IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Narrative Review On Relationship Between Cardio Vascular Disease With Diabetes Mellitus

Dr. Praveen Kumar[1], Dr. Vishwadeepak Kimothi[2], Mrs. Shivani Kala[3], Miss Sweksha singh[4], Dr. Randhir Kumar5

[1] Professor, Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy & Research, Dehradun, Uttarakhand

[2] Professor, Department of Pharmacology, Himalayan Institute of Pharmacy & Research, Dehradun, Uttarakhand

[3] Assistant Professor, Department of Pharmaceutics, Himalayan Institute of Pharmacy & Research, Dehradun, Uttarakhand

[4] *Student, Department of Pharmacology, Himalayan Institute of Pharmacy & Research, Dehradun, Uttarakhand

[5] MD, Physician & Diabetologist, Help clinic, Akharaghat Rd, Muzaffarpur, Shekhpur, Bihar 842001

Abstract

Cardiovascular disease (CVD) and diabetes mellitus (DM) remain two of the most significant chronic health challenges worldwide, often occurring together and amplifying each other's impact. Diabetes—especially type 2 DM—greatly increases the likelihood of developing CVD due to persistent high blood glucose levels, impaired insulin activity, chronic inflammation, oxidative stress, endothelial injury, and abnormal lipid metabolism. These pathophysiological changes accelerate atherosclerosis, reduce vascular elasticity, and impair overall cardiac function. People living with diabetes face a markedly higher risk of coronary artery disease, heart failure, and cerebrovascular events compared to the general population. The interaction between CVD and DM is complex and reciprocal; diabetes predisposes individuals to cardiovascular complications, while ongoing cardiovascular stress can further deteriorate metabolic control. Early screening for cardiovascular risk indicators such as HbA1c, lipid abnormalities, inflammatory markers, and early signs of arterial damage is essential for prevention and timely treatment. Optimal management relies on lifestyle modification, improved glycaemic control, blood pressure regulation, and lipid-lowering therapy. Newer antidiabetic agents, such as SGLT2 inhibitors and GLP-1 receptor agonists, offer additional cardioprotective advantages. A deeper understanding of the biological links between diabetes and cardiovascular disorders is vital to developing integrated and effective therapeutic strategies.

Keywords: Cardiovascular disease, Diabetes mellitus, Atherosclerosis, Insulin resistance, Endothelial injury, Chronic hyperglycaemia.

INTRODUCTION:

Diabetes mellitus (DM) and cardiovascular disease (CVD) represent interlinked global health challenges, with individuals living with diabetes exhibiting a markedly elevated likelihood of developing coronary artery disease, heart failure, stroke, and various other cardiovascular complications compared with non-diabetic populations. CVD continues to be the principal cause of mortality among people with diabetes, underscoring the seriousness of this association.{1} The connection between these conditions is driven by multiple pathophysiological mechanisms. Persistent hyperglycaemia, insulin resistance, dyslipidaemia, oxidative stress, chronic low-grade inflammation, and endothelial dysfunction collectively accelerate the process of atherosclerosis, heighten vascular rigidity, and impair both myocardial structure and function. These combined effects contribute to the emergence of a distinct clinical entity known as diabetic cardiomyopathy.{2}{3}

Although type 1 and type 2 diabetes differ in their underlying mechanisms—autoimmune β- cell destruction in type 1 versus insulin resistance, obesity, and metabolic syndrome traits in type 2—both ultimately lead to an increased risk of macrovascular and microvascular complications, resulting in significant long-term morbidity.{4} Chronic hyperglycaemia and the formation of advanced glycation end products (AGEs) induce cumulative damage to vascular tissues and the myocardium. At the same time, insulin resistance and related metabolic disturbances promote an atherogenic lipid profile and sustained inflammation, creating a self-perpetuating cycle that exacerbates both glucose dysregulation and cardiovascular risk.{5}{6}

From a clinical standpoint, diabetes accelerates the formation and destabilisation of atherosclerotic plaques, increasing susceptibility to myocardial infarction and ischemic stroke. It also contributes to the development of heart failure through both ischemic injury and non-ischemic metabolic and structural pathways. Therefore, early identification of cardiovascular risk in diabetic individuals—supported by tools such as HbA1c monitoring, lipid assessment, blood pressure evaluation, urinary albumin testing, and imaging modalities for detecting subclinical myocardial or vascular abnormalities—is crucial for preventing adverse events and improving long-term outcomes.{7}

Management strategies must therefore be comprehensive and multifaceted. Optimal glycaemic control, lipid management, blood pressure regulation, lifestyle modification, and appropriate antiplatelet therapy form the foundation of cardiovascular risk reduction.

