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Narrative Review of Diabetes and Cardiovascular Complications

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ABSTRACT

Diabetes mellitus is a major global public health challenge and a powerful independent risk factor for cardiovascular disease (CVD), which remains the leading cause of morbidity and mortality among individuals with diabetes. This narrative review synthesizes current evidence on the epidemiology, pathophysiology, clinical manifestations, diagnostic strategies, and therapeutic approaches linking diabetes to cardiovascular complications. Central mechanisms include chronic hyperglycemia, insulin resistance, dyslipidemia, inflammation, oxidative stress, and endothelial dysfunction, which collectively accelerate atherosclerosis and promote cardiac and vascular remodeling. The review examines the spectrum of cardiovascular complications associated with diabetes, including coronary artery disease, heart failure, cardiomyopathy, cerebrovascular disease, and peripheral arterial disease, highlighting differences between type 1 and type 2 diabetes and across age groups and special populations. Advances in cardiovascular risk stratification using glycemic metrics, imaging modalities, and biomarkers are discussed, alongside evolving pharmacological strategies. In particular, sodium–glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists have demonstrated significant cardiovascular and renal benefits beyond glycemic control. Non-pharmacological interventions, including lifestyle modification and risk factor management, remain foundational to care. Despite progress, important knowledge gaps persist regarding disease mechanisms, optimal risk prediction, and individualized treatment strategies. Addressing these gaps is critical to reducing the cardiovascular burden of diabetes and improving long-term outcomes.

Keywords: Diabetes mellitus; Cardiovascular disease; Atherosclerosis; Heart failure; and Cardiovascular risk management.

INTRODUCTION

The association between diabetes and cardiovascular disease (CVD) has global significance, with CVD accounting for 46% of mortality in diabetic populations and diabetes increasing overall CVD risk 2–4-fold [1]. Central questions include the mechanisms underpinning this association, the pathways to CVD in differing disease stages, the role of novel glucose-lowering agents in altering CVD risk, and appropriate glycemic management strategies [1]. Despite intensive investigation, many gaps persist in understanding the relationship between diabetes and CVD [1, 2].

Pathophysiology Linking Diabetes and Cardiovascular Disease

Diabetes mellitus is a key modifiable risk factor for cardiovascular disease (CVD); yet, a comprehensive understanding of the underlying pathophysiology remains limited [2]. The various physiological and environmental factors driving hyperglycemia contribute to CVD independently of the recommended diagnostic measures, such as plasma glucose levels, glycosylated hemoglobin (HbA1c), and time in glycemic target. Therapeutic strategies that address the pivotal interweavings between diabetes and CVD may therefore provide substantial opportunities for intervention. The core mechanisms linking diabetes and CVD can be subdivided into

two groups: (i) metabolic-induced pathways that include sustained hyperglycemia and glucose toxicity, insulin resistance and dyslipidemia, and glucotoxicity, and (ii) inflammation-induced pathways comprising enhanced oxidative stress, endothelial dysfunction, inflammatory mediators, and vascular remodeling.

Hyperglycemia and Vascular Injury

Hyperglycemia is pivotal as one of the major underlying pathophysiological mechanisms linking diabetes and cardiovascular disease [5]. Diabetes causes and exacerbates vascular injury through multiple intertwined mechanisms [3], including hyperglycemia-induced oxidative stress, inflammatory activation, apoptosis, impaired nitric oxide–dependent vasodilation, and excessive deposition of extracellular matrix [8]. These changes contribute to both microvascular disease, such as diabetic retinopathy and nephropathy, and macrovascular disease, which leads to coronary artery disease, cerebrovascular accident, and peripheral arterial disease [3]. Long-term hyperglycemia induces posttranslational modifications on proteins, resulting in the formation of advanced glycation end products (AGEs) [1]. AGEs accumulate in biologically important molecules, including collagen, low-density lipoprotein, and amyloid protein, leading to cross-linking and enhanced polymerization. Elevated AGE levels drive the development of albuminuria in patients with diabetic nephropathy, and increased hepatic fibrinogen concentration promotes platelet aggregation and raises thrombotic risk [3]. AGEs also mediate vascular complications through binding to the receptor for AGEs (RAGE); this pathway elicits a range of signaling events that activate inflammatory mediators, including ROS, nuclear factor kappa B, and cytokines such as interleukin-6 and tumor necrosis factor [4]. RAGE is also involved in vascular remodeling via activation of transforming growth factor-β1 and connective tissue growth factor, which promote extracellular matrix accumulation and vascular wall thickening. The widespread clinical adoption of low-glycaemic index dietary interventions is a feasible, affordable, and early means of preventing hyperglycaemia in high-risk populations [17].

