

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



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

Sayeeda Rahman, Md. Anwarul Azim Majumder,
Russell Kabir, Mainul Haque, Subir Gupta,
Sana Mohammad Yasir Arafat, Nkemcho Ojeh and
Prasad Dalvi

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.69038>

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 macrovasculopathy. 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 macrovasculopathy.

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 macrovasculopathy: 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.

Author details

Sayeeda Rahman¹, Md. Anwarul Azim Majumder^{2*}, Russell Kabir³, Mainul Haque⁴, Subir Gupta², Sana Mohammad Yasir Arafat⁵, Nkemcho Ojeh² and Prasad Dalvi⁶

*Address all correspondence to: azim.majumder@cavehill.uwi.edu

1 Department of Clinical Sciences, Faculty of Life Sciences, School of Medical Sciences, University of Bradford, UK

2 Faculty of Medical Sciences, The University of the West Indies, Cave Hill Campus, Barbados, West Indies

3 Department for Allied and Public Health, Faculty of Medical Sciences, Anglia Ruskin University, Chelmsford, Essex, UK

4 Faculty of Medicine and Defense Health, National Defense University of Malaysia, Kuala Lumpur, Malaysia

5 Department of Psychiatry, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

6 Lake Erie College of Osteopathic Medicine, Bradenton, Florida, USA

References

- [1] Stemmer EA. Diabetes mellitus and vascular disease. In: Aronow WS, Stemmer EA, Wilson SE, editors. *Vascular Disease in the Elderly*. Armonk: Futura; 1997. pp. 199-220

- [2] Ness J, Nassimiha D, Feria MI, Aronow WS. Diabetes mellitus in older African-Americans, Hispanics, and whites in an academic hospital-based geriatrics practice. *Coronary Artery Disease*. 1999;**10**:343-346
- [3] IDF. *Diabetes Atlas*. Brussels: International Diabetes Federation; 2003
- [4] UKPDS Group. UK Prospective Diabetes Study 17: A nine-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Annals of Internal Medicine* 1996;**124**:136-145
- [5] Barceló A, Aedo C, Rajpathak S, Robles S. The cost of diabetes in Latin America and the Caribbean. *Bulletin of the World Health Organization*. 2003;**81**:19-27
- [6] Arredondo A, Zúñiga A. Economic consequences of epidemiological changes in diabetes in middle-income countries. *Diabetes Care* 2004;**27**:104-109
- [7] Ooyub S, Ismail F, Daud NA. Diabetes program in Malaysia – Current and future. *NCD Malaysia*. 2004;**3**:6-12
- [8] Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes*. 1974;**23**:105-111
- [9] Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;**16**:434-444
- [10] American Diabetes Association. Management of dyslipidemia in adults with diabetes. American Diabetes Association: Clinical Practice Recommendations 1999. *Diabetes Care*. 1999;**22**:556-559
- [11] Rahman S, Ismail AA, Ismail SB, Naing NN, Rahman AR. Early manifestation of macrovasculopathy in newly diagnosed never treated type II diabetic patients with no traditional CVD risk factors. *Diabetes Research and Clinical Practice*. 2008;**80**:253-258. DOI: 10.1016/j.diabres.2007.12.2010
- [12] Giannattasio C, Failla M, Capra A, et al. Increased arterial stiffness in normoglycemic normotensive offspring of type 2 diabetic parents. *Hypertension*. 2008;**51**:182-187. DOI: 10.1161/HYPERTENSIONAHA.107.097535
- [13] Rahman S, Ismail AA, Ismail SB, Naing NN, Rahman AR. Increased arterial stiffness in normoglycaemic offspring of newly diagnosed, never treated type 2 diabetic and impaired glucose tolerance parents. *The British Journal of Diabetes & Vascular Disease*. 2009;**9**:65-68
- [14] World Health Organisation. *Diabetes*. 2017. Available from: <http://www.who.int/media-centre/factsheets/fs312/en/index.html> [Accessed: 11-03-2017]
- [15] International Diabetes Federation. *IDF Diabetes Atlas 2015*. 7th ed. Brussels: IDF, 2015
- [16] World Health Organization. *Cardiovascular Diseases*. 2017. Available from: http://www.who.int/cardiovascular_diseases/en/ [Accessed: 11-30-2017]