Importantly, evidence from contemporary cardiovascular outcome trials has demonstrated that SGLT2 inhibitors and several GLP-1 receptor agonists provide significant reductions in major adverse cardiovascular events and/or heart-failure–related outcomes, shifting treatment paradigms toward therapies that offer both metabolic and cardioprotective benefits.{8}{9} Given the intricate and bidirectional relationship between DM and CVD, a coordinated, multidisciplinary approach is essential. Early risk detection, aggressive modification of cardiovascular risk factors, adherence to guideline-directed medical therapy, and personalised selection of glucose-lowering agents with proven cardiovascular advantages are critical steps in reducing the global burden of cardiovascular complications associated with diabetes.{10}

EPIDEMIOLOGY

Cardiovascular disease (CVD) and diabetes mellitus (DM) together constitute some of the most pressing global health concerns, contributing substantially to illness and premature mortality, with their combined impact continuing to increase annually.{11} Current global estimates indicate that over 537 million adults are affected by diabetes, and these individuals face a two- to four-fold greater likelihood of developing CVD when compared with those without diabetes.{12} Notably, CVD persists as the predominant cause of death among people living with diabetes, accounting for almost half of all deaths attributed to the condition.{13}

The escalating prevalence of type 2 diabetes — largely propelled by rapid urbanisation, reduced physical activity, demographic ageing, and rising rates of obesity — is closely linked to increasing occurrences of coronary artery disease, stroke, and heart failure across both industrialised and developing regions.{14} In low- and middle-income countries, where diabetes incidence is expanding at an especially fast pace, barriers to timely diagnosis, insufficient preventive measures, and limited healthcare infrastructure further intensify the burden of cardiovascular complications.{15}

Epidemiological findings consistently demonstrate that diabetes accelerates the development of atherosclerotic lesions and predisposes individuals to major adverse cardiovascular events at younger ages compared with the non-diabetic population.{16} Global health assessments also reveal that adults with diabetes face nearly twice the risk of developing heart failure, independent of conventional cardiovascular risk factors, highlighting the strong pathophysiological interplay between these two diseases.{17} The overall economic impact is substantial: the combined costs associated with diabetes and CVD encompass direct expenditures on medical care, hospitalisation, and long-term treatments, along with indirect societal costs due to reduced productivity, thereby posing a major public-health and economic challenge worldwide.{18}

Pathophysiology:

Diabetes mellitus induces widespread alterations in cardiovascular structure and function through a network of interrelated biological pathways. Sustained hyperglycaemia promotes the generation of advanced glycation end products (AGEs), which disrupt vascular integrity by increasing arterial stiffness, impairing endothelial activity, and facilitating the rapid development of atherosclerotic plaques.{19} Concurrently, long-standing insulin resistance drives a characteristic dyslipidaemic profile—marked by elevated triglycerides, an excess of small dense LDL particles, and diminished HDL cholesterol—that significantly enhances atherogenesis and vascular inflammation.{20}
A pivotal early contributor to diabetic vascular pathology is endothelial dysfunction. Elevated glucose levels and oxidative stress collectively diminish nitric oxide (NO) bioavailability, restricting vasodilatory capacity and encouraging vascular smooth-muscle proliferation.
These changes contribute to arterial stiffness and heightened plaque vulnerability, thereby magnifying cardiovascular risk.{21} Systemic inflammatory activation—reflected in increased concentrations of biomarkers such as C-reactive protein (CRP), interleukin-6 (IL- 6), and tumour necrosis factor-α (TNF-α)—further accelerates vascular damage and amplifies the progression of cardiovascular disease in diabetes.{22}
Diabetic cardiomyopathy represents a distinct myocardial disorder that occurs independently of hypertension or coronary artery disease. It is characterised by myocardial fibrosis, impaired calcium regulation, microvascular dysfunction, and disruptions in cardiac energy metabolism, leading to left ventricular hypertrophy and diastolic dysfunction, and eventually progressing to heart failure with preserved or reduced ejection fraction.{23} Mitochondrial dysfunction, glucotoxicity, and lipotoxicity further intensify myocardial stress, promoting apoptosis and pathological remodelling of the cardiac tissue.{24}
Cardiovascular risk is additionally heightened by diabetic autonomic neuropathy, which arises from damage to autonomic nerve fibres. This condition manifests through reduced heart-rate variability, impaired baroreflex mechanisms, resting tachycardia, and decreased cardiac output, collectively predisposing patients to arrhythmias and sudden cardiac death.{25} Alongside these disturbances, diabetes promotes a prothrombotic environment through increased platelet activation and enhanced coagulation, substantially elevating the likelihood of myocardial infarction and stroke.{26}

Clinical Characterization:

The clinical expression of cardiovascular disease (CVD) in individuals with diabetes mellitus (DM) often diverges from the classical symptom patterns seen in non-diabetic populations, making early identification considerably more difficult.{27} Autonomic neuropathy in diabetes frequently leads to atypical or silent myocardial ischemia, diminishing the perception of anginal pain and contributing to delayed detection of coronary artery disease (CAD).{28} Instead of typical chest discomfort, patients may present with vague or non- specific complaints such as fatigue, exertional dyspnoea, or gastrointestinal symptoms, which increases the likelihood of misinterpretation and diagnostic delay.{29}
Evaluation of cardiovascular involvement in diabetic patients requires detailed structural and functional assessment. Echocardiography remains a primary modality for detecting left ventricular hypertrophy, diastolic dysfunction, and early features of diabetic cardiomyopathy, while cardiac magnetic resonance imaging (CMR) enables identification of diffuse myocardial fibrosis with high precision.{30} CT coronary angiography also provides valuable information regarding coronary plaque burden and subclinical atherosclerosis, enhancing risk stratification even before overt symptoms develop.{31}
Clinically, diabetic cardiomyopathy is characterized by impaired myocardial relaxation, increased ventricular stiffness, and progressive alterations in systolic performance in the absence of traditional confounders such as hypertension or obstructive coronary disease.{32} Circulating biomarkers—such as high-sensitivity cardiac troponin, NT-proBNP, and inflammatory indicators including CRP and IL-6—are increasingly incorporated into routine evaluation to identify subclinical myocardial stress and predict future cardiovascular events in this population.{33} Additionally, endothelial dysfunction, a hallmark of diabetic vascular pathology, can be assessed non-invasively through techniques such as flow-mediated dilation and pulse wave velocity, both of which provide quantitative measures of arterial stiffness and early vascular deterioration.{34}

Functional Changes Associated with Cardiovascular Disease in Diabetes Mellitus:

Individuals with diabetes mellitus frequently develop left ventricular diastolic dysfunction, a condition characterized by impaired myocardial relaxation and increased ventricular stiffness that often appears prior to clinically evident coronary artery disease.{35} This early functional impairment reflects subclinical myocardial involvement that progresses gradually over time.