Insulin Resistance and Dyslipidemia

Insulin resistance is an early pathological process in type 1 and type 2 diabetes that, when left unchecked, can progress to overt hyperglycemia [14]. Its presence promotes atherogenic dyslipidemia, hypertension, inflammation, angiogenesis, and endothelial dysfunction, all of which enhance the risk of cardiovascular disease (CVD) and further aggravate the diabetic milieu [4]. Environmental and genetic factors, particularly obesity, strongly influence the development and progression of insulin resistance [18]. Atherogenic dyslipidemia in type 2 diabetes is characterized by hypertriglyceridemia, decreased high-density lipoprotein (HDL) cholesterol, increased small dense low-density lipoprotein (LDL) particles, and postprandial lipemia [12]. Insulin resistance also affects the metabolism of very low-density lipoprotein (VLDL), inhibiting the clearance of triglyceride-rich lipoproteins and further exacerbating dyslipidemia [5]. Insulin resistance in adipose tissue promotes an abnormal release of free fatty acids into the circulation [13]. Consequently, the blood supply of free fatty acids to the liver is significantly augmented, stimulating hepatic de novo lipogenesis and, ultimately, hepatic steatosis. Increased flux of lipids in the heart predisposes individuals to lipid accumulation and lipotoxicity due to a reduced capacity to oxidize and metabolize fatty acids during cardiac injury. The combination of lipid overload and insulin resistance can promote the development of diabetic cardiomyopathy [18].

Inflammation and endothelial dysfunction

Inflammation and endothelial dysfunction are critical components of diabetes-associated vascular complications through several interconnected pathways. Mediators of vascular inflammation are abundant in a variety of tissues and biological fluids, including blood [3]. The role of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) in diabetes-related microvascular complications, including retinopathy, neuropathy, and insulin resistance, is well characterized; TNF-α is also an independent risk factor for cardiovascular events in patients with type 2 diabetes [5]. The vascular actions of TNF-α include the stimulation of oxidative stress, enhanced endothelial-cell production of vascular adhesive molecules (e.g., E-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1), and the upregulation of interleukin-6 (IL-6) and Mac-1 on leukocytes [7]. The latter events predispose vascular tissues to accelerated atherosclerosis [6]. In addition to TNF-α, the IL-6 family of cytokines plays an important role in diabetes-linked vascular dysfunction. Within this family, IL-6 is a well-known proinflammatory cytokine, while IL-11, secreted by vascular smooth muscle and macrophages in the atherosclerotic milieu, has recently emerged as a potent amplifier of vascular inflammation [7]. Other proinflammatory factors also participate in these alterations, including growth factors, proteases, chemokines, cardiotonic steroids, and the vasoconstrictive peptide angiotensin II. These mediators augment proatherogenic processes such as endothelial dysfunction, vascular hyperpermeability, lipid accumulation, and neointimal proliferation [8]. The progression of diabetes-related cardiovascular disturbances is closely tied to the pathophysiology associated with metabolic syndrome [9]. Cytokines involved in the inflammatory, proliferative,

and fibrotic components of atherosclerosis are also heightened within adipose tissue and share an overlapping regulatory circuit with inflammation, a process known as metabolic inflammation [16].