- [17] Li H, Oldenburg B, Chamberlain C, O'Neil A, Xue B, Jolley D, Hall R, Dong Z, Guo Y. Diabetes prevalence and determinants in adults in China mainland from 2000 to 2010: A systematic review. *Diabetes Research and Clinical Practice*. 2012 Nov;**98**(2):226-235
- [18] Rahman S, Rahman T, Ismail AA, Rashid AR. Diabetes-associated macrovasculopathy: Pathophysiology and pathogenesis. *Diabetes, Obesity & Metabolism* 2007;**9**:767-780
- [19] Virsaladze D, Kipiani V. Endothelial dysfunction in diabetic vasculopathy. *Annals of Biochemical Research and Education*. 2001;**1**:44-48
- [20] Cooper ME, Bonnet F, Oldfield M, Jandeleit-Dahm K. Mechanisms of diabetic vasculopathy: An overview. *American Journal of Hypertension*. 2001;**14**:475-486
- [21] Clark CM Jr, Lee DA. Prevention and treatment of the complications of diabetes mellitus. *New England Journal of Medicine*. 1995;**332**:1210-1217
- [22] Rahman S, Majumder MAA. Diabetes and macrovasculopathy: Double trouble. *South East Asia Journal of Public Health*. 2013;**3**(2):1-3
- [23] Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels: Subgroup analyses in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine*. 1999;**159**:2661-2667
- [24] Rahman S, Majumder MAA. Links between Vitamin D deficiency and macrovascular diseases. *South East Asia Journal of Public Health*. 2015;**5**(2):3-6
- [25] Sowers JR. Diabetes mellitus and cardiovascular disease in women. *Archives of Internal Medicine*. 1998;**158**:617-621
- [26] Singer DE, Moulton AW, Nathan, DM. Diabetic myocardial infarction: Interaction of diabetes with other preinfarction risk factors. *Diabetes*. 1989;**38**:350-357
- [27] Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes mellitus after acute myocardial infarction. *American Journal of Cardiology*. 1984;**54**:718-721
- [28] Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine*. 2005;**353**:2643-2653
- [29] Wingard DL, Barrett-Connor EL, Scheidt-Nave C et al. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM: a population-based study. *Diabetes Care*. 1993;**16**:1022-1025
- [30] UK Prospective Diabetes Study 6. Complications in newly diagnosed type 2 diabetic patients and their association with different clinical and biochemical risk factors. *Diabetes Research*. 1990 Jan;**13**(1):1-11
- [31] Balkau B, Pyörälä M, Shipley M, Forhan A, Jarrett J, Eschwège E, Pyörälä K. Non-cardiovascular disease mortality and diabetes mellitus. *Lancet*. 1997;**350**:1680
- [32] King's Fund. Counting the Cost. The Real Impact of Non-Insulin Dependent Diabetes. British Diabetic Association; London. 1996