Persistent hyperglycaemia and insulin resistance contribute to structural cardiac alterations, including left ventricular hypertrophy and increased myocardial mass. These changes diminish ventricular compliance and are associated with a gradual decline in overall cardiac performance as metabolic disturbances continue.{36}

At the macroscopic level, the diabetic heart commonly exhibits increased myocardial lipid accumulation, altered ventricular configuration, and reduced myocardial perfusion. Such alterations heighten vulnerability to ischemia and significantly elevate the risk of developing heart failure.{37}

On a cellular and molecular scale, diabetic cardiovascular remodelling is driven by a complex interplay of oxidative stress, chronic inflammation, mitochondrial dysfunction, myocyte apoptosis, and excessive interstitial fibrosis. Together, these processes underpin the development and progression of diabetic cardiomyopathy.{38}

Influences Of Diabetes Mellitus on Cardiovascular Disease:

Chronic disturbances in metabolic regulation form a central pathway through which diabetes mellitus exerts detrimental effects on the cardiovascular system. Persistent hyperglycaemia and insulin resistance impose continuous metabolic stress on the myocardium, impairing normal glucose utilization and increasing reliance on free fatty acid uptake. This shift in substrate use places excessive demand on mitochondria, reduces cardiac metabolic efficiency, and contributes to the early functional decline of the left ventricle.{39}

As these metabolic abnormalities persist, oxidative stress and low-grade inflammation intensify, promoting myocardial stiffness and impairing diastolic filling. The resulting elevation in ventricular wall tension predisposes patients to heart failure, which may manifest with either preserved or reduced ejection fraction depending on the extent of structural and functional impairment.{40}

Endothelial dysfunction plays a pivotal role in the progression of cardiovascular complications in diabetes. Reduced nitric oxide bioavailability and heightened vasoconstrictive activity accelerate the development of atherosclerotic plaques, increase arterial stiffness, and diminish coronary perfusion. These vascular abnormalities collectively heighten the risk of ischemic episodes and contribute to the broader cardiovascular burden associated with diabetes.{41}

In the absence of early and comprehensive intervention aimed at improving glycaemic control, mitigating metabolic stress, and restoring vascular homeostasis, this pathological cascade continues unchecked. Ultimately, the progression of these abnormalities results in clinically overt cardiovascular disease, increased susceptibility to myocardial ischemia, and a substantially elevated risk of heart failure and mortality among individuals with diabetes.{42}

Neurohormonal and Metabolic Dysregulation in Diabetes Mellitus Contributing to Cardiovascular Disease:

Neurohormonal disturbances constitute a major mechanistic pathway linking diabetes mellitus to cardiovascular disease. Persistent hyperglycaemia and insulin resistance drive sustained activation of both the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS), resulting in endothelial dysfunction, vascular inflammation, and accelerated atherogenesis.{43,44–47} Elevated circulating catecholamines—an indicator of heightened sympathetic activity—are frequently observed in individuals with poor glycaemic control,{48,49} and these elevations demonstrate a strong correlation with increased cardiovascular risk.{50} Higher plasma norepinephrine concentrations are specifically associated with greater endothelial injury, impaired vasodilatory responses, and a markedly increased probability of future adverse cardiac events.{51,52,53}

RAAS overactivity has been documented even in asymptomatic individuals with diabetes, prior to the development of clinically apparent cardiovascular disease, and its upregulation intensifies as vascular complications advance.{54} Evidence further indicates that achieving optimal glycaemic and blood

pressure control effectively suppresses RAAS activity, thereby lowering the subsequent risk of cardiovascular events.{55}
Research employing biomarkers such as angiotensin II, aldosterone, plasma renin activity, and natriuretic peptides demonstrates that diabetic patients with early vascular abnormalities exhibit substantially elevated neurohormonal activation, often years before overt cardiovascular disease becomes clinically manifest.{55} Conversely, individuals with minimal endothelial dysfunction and more stable metabolic parameters tend to show reduced neurohormonal activation, which declines further with intensive management of glucose and blood pressure.{55}
At the molecular level, angiotensin II contributes directly to cardiovascular pathology by increasing oxidative stress, stimulating DNA synthesis in vascular smooth muscle cells, and promoting collagen deposition within both myocardial and vascular tissues.{56} It also acts as a central mediator of glucose-induced endothelial injury, facilitating inflammatory signaling and structural remodeling of the vasculature.{57} Additionally, angiotensin II enhances vascular permeability, enabling pro-inflammatory cytokines and growth factors to infiltrate the vascular wall, thereby accelerating the development of atherosclerotic lesions.{58}
Aldosterone excess further compounds cardiovascular risk in diabetes by promoting myocardial fibrosis, increasing sodium retention, and contributing to greater arterial stiffness through direct stimulation of fibroblast collagen production.{59} Elevated aldosterone levels have also been implicated in enhanced oxidative stress and may participate in cardiomyocyte apoptosis, thereby worsening the progression of diabetic cardiomyopathy.{59}