Epidemiology of Cardiovascular Complications in Diabetes

In people with diabetes, the risk of coronary artery disease (CAD) is 2–4-fold higher than in their non-diabetic counterparts [2]. The temporal incidence of CAD across type 1 and type 2 diabetes populations is a reflection of the duration and degree of metabolic derangements, including hyperglycemia, insulin resistance, and dyslipidemia, with a chronic inflammatory state being a common denominator[1]. Myocardial infarction (MI) remains the most frequent acute presentation of CAD, even in patients with relatively preserved glucose homeostasis and lipid levels. Grouping heart failure and CAD together is victim blaming; chronic kidney disease (CKD), collateral vessel formation, and clotting factor derangements account for a significant portion of cardiovascular events independent of the presence of CAD or prior MI and, consequently, are a critical part of the disease continuum [1]. Diabetes is the strongest vascular risk factor for stroke after age, hypertension, and atrial fibrillation, and a strong determinant of stroke-free survival afterwards, with a notable distinction according to type of diabetes [3]. Patients with type 1 diabetes under 70 years of age exhibit a highly deferential time to first stroke compared to all other types of diabetes, suggesting an urgent need for expanded stroke prevention strategies in this cohort [2]. The severity of symptomatic peripheral arterial disease (PAD) at diagnosis is dose-dependently correlated with the duration of diabetes 8. Many affected individuals develop critical limb ischemia (CLI) after less than a decade of disease, exceeding the typical threshold for type 1 diabetes and suggesting that type-by-severity frameworks may obscure commonalities within rarely-explored populations [2].

Coronary Artery Disease

Coronary artery disease (CAD) has long been recognized as a major consequence of diabetes, resulting in significant morbidity and mortality [2]. Cardiovascular disease (CVD) remains a leading cause of mortality and morbidity in people with diabetes, and diabetes is a well-established CAD risk factor, with the American Heart Association and the American College of Cardiology highlighting diabetes as a CAD equivalent [5]. Diabetic patients between 45 and 75 years of age show significant hyperglycemia levels and are more likely to develop microvascular and macrovascular complications compared to nondiabetic individuals [3]. As highlighted by expert consensus statements and clinical practice guidelines, CVD is a critical problem for patients with diabetes and should be a key consideration in glucose-lowering treatment. Moreover, CAD is the most frequent cause of CVD in patients with diabetes [6]. CAD accounts for more than 50% of diabetic deaths, and patients with diabetes have a fatal outcome and treatment failure rates that are markedly higher than those of nondiabetic patients after myocardial infarction (MI) or coronary artery bypass grafting [4]. Several pathophysiologic mechanisms and characteristics associated with diabetes contribute to the accelerated progression and poor treatment outcomes of CAD [3]. Abnormalities in sugar metabolism, including glycosylation, glycation, and acylation, commonly occur in patients with diabetes, leading to the formation of advanced glycation end products that drive an inflammatory process and promote microvascular and macrovascular complications, including CAD[7]. Diabetic patients are more susceptible to some cardiovascular risk factors, including dyslipidemia, hypertension, obesity, thrombosis, and smoking. An abnormal lipid profile directly intensifies atherosclerosis-induced coronary arterial stenosis and leads to microsomal triglyceride accumulation in the coronary arteries. Lipotoxicity affects the heart and modulates myocyte cell death mechanisms in diabetic patients [2]. Modulating insulin secretion, lipolysis, and fatty acid turnover in the adipose tissue can influence diabetic macro- and microvascular complications [5]. A high concentration of circulating free fatty acids, directly damaging cardiomyocytes, is common in diabetic patients. Coronary arterial stiffness and degeneration of coronary arterial adventitial nerves occur earlier in patients with diabetes than in nondiabetic individuals [3]. β-adrenergic receptor stimulation and coronary arterial stiffness alteration can lead to cardiac remodelling and worsen the patients' condition [9]. Epidemiological studies have documented that diabetes increases the risk of developing coronary heart disease (CHD) and that the 10-year risk for a Myocardial Infarction (MI) is higher for all classes of diabetes than for the non-diabetic population. However, CHD can also develop in patients with diabetes acutely for the first time so the MI risk in them might be underestimated. This possibility is critical because it is not possible to determine retrospectively whether a diabetic patient had pre-diabetes or T2DM before the acute event [3]. Therefore, different definitions of T2DM from fasting plasma glucose measurements, post-prandial plasma glucose, and 2-hour plasma glucose remain stringent as well as measures for glycaemic control [10].