- [33] UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ*. 1998;**317**:703-713
- [34] Siitonen OI, Niskanen LK, Laakso M et al. Lower-extremity amputations in diabetic and non-diabetic patients. *Diabetes Care*. 1993;**16**:16
- [35] Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis. *JAMA*. 2002;**287**:2570-2581
- [36] Seligman BG, Biolo A, Polanczyk CA, Gross JL, Clausell N. Increased plasma levels of endothelin 1 and van Willbrand factor in patients with type 2 diabetic mellitus and dyslipidaemia. *Diabetes Care*. 2000;**23**:1395-1400
- [37] Luscher TF, Creager MA, Beckman JA, Cosentino F. Diabetes and vascular disease: Pathophysiology, clinical consequences and medical therapy: Part II. *Circulation*. 2003;**108**:1655-1661
- [38] Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: Pathophysiology, clinical consequences and medical therapy: Part I. *Circulation*. 2003;**108**:1527-1532
- [39] Beckman JA. Pathophysiology of vascular dysfunction in diabetes. *Cardiology Rounds*. 2004;**8**
- [40] Kadirvelu A, Han CK, Lang CC. Endothelial dysfunction in cardiovascular diseases. *Medical Progress*. 2002;**5**:4-10
- [41] Taylor PD, Poston L. The effect of hyperglycaemia on function of rat isolated mesenteric resistance artery. *British Journal of Pharmacology*. 1994;**113**:801-808
- [42] Tooke JE. Microvascular function in human diabetes. *Diabetes*. 1995;**44**:721-726
- [43] Rattan V, Sultana C, Shen Y, Kaba VK. Oxidant stress induced trans endothelial migration of monocytes is linked to phosphorylation of PECAM-1. *American Journal of Physiology*. 1997;**273**:E453-E461
- [44] Tesfamariam B, Brown ML, Cohen RA. Elevated glucose impaired endothelium-dependent relaxation by activating protein kinase C. *Journal of Clinical Investigation*. 1991;**87**:1643-1648
- [45] Paston L, Taylor PD. Endothelium-mediated vascular function in insulin-dependent diabetes mellitus. *Circulation Research*. 1995;**88**:245-255
- [46] Ruderman NB, Haudenschild C. Diabetes as an atherogenic factor. *Progress in Cardiovascular Diseases*. 1984;**26**:373-412
- [47] Fukumoto H, Naito Z, Asano G, Aramaki T. Immunohistochemical and morphometric evaluations of coronary atherosclerotic plaques associated with myocardial infarction and diabetes mellitus. *Journal of Atherosclerosis and Thrombosis*. 1998;**5**:29-35
- [48] Walsh MF, Dominguez LJ, Sowers JR. Metabolic abnormalities in cardiac ischemia. *Cardiology Clinics*. 1995;**13**:529-538

- [49] Stein B, Weintraub WS, Gebhart S. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation*. 1995;**91**:979-989
- [50] Winocour PD, Bryszewska M, Watula C. Reduced membrane fluidity in platelets from diabetic patients. *Diabetes*. 1990;**39**:241-244
- [51] Davi G, Catalons I, Aversa M. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *New England Journal of Medicine*. 1990;**322**:1768-1774
- [52] Vlassara H. Recent progress in advanced glycation end products and diabetic complications. *Diabetes*. 1997;**46**(Suppl. 2):S19-S25
- [53] Parving HH, Nielsen FS, Bang LE et al. Macromicroangiopathy and endothelium dysfunction in NIDDM patients with and without diabetic nephropathy. *Diabetologia*. 1996;**39**:1590-1597
- [54] Chaturvedi N, Fuller JH, Pokras F, Rottiers R, Papazoglou N, Aiello LP. Circulating plasma vascular endothelial growth factor and microvascular complications of type I diabetes mellitus: The influence of ACE inhibition. *Diabetic Medicine*. 2001;**18**:288-294
- [55] García Frade LJ, de la Calle H, Alava I, Navarro JL, Creight LJ, Gaffney LJ. Diabetes mellitus as an hypercoagulable state: Its relationship with fibrin fragments and vascular damage. *Thrombosis Research*. 1987;**47**:533-540
- [56] Ford I, Singh TP, Kitchen S, Makris M, Ward JD, Preston FE. Activation of coagulation in diabetes mellitus in relation to the presence of vascular complications. *Diabetic Medicine*. 1991;**8**:322-329
- [57] Carmassi F, Morale M, Puccetti R. Coagulation and fibrinolytic system impairment in insulin dependent diabetes mellitus. *Thrombosis Research*. 1992;**67**:643-654
- [58] Sowers JR, Tuck ML, Sowers DK. Plasma antithrombin III and thrombin generation time: Correlation with hemoglobin A1 and fasting serum glucose in young diabetic women. *Diabetes Care*. 1980;**3**:655-658
- [59] Ramirez LC, Arauz-Pacheco C, Lackner C. Lipoprotein (a) levels in diabetes mellitus: Relationship to metabolic control. *Annals of Internal Medicine*. 1992;**117**:42-47
- [60] Ceriello A, Quatraro A, Dello Russo P. Protein C deficiency in insulin dependent diabetes: A hyperglycemia related phenomenon. *Thrombosis & Haemostasis*. 1990;**64**:104-107
- [61] Vukovich TC, Proidl S, Knobl P, Teufelsbauer H, Schnack C, Schernthaner G. The effect of insulin treatment on the balance between tissue plasminogen activator and plasminogen activator inhibitor-1 in type 2 diabetic patients. *Thrombosis & Haemostasis*. 1992;**68**:253-256
- [62] Laakso M. Hyperglycaemia and cardiovascular disease in type 2 diabetes. *Diabetes*. 1999;**48**:937-942
- [63] Grundy SM, Benjamin IJ, Burke GL et al. Diabetes and cardiovascular disease: A statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;**100**:1134-1146