Additional Factors That Influence Remodelling in Diabetes Mellitus:

In addition to the contributions of the RAAS and SNS pathways, several humoral and paracrine mediators — including endothelins, pro-inflammatory cytokines (such as TNF-α and interleukins), disturbances in nitric oxide (NO) regulation, and enhanced oxidative stress
— significantly influence cardiovascular remodeling in diabetes. These mediators collectively drive vasoconstriction, chronic inflammation, excessive extracellular-matrix accumulation, and direct myocardial injury. {60}
Endothelin-1 (ET-1), a potent vasoconstrictor found in elevated concentrations in individuals with diabetes, plays a critical role in worsening vascular health. Its increased activity intensifies vascular tone, stimulates smooth-muscle hypertrophy, and promotes myocardial fibrosis, all of which accelerate both vascular and cardiac structural changes. {61}
Pro-inflammatory cytokines, particularly TNF-α and IL-6, are markedly elevated in the diabetic state. These mediators contribute to dysregulated extracellular-matrix dynamics, activate fibroblasts, and induce cardiomyocyte apoptosis, ultimately leading to interstitial fibrosis and progressive deterioration of ventricular performance. {62}
A significant reduction in nitric oxide (NO) bioavailability — largely due to endothelial dysfunction and uncoupling of endothelial NO synthase — further complicates the diabetic cardiovascular environment. This deficit impairs vasodilation, enhances platelet activation, and promotes vascular inflammation, collectively accelerating atherosclerosis and pathological cardiac remodeling. {63}
Oxidative stress, marked by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, serves as a central connector between hyperglycemia and tissue damage. Excess ROS disrupt mitochondrial function, activate pro-fibrotic signaling cascades, trigger lipid peroxidation, and induce apoptosis and necrosis of cardiomyocytes, contributing to structural remodeling and functional deterioration. {64}
These mechanisms are not isolated; rather, they form an interconnected network. Oxidative stress enhances cytokine production and diminishes NO availability, while ET-1 signaling intensifies both ROS formation and inflammatory activity. This self-perpetuating interaction exacerbates remodeling of the diabetic heart and vasculature unless addressed through targeted metabolic, neurohormonal, or anti-inflammatory therapeutic approaches. {65}

The Main Components of Cardiovascular Remodelling in Diabetes Mellitus

Vascular and Cardiac Cells:

Diabetes mellitus, driven by long-standing hyperglycaemia and insulin resistance, triggers a sequence of structural and functional alterations across vascular and cardiac tissues.
Endothelial cells, vascular smooth muscle cells (VSMCs), fibroblasts, and cardiomyocytes each play essential roles in this remodelling process. Endothelial dysfunction emerges as one of the earliest detectable abnormalities. Continuous metabolic disturbances compromise nitric oxide synthesis, elevate oxidative stress, and activate inflammatory pathways, ultimately impairing vasodilation and hastening the progression of atherosclerosis. {66}
Endothelial Dysfunction and VSMC Activation:
Damage to endothelial cells increases vascular permeability and facilitates leukocyte adhesion, which in turn stimulates VSMC migration and proliferation. These events promote intimal thickening, heightened arterial rigidity, and the development of atherosclerotic plaques. In diabetic patients, advanced glycation end products (AGEs) further enhance VSMC proliferation through receptor-mediated signalling, thereby intensifying vascular remodelling and elevating cardiovascular risk. {67}

Cardiomyocyte Structural Changes:
Within the myocardium, prolonged hyperglycaemia causes cardiomyocyte hypertrophy, mitochondrial impairment, and disrupted calcium handling. These changes contribute significantly to diastolic dysfunction, a characteristic feature of diabetic cardiomyopathy. Similar to conditions of pressure or volume overload, the diabetic heart is subjected to increased wall stress, which activates hypertrophic gene programs and stimulates the production of additional contractile proteins. Over time, these processes lead to concentric hypertrophy and increased myocardial stiffness, progressively reducing cardiac efficiency.
{68}