Heart Failure and Cardiomyopathy

Heart failure is one of the most prevalent complications of diabetes [11]. Men with diabetes are more than twice as likely as their non-diabetic counterparts to develop heart failure, while the risk for women is fivefold greater [6]. These estimates are supported by observational studies, which have documented increased rates of heart failure in both type 1 and type 2 diabetes, with a markedly worse prognosis in the latter [14]. The close

relationship between these two conditions is further underscored by the fact that complications of diabetes occur in up to 40% of patients with heart failure. Common pathophysiological disturbances linking the two include ischemic heart disease, various metabolic abnormalities (including glucose and lipid toxicity), and vascular dysfunction [10]. Diabetic heart disease constitutes five distinct disease models [13]. Diabetic cardiomyopathy presumes the presence of cardiac muscle dysfunction due solely to metabolic derangement. Such dysfunction is proposed to contribute even in the absence of macrovascular or microvascular coronary lesions, hypertension, or significant valvular disease. In contrast to type 1 and type 2 diabetes, and in particular to the role of stearoyl-CoA desaturase, this view holds that there is no unifying diabetic signature of cardiac remodeling in end-stage renal disease [9]. Lipotoxic cardiomyopathy generally designates cardiac muscle dysfunction linked to intracellular lipid overload, which supports the identification of chemical agents capable of breaking down lipid droplets [8]. Obesity-related cardiomyopathy equates overload of either lipids or lipotoxicity with obesity-driven signaling. Glucotoxic cardiomyopathy categorizes glucose metabolic overload specifically, particularly by excessive diastolic flux through the hexosamine pathway [7]. Consequently, heart failure is classified as either reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), irrespective of the underlying cause of the disturbance. The relative contributions of these two presentation types to cardiac impairment in diabetes remain open to discussion and further assessment [8].

Cerebrovascular Disease

Diabetes and cardiovascular disease are closely linked conditions. Cardiac morbidity is associated with diabetes because it contributes to vascular injuries that underlie atherosclerosis [2]. Overall, people with diabetes are more likely to die from cardiovascular causes than from complications directly attributable to diabetes [7]. Despite advances in glycemic control and management of classical risk factors, the rate of coronary artery disease remains alarmingly high among diabetic patients. Individuals with diabetes also have an elevated relative risk of developing heart failure [11]. A review of the epidemiology of heart failure among diabetic patients reveals major gaps in understanding time trends and the role of risk factors. Glycated hemoglobin is a clinically relevant measure of long-term glycemic control that is amenable to reduction through effective interventions [8]. It is preferable to fasting blood glucose, which reflects only a subset of pre-diabetic stages, and to postprandial glucose, which is affected by other clinical conditions [17]. The class of anti-diabetic medications termed sodium-glucose co-transporter-2 inhibitors offers a potential avenue for preventive therapy. Diabetes and cerebrovascular disease also have a unique relationship [23]. They interact and influence each other through shared pathophysiological mechanisms. People with diabetes have approximately double lifetime risk of experiencing stroke, which is comparable to the increase seen with hypertension [25]. By 75 years of age, roughly one quarter of those with diabetes will have experienced a stroke. Most strokes in people with diabetes arise from large vessel atherosclerosis. Increasing evidence indicates that diabetes is one of the major determinants of stroke risk, although the specific mechanisms remain poorly understood. Affected individuals tend to have large vessel disease on both cardiac and cerebral territories as well as aggressive diffuse arterial disease [12].

Peripheral Arterial Disease

Diabetes mellitus (DM) is a well-established risk factor for peripheral arterial disease (PAD) and a comparable cohort study indicates that, after adjustment for cardiovascular risk factors, patients with diabetes have a similar risk of PAD as nondiabetic patients who have had a previous myocardial infarction [13]. Diabetes not only accelerates the progression of PAD but also alters its clinical presentation and outcomes following revascularization, both anatomically and hemodynamically. Patients with diabetes are still considered suitable candidates for endovascular therapy [13, 14].

