclusion and recommendations

CV complications are the major causes of morbidity and mortality in patients with T2DM. Macrovascular complications are more common, and most diabetic patients develop or die of macrovascular diseases, predominantly by developing CVD.

The initiators of vasculopathy that ultimately develop into long-term complications can be controlled and avoided by strict glycemic control, maintaining normal lipid profiles, regular physical exercise, adopting a healthy lifestyle and pharmacological interventions. Studies have shown that lifestyle interventions help in prevention and reduction of CV risk factors; however, there is a lack of studies investigating effects of lifestyle modifications on long-term CV outcomes that need to be addressed. Similarly, because the intensive glycemic control in T2DM patients did not show consistent beneficial effects on CV events, such a strict glycemic control needs to be revisited. Contrary to the disappointing results of intensive glucose control in prevention of CVD, intensive control of blood pressure using anti-hypertensive drugs, normalization of lipid profiles using lipid-lowering agents, and prevention of atherosclerosis and vascular thrombosis with antiplatelet therapy have been found to be beneficial.

Health promotion and patient education should be given priority to combat CV complications in T2DM patients. A multidisciplinary approach involving patients, health professionals, and researchers should be undertaken to reduce the incidence and prevalence of T2DM and CVD, and improve the quality of life and well-being of patients.

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