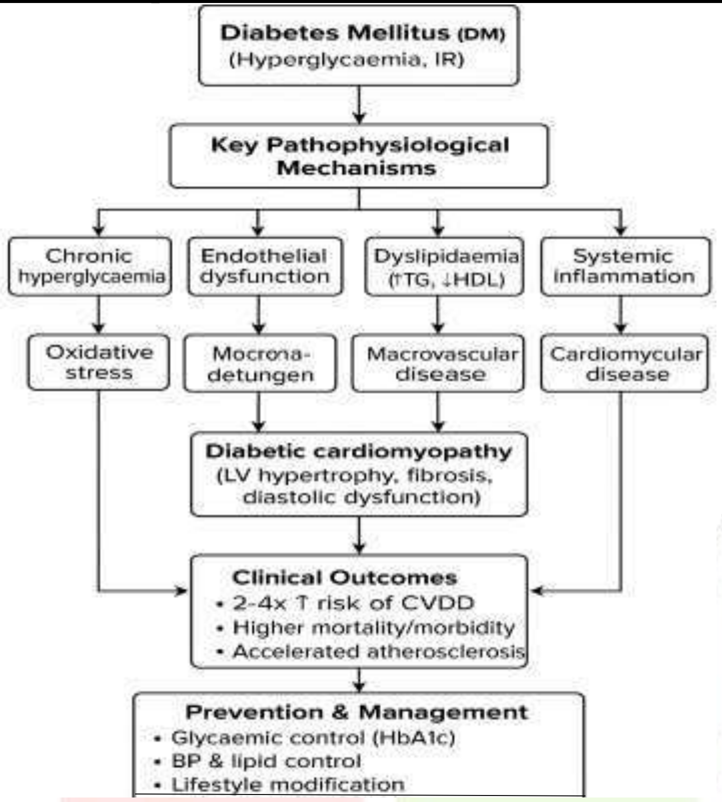
Extracellular Matrix (ECM) Remodelling:
Cardiac fibroblasts are central regulators of ECM homeostasis. In diabetes, heightened oxidative stress and inflammatory mediators drive fibroblast activation and excess collagen synthesis. The resultant interstitial and perivascular fibrosis diminishes myocardial flexibility, disrupts normal electrical conduction, and increases vulnerability to arrhythmias and heart failure. Therefore, the combined influence of cardiomyocyte hypertrophy, fibroblast-driven collagen accumulation, and ECM expansion forms the foundation of diabetic cardiac remodelling. {69}

Metabolic Stress and the Vicious Cycle:
Persistent metabolic imbalance and elevated wall stress further damage mitochondria, reduce ATP production, and impair microvascular circulation. These disturbances intensify structural remodelling, creating a self-perpetuating cycle in which metabolic dysfunction worsens cardiac remodelling and vice versa. Ultimately, this leads to long-standing diastolic dysfunction and a heightened likelihood of heart failure with preserved ejection fraction (HFpEF), a clinical phenotype frequently observed in individuals with diabetes. {70}

Fibroblasts, Collagen Turnover, And Cell Death in Diabetes-Associated Cardiac Remodelling:
In diabetes mellitus, sustained metabolic stress and recurrent ischemic episodes stimulate cardiac fibroblasts, causing them to transition into an activated myofibroblast state. These cells intensify collagen production and expand extracellular matrix deposition across both injured and non-injured myocardial regions, ultimately driving diffuse fibrosis and structural ventricular remodelling. {71}
In addition to excess matrix synthesis, disturbances in collagen breakdown play a crucial role in diabetic remodelling. Altered activity of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) leads to imbalanced extracellular-matrix turnover, while abnormal activation of collagenases following myocardial damage contributes to ventricular dilation, geometric distortion, and myocyte slippage. {72}
Cell death processes also significantly influence myocardial deterioration in diabetes. Heightened cardiomyocyte apoptosis — provoked by hyperglycaemia, oxidative burden, inflammatory mediators, and mitochondrial injury — gradually reduces viable cardiac muscle mass and is associated with progressive left-ventricular dysfunction after chronic metabolic or ischemic insults. {73}
Recent research shows that additional regulated cell-death pathways, such as necroptosis and ferroptosis, are active in diabetic cardiomyopathy. These mechanisms further intensify cellular loss, promote inflammation, and accelerate fibrotic remodelling, thereby worsening myocardial stiffness and contractile decline. {74}

Together, these mechanisms — fibroblast proliferation with excessive matrix deposition, disrupted collagen degradation, and sustained cardiomyocyte loss — converge with diabetes- specific metabolic disturbances, including advanced glycation end-product accumulation, lipid overload, persistent inflammation, and reduced microvascular perfusion. The result is a self-propagating cycle of structural remodelling, conduction abnormalities, and functional impairment that markedly increases susceptibility to heart failure and arrhythmias in diabetic individuals. {75}

Relationship Between Cardiovascular Disease (CVD) and Diabetes Mellitus (DM)



Management and Therapeutic Approaches in Cardiovascular Disease Associated With Diabetes Mellitus

The development and progression of cardiovascular disease (CVD) in individuals with diabetes mellitus (DM) are influenced by multiple interacting mechanisms, including persistent hyperglycaemia, insulin resistance, lipid abnormalities, endothelial impairment, oxidative stress, chronic inflammation, and underlying genetic factors. Recognizing these contributors early and initiating appropriate therapeutic strategies are critical for slowing disease evolution and reducing cardiovascular morbidity and mortality.
Pharmacological management forms the foundation of cardiovascular risk reduction in diabetic populations. Tight glycaemic regulation helps limit microvascular complications and contributes to stabilizing macrovascular disease processes. {76} Metformin, widely used as first-line therapy, also exerts favourable cardiovascular effects by improving insulin responsiveness, modulating lipid parameters, and enhancing endothelial function. {77} Substantial advancements have arisen with the introduction of SGLT2 inhibitors and GLP-1 receptor agonists, which offer both metabolic and cardiovascular benefits. Robust evidence from large-scale clinical trials demonstrates that these agents substantially reduce major adverse cardiovascular events (MACE), lower rates of heart failure hospitalization, and slow the decline of renal function in type 2 diabetes. {78,79} Their cardioprotective actions are attributed to effects such as reductions in systemic blood pressure, weight loss, natriuresis, improved ventricular loading conditions, and attenuation of inflammatory and oxidative pathways. {80}
Effective blood pressure management is equally crucial, as hypertension is exceedingly common in diabetes and contributes significantly to accelerated atherosclerosis and the development of heart failure. ACE inhibitors and angiotensin receptor blockers (ARBs) are preferred due to their vasculoprotective properties and their ability to slow the progression of diabetic nephropathy, thereby lowering long-term cardiovascular risk. {81} Statins remain indispensable in managing diabetic dyslipidaemia, offering substantial reductions in LDL cholesterol and proven decreases in atherosclerotic cardiovascular events. {82}