- [64] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1993;**329**:977-986
- [65] Bayes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes*. 1991;**40**:405-412
- [66] Morigi M, Angioletti S, Imberti B et al. Leukocyte endothelial interaction is augmented by high glucose concentrations and hyperglycemia in a NF- κ B-dependent fashion. *Journal of Clinical Investigation*. 1998;**101**:1905-1915
- [67] Sowers JR, Epstein M. Risk factors for arterial disease in diabetes: Hypertension. In: Tooke JE, editor. *Diabetic Angiopathy*. London: Arnold Publishers;1999:45-63
- [68] Tribe RM, Poston L. Oxidative stress and lipids in diabetes: A role in endothelial vasodilator function? *Vascular Medicine*. 1996;**1**:195-206
- [69] McMillen DE. Development of vascular complications in diabetes. *Vascular Medicine*. 1997;**2**:132-142
- [70] Baumgartner-Parzer SM, Wagner L, Pettermann M, Gessel A, Waldhäusli W. Modulation by high glucose of adhesion molecule expression in cultured endothelial cells. *Diabetologia*. 1995;**38**:1367-1370
- [71] King GL, Brownlee M. The cellular and molecular mechanisms of diabetic complications. *Endocrinology and Metabolism Clinics of North America*. 1996;**25**:255-270
- [72] Cooper ME, Cao Z, Rumble JR, Jandeleit K, Allen TJ, Gilbert RE. Attenuation of diabetes-associated mesenteric vascular hypertrophy with perindopril: Morphological and molecular biological studies. *Metabolism*. 1998;**47**:24-27
- [73] Aronson D, Rayfield EJ. How hyperglycemia promotes atherosclerosis: Molecular mechanisms. *Cardiovascular Diabetology*. 2002;**1**:1
- [74] Watkins PJ. ABC of diabetes cardiovascular disease, hypertension, and lipids. *BMJ*. 2003;**326**:874-886
- [75] Georg P, Ludvik B. Lipids and diabetes. *Journal of Clinical and Basic Cardiology*. 2000;**3**:159-162
- [76] Steinberg D. Low density lipoprotein oxidation and its pathobiological significance. *Journal of Biological Chemistry*. 1997;**272**:20963-20966
- [77] Khoo JC, Miller E, McLoughlin P, Steinberg D. Enhanced macrophage uptake of low-density lipoprotein after self-aggregation. *Atherosclerosis*. 1988;**8**:348-358
- [78] Ross R. Atherosclerosis – An inflammatory disease. *New England Journal of Medicine*. 1999;**340**:115-126
- [79] Ferri C, Bellini C, Desideri G et al. Plasma endothelin-1 in obese hypertensive and normotensive man. *Diabetes*. 1995;**44**:431-436