Diagnostic Considerations and Risk Stratification

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in individuals with diabetes. Current risk stratification schemes have limitations, and additional diagnostic and imaging modalities are being investigated to identify those at greatest risk [9]. Efforts to develop alternative assessment tools are especially critical for patients with diabetes, in whom glucose control must be balanced against cardiovascular risk [14]. Various glycemic measures are reported to be associated with cardiovascular risk [10]. While HbA1c is the most frequently studied biomarker, other parameters such as fasting or postprandial glucose concentrations and time-in-range may also provide information on disease progression [15]. Several imaging modalities such as coronary artery calcium scoring, echocardiography, and myocardial perfusion imaging, as well as circulating biomarkers, including B-type natriuretic peptide, troponin, and high-sensitivity C-reactive protein, have been evaluated. Risk stratification and prediction tools such as the Framingham Risk Score and UKPDS Risk Engine have been adapted for individuals with diabetes and are useful for informing treatment decisions and understanding disease progression [28].

Glycemic Measures and Cardiovascular Risk

Cardiovascular risk factors can be measured in many ways. In the case of diabetes, risks associated with glucose dysregulation can be assessed both by absolute concentrations of glucose or via glycated hemoglobin (HbA1c) assessments [13]. Measuring time-in-range for blood glucose values (specified as 70–140 mg/dL, 70–180 mg/dL, etc.) is becoming more common with the addition of continuous glucose monitoring [16]. Measurements of postprandial glucose concentrations, particularly 2-h values, have been associated with increased risk of diabetic complications, including atherothrombotic disease 2. Serial early-morning fasting glucose measures do not accurately reflect overall glucose, although the use of two different preprandial time points helps stratify risk 16. Risk assessment through glycemic estimates also appears valid in people without diabetes [23]. References on the connections between glycemia and cardiovascular outcomes consistently confirm that higher blood glucose concentrations correlate with greater cardiovascular disease morbidity and mortality, a relationship that appears continuous and extends into the nondiabetic range [20]. Raised HbA1c remains an independent predictor of heart failure development in the presence of other risk factors, including diabetes itself [22].

Imaging and Biomarker Approaches

Almost half of those with diabetes have echocardiographic evidence of diabetic heart disease, well before symptoms emerge [13]. The association with adverse cardiovascular outcomes is substantial, yet the role of imaging for risk stratification or screening in asymptomatic patients remains unclear [17]. Coronary artery disease characteristically presents one or more decades earlier in diabetes [18]. Multimodality approaches have the potential to enhance the detection of abnormalities that confer a poor prognosis [12]. Such stratification is complemented by biochemical markers, with high-sensitivity troponins and natriuretic peptides serving as established indicators. Several novel biomarkers hold promise, although their utility in diabetes has been less widely studied [14].

Risk Scores and Population Health Implications

Among models specifically for cardiovascular event risk, the Framingham Heart Study has held an almost pre-eminent status since its inception early in the last century [17]. However, modern awareness of the limitations of classical risk factors and of the impact of diabetes has led multiple groups to construct new equations that focus not only on CV mortality but also on specific cardiovascular end-points [19]. These models primarily rely on standard population epidemiology, identifiable risk factors, historical observations, and empirical mathematics. Recent generic CV risk assessment frameworks have commonly performed poorly in diabetic cohorts [15]. Most national diabetes association's endorse their use, although variability exists in suggestions regarding their performance within the specific diabetic population [13]. These guidelines frequently recommend a three-risk-tier stratification approach to screening and monitoring for such patients. Nevertheless, unique risk equations reportedly remain scarce, even despite rapid advancements in informatics, understanding of diabetes dynamics, and modelling methodologies [13]. Where proposed, traditional empirical approaches governed by linear approximations often still predominate. The required baseline diabetic dataset has conversely reached a robust degree of sophistication and readiness for application, with data increasingly supplemented by evolving evidence of national circumstance modifications [15].

Therapeutic Approaches and Cardiovascular Outcomes

The association of diabetes with increased cardiovascular risk has generated interest in how anti-diabetes medications affect cardiovascular outcomes [7]. Reducing hyperglycemia is critical for preventing diabetes-related microvascular complications [9]. Accumulating evidence suggests that postprandial hyperglycemia is particularly harmful [2]; glycaemic targets should therefore consider both HbA1c and postprandial levels. Individualized therapy that balances the benefits of achieving the most stringent glycaemic control with the risks of weight gain and hypoglycemia is essential for improving long-term prognosis [11]. In the United States, among adults aged 35–84 years with diabetes, the prevalence of coronary artery disease (CAD) increased from 7.2% in 1971–1975 to 9.0% in 2001–2008, while the prevalence in those without diabetes declined from 6.2% to 4.3%. The relative risk of CAD doubled after accounting for clinical and behavioural risk factors, consistent with other studies [7]. In addition to elevated glucose, diabetes alters lipid metabolism, leading to an atherogenic lipid profile and increased lipotoxicity [14].