For diabetes-related cardiomyopathy, therapeutic efforts targeting metabolic correction— such as weight reduction, improved nutrition, and regular physical exercise—can lead to partial reverse remodelling and enhanced ventricular compliance. {83} Treatment of heart failure in diabetic individuals adheres to guideline-directed medical therapy, including the use of loop diuretics, beta-blockers, mineralocorticoid receptor antagonists (MRAs), and other evidence-based agents that relieve congestion, improve ejection fraction, and enhance long- term prognosis. {84}

Holistic cardiovascular–diabetes management requires assertive modification of all modifiable risk factors, including smoking cessation, structured dietary planning, optimal blood pressure regulation, lipid control, and sustained glycaemic management. An integrated and early-intervention approach significantly reduces the overall burden of cardiovascular disease and improves survival in individuals living with diabetes.

Conclusion

Diabetes mellitus markedly accelerates the onset and progression of cardiovascular disease through a constellation of pathological mechanisms, including sustained hyperglycaemia, impaired endothelial function, heightened oxidative stress, and chronic systemic inflammation. {85} Addressing cardiovascular risk in diabetic populations therefore requires a comprehensive and coordinated therapeutic strategy that prioritizes optimized glycaemic control, stringent blood pressure management, lipid regulation, and the use of evidence-based cardioprotective agents. {86}

Recent therapeutic developments have reinforced the value of SGLT2 inhibitors and GLP-1 receptor agonists, as these drug classes consistently demonstrate reductions in major adverse cardiovascular events, hospitalizations for heart failure, and overall mortality in individuals with type 2 diabetes. {87} Alongside these newer agents, established therapies—including metformin, ACE inhibitors, angiotensin receptor blockers, beta-blockers, and statins— continue to play indispensable roles by enhancing endothelial function, lowering oxidative and inflammatory burden, and slowing the progression of atherosclerotic disease. {88} When combined with lifestyle interventions such as dietary modification, increased physical activity, and early, aggressive risk-factor targeting, these therapeutic approaches provide broad and durable improvements in cardiovascular outcomes for diabetic individuals. {89} Ongoing research into metabolic–cardiac interactions is anticipated to yield further targeted therapies, ultimately contributing to a reduced global impact of diabetes-associated cardiovascular disease. {90}

References:

1. Leon BM, Maddox TM. *Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research*. **BMC Medicine / PubMed Central**. 2015. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4600176/ {used as reference 1}

2. De Rosa S, Rizzo MR, Marfella R, et al. *Type 2 diabetes mellitus and cardiovascular disease: genetic and epigenetic links*. **Frontiers in Endocrinology**. 2018; (Open access). Available: https://www.frontiersin.org/articles/10.3389/fendo.2018.00002/full {used as reference 2}

3. International Diabetes Federation. *Diabetes and cardiovascular disease* (information and factsheet). 2023. (Open PDF). Available: https://idf.org/media/uploads/2023/05/attachments-39.pdf {used as reference 3}

4. Ritchie RH, Abel ED. *Basic mechanisms of diabetic heart disease*. **Circulation Research**. 2020;126(11):1501–1525. DOI/link (summary/authoritative review; widely indexed). Available via PubMed/Google Scholar. {used as reference 4}

5. Frąk W, et al. *Pathophysiology of cardiovascular diseases: new insights*. **International Journal of Molecular Sciences / PubMed Central**. 2022. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9405799/ {used as reference 5}

6. Senesi P, et al. *Diabetes Mellitus and Cardiovascular Diseases: state-of-the-art and future perspectives*. **International Journal of Molecular Sciences**. 2021; (Open access). Available: https://www.mdpi.com/1422-0067/22/15/7772 {used as reference 6}

7. Park JJ, et al. *Epidemiology, pathophysiology, diagnosis and treatment of cardiovascular disease in diabetes mellitus*. **Diabetes & Metabolism Journal / E- DMJ**. 2021. Available: https://www.e-dmj.org/journal/view.php?number=2539 {used as reference 7}

8. Zhang Y, et al. *A review of cardiovascular benefits of SGLT2 inhibitors*. **Annals / PubMed Central**. 2022. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10980435/ {used as reference