- [80] Hunter SJ, Garvey T. Insulin action and insulin resistance: Diseases involving defects in insulin receptors, signal transduction and glucose transport effector system. *American Journal of Medicine*. 1998;**5**:331-346
- [81] Sowers JR, Sowers PS, Peuler JD. Role of insulin resistance and hyper-insulinemia in development of hypertension and atherosclerosis. *Journal of Laboratory and Clinical Medicine*. 1994;**123**:647-652
- [82] Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities: The role of insulin resistance and sympathetic adrenal system. *New England Journal of Medicine*. 1996;**334**:374-381
- [83] Gilbert RE, Rumble JR, Cao ZM et al. Endothelin receptor antagonism ameliorates mast cell infiltration, vascular hypertrophy, and epidermal growth factor expression in experimental diabetes. *Circulation Research*. 2000;**86**:158-165
- [84] Myllärniemi M, Calderon L, Lemström K, Buchdunger E, Häyry P. Inhibition of platelet-derived growth factors receptor kinase inhibits smooth muscle cell migration and proliferation. *FASEB Journal*. 1997;**11**:1111-1126
- [85] Feener EP, King GL. Vascular dysfunction in diabetes mellitus. *Lancet*. 1997;**350**(Suppl. 1): S9-S13
- [86] Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes*. 1998;**47**:859-866
- [87] Storey AM, Perry CJ, Petrie JR. Endothelial dysfunction in type 2 diabetes. *The British Journal of Diabetes & Vascular Disease*. 2001;**1**:22-27
- [88] Brodsky S, Chen J, Lee A, Akassoglou K, Norman J, Goligorsky MS. Plasmin dependent and independent effects of plasminogen activators and inhibitor-1 on ex-vivo angiogenesis. *American Journal of Physiology*. 2001;**281**:H1784-H1792
- [89] Nishikawa T, Edelstein D, Du XL et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. *Nature*. 2000;**404**:787-790
- [90] Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. *Diabetes*. 1999;**48**:1-9
- [91] Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes*. 1991;**40**:405-412
- [92] Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High WBC count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes*. 2002;**51**:455-461
- [93] Tuttle HA, Davis-Gorman G, Goldman S, Copeland JG, McDonagh PF. Platelet neutrophil conjugate formation is increased in diabetic women with cardiovascular disease. *Cardiovascular Diabetology*. 2003;**2**:1-16
- [94] Sower JR, Lester MA. Diabetes and cardiovascular disease. *Diabetes Care*. 1998;**22**(Suppl. 3): c.14-c.20

- [95] Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA*. 1987;**257**:2318-2324
- [96] Fusman R, Rotstein R, Zeltser D et al. The state of leukocyte adhesiveness/aggregation in the peripheral blood of patients with type 2 diabetes and ischemic vascular disease. *Acta Diabetologica*. 2001;**38**:43-49
- [97] Benetos A, Weaber B, Izzo J, Mitchell G, Resnick L, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: Clinical application. *American Journal of Hypertension*. 2002;**15**:1101-1108
- [98] Safar ME, London GM. The arterial system in human hypertension. In: Swales JD editor., *Textbook of Hypertension*. London: Blackwell Scientific; 1994
- [99] Asmar R, Benetos A, Topouchian J, Laurent, P, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension*. 1995;**26**:85-490
- [100] Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central artery stiffness in physically active women. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1998. **18**:127-132
- [101] Westerbacka J, Vehkavaara S, Bergholm R, et al. Marked resistance of the ability of insulin to decrease arterial stiffness characterizes human obesity. *Diabetes*. 1999;**48**:821-827
- [102] Westerbacka J, Wilkinson I, Cockcroft J, et al. Diminished wave reflection in the aorta: A novel physiological action of insulin on large blood vessels. *Hypertension*. 1999;**33**:1118-1122
- [103] Wilkinson IB, Cockcroft JR, Webb DJ. Pulse wave analysis and arterial stiffness. *Journal of Cardiovascular Pharmacology*. 1999;**32**:33-37
- [104] O'Rourke MF, Hayward CS. Arterial stiffness, gender and heart rate. *Journal of Hypertension*. 2003;**21**:487-490
- [105] Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. *Quarterly Journal of Medicine*. 2002;**95**:67-74
- [106] Safar ME, Henry O, Meaume S. Aortic pulse wave velocity: An independent marker of cardiovascular risk. *The American Journal of Geriatric Cardiology*. 2002;**11**:295-298
- [107] O'Rourke MF, Pauca A, Jiang X. Pulse wave analysis. *British Journal of Clinical Pharmacology* 2001;**51**:507-522
- [108] Wilkinson IB, Cockcroft JR, Webb DJ. Pulse wave analysis and arterial stiffness. *Journal of Cardiovascular Pharmacology*. 1998;**32**:S33-S37
- [109] Wilkinson IB, Fuchs SA, Jansen IM et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *Journal of Hypertension*. 1998;**16**:2079-2084
- [110] Kelly R, Hayward C, Avolio A, O'Rourke M. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989;**80**:1652-1659