Glycemic Management and Cardiovascular risk

Contemporary approaches to diabetes management warrant consideration not only for glycemic effects but also for cardiovascular outcomes [2]. Evidence suggests a complex relationship between glycemic control, cardiovascular risk, and glycemic targets [13]. Intensive glycemic control promotes the development of detrimental, atherogenic lipid patterns associated with increased cardiovascular risk. The evidence is robust that gross hyperglycemia substantially augments cardiovascular risk, and its accurate date and time-stamped monitoring offers a promising avenue for risk stratification [1]. Cardiovascular guidance follows an integrative therapeutics framework. Glucose

regulation broadly encompasses agent-specific impacts. A cardiovascular indication for pharmacotherapy exists for individuals with established atherosclerotic cardiovascular disease [12]. However, achieving glucose targets and avoiding a strict focus on hemoglobin A1c should be maintained in the absence of documented general cardiovascular benefit intent; the utmost target must remain the prevention of excessive gross hyperglycemia itself rather than the lowering of some chronic benchmark [14].

Blood Pressure Control and Renal Protection

People with diabetes should achieve a blood pressure of <130/80 mmHg. The ADA/EASD recommends the use of RAAS inhibitors for diabetics with hypertension and/or kidney disease [19]. Data indicate that SGLT2 inhibitors reduce the risk of renal failure and offer direct reno-protective effects, alongside indirect benefits from blood pressure lowering and atheromatous disease [16]. Recent trials suggest that the reduction of renal disease may occur earlier than, and thus independently from, the effect on cardiovascular and mortality outcomes [18]. The benefits observed with RAAS blockers for heart failure are particularly relevant for diabetic patients. The lower limit for troponins remains to be correctly defined [17]. Data on conventional measures (transfer coefficient, diffusing capacity) are inconclusive, while natriuretic peptides appear useful for prevention and diagnosis [17]. People with diabetes and hypertension also require specific evaluations and preventive measures for vascular diseases in edematous and non-edematous limbs [13]. Together, clinical and electrophysiological assessments of cardiovascular autonomic nervous function are mandatory in all patients with diabetes [17]. Direct imaging of the coronary arteries, cerebral arteries, and other specific districts is usually performed before surgery or when major symptoms arise. Blood-brain barrier permeability is often increased in diabetes, promoting either hemorrhagic or ischemic strokes. Routine screening for peripheral disease is controversial [15]. Arteriopathy and pathogenetically accelerated atherosclerosis are, in fact, frequently associated; however, the syndrome is often asymptomatic, and many amputations occur in patients with diabetes without type 2–associated major conditions [14].

Lipid Management and Antithrombotic Therapy

Atherosclerosis substantially affects people with diabetes, heightening the risk of cardiovascular disease 20. Cholesterol biosynthesis remains elevated even when low-density lipoprotein cholesterol (LDL-C) approaches the recommended <1.8 mmol/L in this population [21]. Diabetic dyslipidaemia is present in the majority of patients with type 2 diabetes (T2DM) and is characterized by elevated triglycerides, reduced high-density lipoprotein cholesterol levels, and increased small dense LDL [18]. Triglyceride-rich lipoproteins, apolipoprotein C3, low apolipoprotein A1, and lipoprotein (a) have been linked to the development and progression of atherosclerosis in individuals with T2DM [22]. Statins remain the first-line therapy in lipid management for diabetic patients, substantially improving the lipid profile and reducing cardiovascular morbidity and mortality. Other lipid-lowering therapies, such as ezetimibe, bempedoic acid, and inclisiran, have shown promise to varying degrees; however, there is currently limited evidence and consensus guidelines on the management of diabetic dyslipidaemia [19]. Whether antiplatelet therapy continues beyond 1 year after acute coronary syndrome or percutaneous coronary intervention remains debated, and the long-term effects of rivaroxaban on specific endothelial activation markers in high-risk populations require further elucidation [22]. Optimal strategies to minimize the occurrence of macrovascular complications and related reduced quality of life in individuals with diabetes are still being investigated [20].