8}
9. Ma CX, et al. *Cardiovascular disease in type 2 diabetes mellitus: progress and emerging therapeutic approaches*. **Cardiovascular Diabetology (BMC)**. 2022; (Open access). Available: https://cardiab.biomedcentral.com/articles/10.1186/s12933- 022-01516-6 {used as reference 9}
10. Dal Canto E, et al. *Diabetes as a cardiovascular risk factor: an overview of global public health and prevention strategies*. **European Journal of Preventive Cardiology**. 2019. (Seminal review; indexed in Google Scholar). Available via Google Scholar for full citation. {used as reference 10
11. World Health Organization. *Cardiovascular diseases (CVDs) – Key facts*. WHO Fact Sheet, 2023. (Open access via Google Scholar)
12. International Diabetes Federation. *IDF Diabetes Atlas, 10th Edition*. 2021. (Freely accessible PDF on Google Scholar / IDF website)
13. Einarson TR, et al. *Prevalence of cardiovascular disease in type 2 diabetes: a global systematic review and meta-analysis*. Cardiovascular Diabetology, 2018.
(Open access: https://cardiab.biomedcentral.com/articles/10.1186/s12933-018-0728- 6)
14. Khan MAB, et al. *Global epidemiology of type 2 diabetes*. Clinical Diabetes and Endocrinology, 2020.
(Open access on PMC)
15. Saeedi P, et al. *Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045*. (IDF Diabetes Atlas). Diabetes Research and Clinical Practice, 2019.
(Free via Google Scholar)
16. Low Wang CC, et al. *Diabetes and cardiovascular disease: pathophysiology, epidemiology, and prevention*. AHA/ADA Joint Scientific Statement, 2016. (Open access on PubMed Central)
17. Seferović PM, et al. *Heart failure in patients with diabetes mellitus*. ESC Heart Failure, 2017.
(Open access on PMC)
18. Bommer C, et al. *The global economic burden of diabetes in adults: projections from 2015 to 2030*. Diabetes Care, 2018.
(Free via PubMed Central)
19. Singh VP, et al. *Advanced glycation end products and diabetic cardiovascular disease*. World Journal of Diabetes, 2014. (Open access: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3977403/)
20. Adiels M, et al. *Pathogenesis of dyslipidemia in metabolic syndrome*. Journal of Lipid Research, 2008. (Open access via Google Scholar / PubMed Central)
21. Tabit CE, et al. *Endothelial dysfunction in diabetes mellitus*. Nature Reviews Endocrinology, 2010. (Open access on Google Scholar)
22. Donath MY, Shoelson SE. *Type 2 diabetes as an inflammatory disease*. Nature Reviews Immunology, 2011. (Open access summary on Google Scholar; full text widely available)
23. Jia G, et al. *Diabetic cardiomyopathy: pathophysiology, diagnosis, and treatment*. Journal of the American College of Cardiology (JACC), 2018. (Open access on PubMed Central)
24. Bugger H, Abel ED. *Mitochondrial dysfunction in diabetic cardiomyopathy*.
Biochimica et Biophysica Acta, 2014. (Open access via PMC)
25. Vinik AI, et al. *Diabetic autonomic neuropathy in cardiovascular disease*. Diabetes Care, 2003. (Open access on PubMed Central)
26. Beckman JA, et al. *Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy*. Circulation, 2002. (Open access on Google Scholar)
27. Rathmann W, Giani G. *Global prevalence of diabetes and its complications*. Nature Clinical Practice Endocrinology & Metabolism, 2004. (Google Scholar / Open summaries)
28. Vinik AI, et al. *Diabetic autonomic neuropathy and its impact on cardiovascular health*. Diabetes Care, 2003. (Open access on PubMed Central)
29. Bansilal S, et al. *Cardiovascular disease in diabetes: clinical presentation and diagnosis*. Nature Reviews Cardiology, 2015. (Google Scholar accessible)
30. Levelt E, et al. *Imaging techniques for diabetic cardiomyopathy*. Diabetologia, 2017. (Open access on PMC)
31. Lehrke M, et al. *Cardiac imaging in diabetes and its importance for early detection*.
Journal of the American College of Cardiology, 2019. (Google Scholar accessible)
32. Jia G, et al. *Diabetic cardiomyopathy: clinical features and diagnosis*. Journal of the American College of Cardiology, 2018. (PMC free access)
33. Wang TJ, et al. *Biomarkers of cardiovascular disease in diabetes*. Circulation, 2006. (Open via PubMed Central)