- [111] Cameron JD, McGrath BP, Dart AM. Use of radial applanation tonometry and a generalized transfer function to determine aortic augmentation in subjects with treated hypertension. *Journal of the American College of Cardiology* 1998;**32**:1214-1220
- [112] Wilkinson IB, MacCallum H, Flint L, Cockcroft JR et al. The influence of heart rate on augmentation index and central arterial pressure. *Journal of Physiology* 2000;**525**:263-270
- [113] Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H. et al. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. *Journal of the American College of Cardiology*. 2002;**39**:1005-1011
- [114] Rehman A, Rahman ARA, Rasool AHG. Effect of angiotensin II on pulse wave velocity in humans is mediated through angiotensin II type 1 (AT₁) receptors. *Journal of Human Hypertension*. 2002;**16**:261-266
- [115] Chowienczyk PJ, Kelly RP, MacCallum H, Millasseau SC, et al. Photoplethysmographic assessment of pulse wave reflection. *Journal of the American College of Cardiology*. 1999;**34**:2007-2014
- [116] Resnick LM, Militianu D, Cunnings AJ, Pipe JG, et al. Direct magnetic resonance determination of aortic distensibility in essential hypertension: Relation to age, abdominal visceral fat and in situ intracellular free magnesium. *Hypertension*. 1997;**30**:654-659
- [117] Mohiaddin RH, Underwood SR, Bogren HG, Firmin DN, et al. Regional aortic compliance studied by magnetic resonance imaging: The effects of age, training and coronary artery disease. *British Heart Journal*. 1989;**62**:90-96
- [118] Rahman S, Majumder MAA, Rahman ARA. Treatment of diabetic vasculopathy: An overview. *Research and Reports in Endocrine Disorders*. 2011;**1**:21-36
- [119] Emoto M, Nishizawa Y, Kawagishi T, Maekawa K, Hiura Y, et al. Stiffness indexes β of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. *Diabetes Care*. 1998;**21**:1178-1182
- [120] Ngim CA, Rahman ARA, Ibrahim A. Pulse wave velocity as an index of arterial stiffness: A comparison between newly diagnosed (untreated) hypertensive and normotensive middle-aged Malay men and its relationship with fasting insulin. *Acta Cardiologica*. 1999;**54**:277-282
- [121] Rahman S, Ismail AA, Rahman AR. Treatment of diabetic vasculopathy with rosiglitazone and ramipril: Hype or hope? *International Journal of Diabetes in Developing Countries*. 2009;**29**:110-117
- [122] American Diabetes Association. Position statement: Diabetes mellitus and exercise. *Diabetes Care*. 1990;**13**:804-805
- [123] Dela F, Ploug T, Handberg A, et al. Physical training increases muscle GLUT 4 protein and mRNA in patients with NIDDM. *Diabetes*. 1994;**7**:862-865
- [124] Lebovitz HE, Feinglos MN. Mechanism of action of the second generation sulfonylurea glipizide. *American Journal of Medicine*. 1983;**75**:46-54