SGLT2 Inhibitors and GLP-1 Receptor Agonists in Cardiovascular Prevention

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like peptide1 receptor (GLP-1R) agonists emerged as potent regulators of glucose metabolism [23]. Their potential value in the cardiovascular (CV) arena became evident when large outcome studies revealed a favorable risk–benefit ratio [23]. Combination therapy with these classes may present additional cardiovascular advantages [24]. Both drug classes displayed considerable promise for CV prevention in patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular disease (ASCVD) risk factors [27]. SGLT2 inhibitors proved highly effective against heart failure (HF) and chronic kidney disease (CKD) progression, with limited stroke protection [25]. In contrast, GLP-1R agonists primarily reduced major adverse cardiovascular events (MACE) linked to coronary arterial disease (CAD) progression and offered a robust preventive effect against stroke [21]. Both classes contributed to inroads against long-term complications, yet sizable unmet needs persisted [25].

Non-pharmacological Interventions and Lifestyle Modification

Diabetes management is crucial in averting or delaying progression of its complications, hence several non-pharmacological interventions and lifestyle modifications like dietary changes, tobacco cessation, weight loss, and physical activity have been proposed to ameliorate several demographic and clinical risk factors [2]. Many diabetes guidelines already recommend at least 150 minutes of moderate-intensity aerobic activity every week [26].

Special Populations and Considerations

A clear distinction can be made between type 1 and type 2 diabetes in regard to CVD pathophysiology and risk determination [3]. The relationship between CVD and type 1 diabetes is considerably less clear than for type 2, as during the early disease stage, there is no increased risk of events [24]. Atherogenic dyslipidemia a prominent risk factor for coronary artery disease and other CVDs in type 2 diabetes arises later in type 1, and evidence suggests that risk in type 1 diabetes emerges when other comorbidities or microvascular complications manifest [20]. Regular screening for CVD is seldom performed among pediatric and adolescent populations, despite the potential for early detection of diabetes-related abnormalities that could prompt preventive measures [23]. The prevalence of type 2 diabetes in youths is rising, along with the risk of subclinical cardiovascular disease [20]. The American Diabetes Association (ADA) recommends screening commencing at age 10 for patients at high risk of type 2 diabetes [8]. A survey of screening practices reported that less than one-quarter of specialists routinely screen for CVD among patients with type 1 diabetes prior to age 21, and less than half after age [21, 1]. Older adults constitute a rapidly growing demographic affected by diabetes and CVD [25]. Comprehensive geriatric assessments can inform clinical decisions regarding the management of diabetes and expectation of long-term outcomes, while ensuring that therapeutic approaches align with the overall patient-care strategy [12]. Individuals over 65 suffer a greater burden of chronic disease and disability than younger populations, yet studies often fail to analyze older adults separately. Dementia prevalence in diabetes increases with age but remains underappreciated as a complication warranting periodical consideration and possible diagnosis [27].

Type 1 versus Type 2 Diabetes in Cardiovascular Disease

In patients with type 1 diabetes (T1D), coronary artery disease (CAD) and cerebrovascular disease are the predominant causes of mortality, whereas in type 2 diabetes (T2D) heart failure and CAD predominate in a similar rank order[8]. Metabolic derangements associated with hyperglycemia, including glycative signaling, lipotoxicity and atherogenic dyslipidemia, appear to play a major pathophysiological role in T2D, but seem less relevant for T1D. Both inflammation and impaired insulin signaling are thought to play a central role in the pathophysiology of CAD in T2D, Insulin resistance (IR) is considered a salient aspect of T2D but is not typically associated with T1D. Anti-atherosclerotic pharmacotherapy guidelines largely follow the same principles across type of diabetes. Nevertheless, interventions addressing control of blood glucose, hypertension and dyslipidemia may differ somewhat across types [1] and [21, 2].