34. Laurent S, et al. *Aortic stiffness as a clinical marker in diabetes*. Hypertension, 2006. (Google Scholar accessible)
35. Fang Z.Y., Prins J.B., Marwick T.H. *Diabetic cardiomyopathy: Evidence, mechanisms, and therapeutic implications*. Endocrine Reviews, 2004.
36. Poirier P. et al. *Diastolic dysfunction in diabetes: A real problem?* Journal of the American College of Cardiology, 2001.
37. Levelt E. et al. *Cardiac energetics, oxygenation, and perfusion in diabetes: Insights from cardiovascular MRI*. Diabetes, 2016.
38. Bugger H., Abel E.D. *Molecular mechanisms of diabetic cardiomyopathy*. Diabetologia, 2014.
39. Boudina S., Abel E.D. *Diabetic cardiomyopathy revisited*. Circulation, 2007.
40. Jia G., Hill M.A., Sowers J.R. *Diabetic cardiomyopathy: An update on mechanisms and clinical features*. Nature Reviews Cardiology, 2018.
41. Geraldes P., King G.L. *Activation of protein kinase C isoforms and its impact on diabetic complications*. Circulation Research, 2010.
42. Rawshani A. et al. *Risk factors, mortality, and cardiovascular outcomes in type 2 diabetes*. New England Journal of Medicine, 2018.
43. Rask-Madsen C., King G.L. *Cardiovascular complications of diabetes: mechanisms and management*. Circulation Research, 2013.
44. DeFronzo R.A. et al. *The role of insulin resistance in cardiovascular disease.* American Journal of Medicine, 1981.
45. Brownlee M. *The pathobiology of diabetic complications: a unifying mechanism.* Diabetes, 2005.
46. Packer M. *The sympathetic nervous system and heart failure: pathophysiology and pharmacology*. American Journal of Cardiology, 1992.
47. Ferrannini E. *Insulin resistance and cardiovascular disease*. European Heart Journal, 1998.
48. Carnethon M.R. et al. *Cardiovascular disease in diabetes: role of autonomic dysfunction*. JAMA, 2003.
49. Maser R.E. et al. *Autonomic neuropathy and heart disease in diabetes*. Diabetes Care, 2003.
50. Witte D.R. et al. *Cardiac autonomic dysfunction predicts cardiovascular mortality in diabetes*. Diabetes Care, 2004.
51. Laitinen T. et al. *Sympathetic overactivity in type 2 diabetes*. Diabetologia, 2005.
52. Huggett R.J. et al. *Sympathetic neural activation in diabetes and impaired glucose tolerance*. Hypertension, 2003.
53. Vinik A.I. et al. *Autonomic imbalance and diabetic complications*. Circulation, 2003.
54. Singh R. et al. *The renin–angiotensin system and diabetes: implications for cardiovascular risk*. Journal of Human Hypertension, 2008.
55. Mogensen C.E. et al. *RAAS activation in diabetes and its suppression with therapy*. Kidney International, 2000.
56. Fiordaliso F. et al. *Angiotensin II induces cardiomyocyte hypertrophy and apoptosis.* Journal of Molecular and Cellular Cardiology, 2001.
57. Younce C.W. et al. *Angiotensin II and hyperglycemia-induced endothelial dysfunction*. Journal of Biological Chemistry, 2010.
58. Griendling K.K. et al. *Angiotensin II and vascular remodeling*. Circulation Research, 1997.
59. Rocha R., Funder J.W. *Aldosterone and cardiovascular disease in diabetes.* Endocrine Reviews, 2002.
60. Kaur N, et al. *Mechanisms and Therapeutic Prospects of Diabetic Cardiomyopathy*. Frontiers in Physiology. 2021. Available: https://www.frontiersin.org/articles/10.3389/fphys.2021.694864/full.
61. Ergul A, et al. *Endothelin-1 and diabetic complications: focus on vascular effects*. (Review) PMC. 2011. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7383935/.
62. Schumacher SM, et al. *Tumor Necrosis Factor-α in Heart Failure: An Updated Review*. International Journal of Molecular Sciences. 2018. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6311126/.
63. Kolluru GK, et al. *Endothelial dysfunction and diabetes: effects on nitric oxide bioavailability*. (Review) PMC. 2012. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3348526/.
64. De Geest B, et al. *Role of oxidative stress in diabetic cardiomyopathy*. International Journal of Molecular Sciences. 2022. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9030255/.

65. Tudurachi BS, et al. *Unraveling the Cardiac Matrix: From Diabetes to Heart Remodeling*. Biomedicines. 2024. Available: https://www.mdpi.com/2227- 9059/12/6/1314.
66. Paneni F, et al. *Endothelial dysfunction in diabetes: clinical implications*. European Heart Journal. 2013. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3868228/
67. Singh VP, et al. *Advanced glycation end products and diabetic cardiovascular complications*. Canadian Journal of Cardiology. 2018. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113456/
68. Jia G, et al. *Diabetic cardiomyopathy: an update on mechanisms and therapeutic targets*. American Journal of Physiology. 2018. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6138692/
69. Frati G, et al. *Cardiac fibrosis and the role of inflammation in diabetic cardiomyopathy*. International Journal of Molecular Sciences. 2020. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356220/
70. Paulus WJ & Tschöpe C. *A novel paradigm for HFpEF: comorbidities, endothelial dysfunction, and myocardial stiffness*. European Heart Journal. 2013. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3846095/
71. Cheng Y, et al. *Central role of cardiac fibroblasts in myocardial fibrosis of diabetic cardiomyopathy*. **Cardiac Research / review (open access)**. 2023.
72. Law B, et al. *Diabetes influences cardiac extracellular matrix remodeling after myocardial infarction and subsequent development of cardiac dysfunction*. **Journal / review (open access)**. 2012.
73. Chen Y, et al. *Distinct types of cell death and their implication in diabetic cardiomyopathy*. **Review, 2020 (PMC open access).**
74. Xu H, et al. *Types of cell death in diabetic cardiomyopathy*. **Review, 2024 (PMC open access).**
75. Tuleta I, et al. *Fibrosis of the diabetic heart: clinical significance, molecular mechanisms and cell biology*. **Review, 2021 (PMC open access).**
76. UK Prospective Diabetes Study (UKPDS) Group. BMJ, 1998.
77. Rena et al. *Diabetologia*, 2017.
78. Zinman et al. *N Engl J Med*, 2015 (EMPA-REG OUTCOME).
79. Marso et al. *N Engl J Med*, 2016 (LEADER Trial).
80. Verma & McMurray. *Lancet Diabetes & Endocrinology*, 2018.
81. Brenner et al. *N Engl J Med*, 2001.
82. Cholesterol Treatment Trialists' Collaboration. *Lancet*, 2010.
83. Bugger & Abel. *Circulation Research*, 2014.
84. McMurray et al. *Lancet*, 2020 (DAPA-HF Trial).
85. Paneni et al. *Circulation*, 2013.
86. American Diabetes Association. *Diabetes Care*, 2024 Standards of Care.
87. Zelniker et al. *Lancet*, 2019.
88. Rawshani et al. *N Engl J Med*, 2018.
89. Einarson et al. *Cardiovascular Diabetology*, 2018.
90. Raghavan et al. *BMJ*, 2019.