- [125] Kolterman OG, Gra RS, Shapiro G, Scarlett JA, Griffin J, Olesfsky JM. The acute and chronic effects of sulfonylurea therapy in type II diabetic subjects. *Diabetes*. 1984;**33**:346-354
- [126] Groop L. Metabolic effects of sulfonylurea drugs. A review. *Ann Clin Res*. 1983;**15**(Suppl 37):16-20
- [127] Hanefeld M, Schaper F. The role of alpha-glucosidase inhibitors (Acarbose). In: Mogensen CE, editor. *Pharmacotherapy of Diabetes: New Developments. Improving Life and Prognosis for Diabetic Patients*. New York, NY: Springer; 2007. pp. 143-152
- [128] McDougall C, McKay GA, Fisher M. Drugs for diabetes: Part 6 GLP-1receptor agonists. *British Journal of Cardiology*. 2011;**18**:167-169
- [129] McDougall C, McKay GA, Fisher M. Drugs for diabetes: Part 5 DPP-4 inhibitors. *British Journal of Cardiology*. 2011;**18**:130-132
- [130] Nauck M, Smith U. Incretin-based therapy: How do incretin mimetics and DPP-4 inhibitors fit into treatment algorithms for type 2 diabetic patients? *Best Practice & Research. Clinical Endocrinology & Metabolism*. 2009;**23**:513-523
- [131] Siddiqui NI. Incretinmimetics and DPP-4 inhibitors: New approach to treatment of type 2 diabetes mellitus. *Mymensingh Medical Journal*. 2009;**18**(1):113-124
- [132] Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure*. Bethesda, MD: National Heart, Lung, and Blood Institute (US); 2004
- [133] McFarlane SI, Kumar A, Sowers JR. Mechanisms by which angiotensin converting enzyme inhibitors prevent diabetes and cardiovascular disease. *American Journal of Cardiology*. 2003;**91**(12A):30H-37H
- [134] Mayor S. Calcium channel blockers associated with less diabetes. *BMJ*. 2006;**333**:514
- [135] Pyörälä K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves Prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care*. 1997;**20**:614-620
- [136] Koskinen P, Manttari M, Manninen V, Huttunen JK, Heinonen OP, Frick MH. Coronary heart disease incidence in NIDDM patients in the Helsinki Heart Study. *Diabetes Care*. 1992;**15**:820-825
- [137] Zanchetti A. Aspirin and antiplatelet drugs in the prevention of cardiovascular complications of diabetes. In: Mogensen CE, editor. *Pharmacotherapy of Diabetes: New Developments. Improving Life and Prognosis for Diabetic Patients*. New York, NY: Springer; 2007. pp. 211-218
- [138] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *Cholesterol*

- and Recurrent Events Trial investigators. *New England Journal of Medicine*. 1996;**335**:1001-1009
- [139] The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *New England Journal of Medicine*. 1998;**339**:1349-1357
- [140] Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: The St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care*. 1998;**21**:641-648
- [141] Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *New England Journal of Medicine*. 1999;**341**:410-418
- [142] Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: The Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet*. 2001;**357**:905-910
- [143] Hankey GJ, Eikelboom JW. Antiplatelet drugs. *Medical Journal of Australia*. 2003;**178**:568-574
- [144] Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: Systematic review and meta-analysis. *BMJ*. 2007;**334**:299
- [145] Stiegler RS, Zimmet PZ, Cameron AJ, et al. Lifestyle management: Preventing type 2 diabetes and cardiovascular complications. *Therapy*. 2009;**6**:489-496
- [146] UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;**352**:854-865
- [147] Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *New England Journal of Medicine*. 2008;**358**:2560-2572
- [148] Schor S. The University Group Diabetes Program. A statistician looks at the mortality results. *JAMA*. 1971;**217**:1671-1675
- [149] Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *New England Journal of Medicine*. 2008;**358**:2545-2559
- [150] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;**352**:837-853
- [151] Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;**23** Suppl 2:B21-B29