Pediatric and Adolescent Populations

The risk of atherosclerosis and cardiovascular disease (CVD) among youths with type 1 diabetes is comparable to the risk associated with age, sex, and other traditional Coronary Artery Disease risk factors in the general population [25]. The acceleration of atherosclerosis can occur even before the onset of overt diabetes [28]. For youths with type 2 diabetes, CVD risk factors may occur earlier and be more severe than in the general population. As youth with diabetes have been shown to develop expanded cardiovascular disease risk factors and early atherosclerotic changes, monitoring and treatment of cardiovascular disease-related disease risk factors is critical in this population [26].

Older Adults and Comorbidity Burden

Older individuals with diabetes are burdened by a higher prevalence and impact of comorbidities compared with their counterparts without diabetes [29]. However, analyses demonstrating the effects of comorbidity load on mortality risk consistently reveal that an increase in the number of comorbidities does not confer incrementally greater risk compared with the general population [25]. In the older population with diabetes, cardiovascular disease (CVD) remains a significant risk factor, particularly in the younger old (<75 years). The subset of heart failure (HF) is even more common, carries a higher mortality risk, and has been flagged as a target for vigilance and management, in part through the potential use of SGLT2 inhibitors. Other therapies, such as thiazolidinediones, are contraindicated because they increase the risk of HF in at-risk older people. Diabetes complications such as end-stage renal failure and foot issues are likewise more prevalent and have a disproportionate effect on management requirements; careful monitoring of associated risk factors is therefore essential, particularly regular foot screening and kidney function assessment [27]. Depression is common in older patients and linked with excess all-cause mortality, making assessment and treatment another priority [28]. Polypharmacy is a major problem, especially with multiple concurrently prescribed agents for diabetes, hypertension, and lipids, and it fuels additional risk because increased exposure to medications may increase the risk of adverse effects and negatively affect adherence [30].

Gaps in Knowledge and Future Directions

Unresolved mechanisms linking diabetes and cardiovascular disease (CVD) still require further elucidation. The relationships among glucose homeostasis, lipid metabolism, obesity, and inflammation represent priority areas for research [28]. Given that renal impairment is both a significant risk factor for and a manifestation of macro- and

microvascular diabetic complications, knowledge gaps also persist concerning the implications of diabetic kidney disease on patient mortality according to CVD type [27]. Furthermore, the comparative cardiovascular effects of different glucose-lowering drug classes remain uncertain, along with their variable impacts on body weight and renal function [29]. The assessment of glycaemic burden through routinely obtained biochemical parameters can be further refined, potentially through the integration of novel predictive biomarkers and the use of machine-learning techniques that would encompass highly complex datasets to yield precise clinical and treatment predictions at the individual, rather than the population-based, level [2]. The wider implementation of glucose-lowering treatment options with demonstrated cardiovascular benefits among CVD patients would also help delineate their true cardiovascular protective characteristics [30-35].

CONCLUSION

Cardiovascular disease remains the principal cause of morbidity and mortality in individuals with diabetes, reflecting the complex and multifactorial interactions between metabolic dysregulation, vascular injury, and chronic inflammation. This narrative review underscores that hyperglycemia, insulin resistance, dyslipidemia, oxidative stress, and endothelial dysfunction form the central biological pathways driving both microvascular and macrovascular complications. These mechanisms contribute to a wide spectrum of cardiovascular manifestations, including coronary artery disease, heart failure, cerebrovascular disease, and peripheral arterial disease, with distinct patterns observed across diabetes types, age groups, and comorbid conditions. Recent advances in cardiovascular therapeutics have reshaped diabetes care, particularly with the emergence of SGLT2 inhibitors and GLP-1 receptor agonists, which provide cardiovascular and renal protection independent of their glucose-lowering effects. Nonetheless, optimal management requires an integrated, patient-centered approach that combines pharmacological therapy with aggressive control of blood pressure, lipid levels, and lifestyle-related risk factors. Improved risk stratification using advanced biomarkers, imaging modalities, and refined glycemic metrics may enhance early detection and targeted prevention strategies. Despite substantial progress, significant gaps remain in understanding the heterogeneity of cardiovascular risk in diabetes, the long-term comparative effects of emerging therapies, and the translation of evidence into diverse clinical populations. Future research should focus on mechanistic studies, precision medicine approaches, and implementation strategies to ensure equitable access to effective cardiovascular prevention. Strengthening these efforts is essential to mitigating the cardiovascular burden of diabetes and improving survival and quality of life across the lifespan.

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