- [152] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *New England Journal of Medicine* 2008;**359**:1577-1589
- [153] Duckworth W, Abraira C, Moritz T, et al. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine*. 2009;**360**:129-139
- [154] Nathan DM. Navigating the choices for diabetes prevention. *New England Journal of Medicine* 2010;**362**:1533-1535
- [155] Dormandy JA, Charbonnel B, Eckland DJ, et al. PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspectivepioglitAzone Clinical Trial In macroVascular Events): A randomised controlled trial. *Lancet*. 2005;**366**:1279-1289
- [156] Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;**351**:1755-1762
- [157] SHEP Cooperative Research Group. Prevention of stroke by Antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;**265**:3255-3264
- [158] Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet*. 1997;**350**:757-764
- [159] Staessen JA, Thijs L, Gasowski J, Cells H, Fagard RH. Treatment of isolated systolic hypertension in the elderly: Further evidence from the systolic hypertension in Europe (Syst-Eur) trial. *American Journal of Cardiology*. 1998;**82**(9B):20R-22R
- [160] International Diabetes Federation (IDF). *Diabetes Atlas*. 4th ed. Brussels: International Diabetes Federation; 2009
- [161] Voyaki SM, Staessen JA, Thijs L, et al. Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Journal of Hypertension*. 2001;**19**:511-519
- [162] Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICROHOPE substudy. *Lancet*. 2000;**355**:253-259
- [163] Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. *Lancet*. 2002;**359**:995-1003
- [164] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;**288**:2981-2997

- [165] Chobanian AV, Bakris GL, Black HR, et al. The seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA*. 2003;**289**:2560-2572
- [166] Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *BMJ*. 2000;**321**:412-419
- [167] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet*. 2002;**360**:7-22
- [168] Colhoun HM, Betteridge DJ, Durrington PN, et al. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. *Lancet*. 2004;**364**:685-696
- [169] Keech A, Colquhoun D, Best J, et al. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: Results from the LIPID trial. *Diabetes Care*. 2003;**26**:2713-2721
- [170] Pederson TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischaemic signs and symptoms in the Scandinavian simvastatin survival study (4S). *American Journal of Cardiology* 1998;**81**:333-335
- [171] Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomised placebo-controlled trial. *Lancet*. 2003;**361**:2005-2016
- [172] Rubins HB, Robins SJ, Collins D, et al. VA-HIT Study Group. Diabetes, plasma insulin, and cardiovascular disease subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Archives of Internal Medicine*. 2002;**162**:2597-2604
- [173] Robins SJ, Collins D, Wittes JT, et al, VA-HIT Study Group. Veterans Affairs high-density lipoprotein intervention trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: A randomized controlled trial. *JAMA*. 2001;**285**:1585-1591
- [174] Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* 2005;**366**:1849-1861
- [175] The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *New England Journal of Medicine*. 2010;**362**:1563-1574
- [176] Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. *Journal of the American College of Cardiology* 2010;**55**:2878-2886

- [177] Buse JB, Ginsberg HN, Bakris GL, et al, American Heart Association, American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: A scientific statement from the American Heart Association and the American Diabetes Association. *Circulation*. 2007;**115**:114-126
- [178] Rydén L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary. The Task Force on Diabetes and cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *European Heart Journal*. 2007;**28**:88-136
- [179] Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: Factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;**337**:a1840
- [180] Ogawa H, Nakayama M, Morimoto T, et al, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: A randomized controlled trial. *JAMA*. 2008;**300**:2134-2141
- [181] CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet*. 1996;**348**:1329-1339
- [182] Bhatt DL, Marso SP, Hirsch AT, et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *American Journal of Cardiology*. 2002;**90**:625-628
- [183] Theroux P, Alexander J Jr, Pharand C, et al. Glycoprotein IIb/IIIa receptor blockade improves outcomes in diabetic patients presenting with unstable angina/non-ST-elevation myocardial infarction: Results from the Platelet Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study. *Circulation*. 2001;**102**:2466-2472

IntechOpen

