JOURNAL OF DIABETES RESEARCH AND MANAGEMENT
Jan-Jun 2025, VOL. 1, ISSUE 1, pp. 3-6
https://doi.org/10.61577/jdrm.2025.100002

RESEAPRO JOURNALS

REVIEW

OPEN ACCESS

Risk of cardiovascular complications in type 2 diabetes

Gary Hongoro

Department of Health Sciences, University of Pretoria, Pretoria, South Africa

ABSTRACT

Type 2 diabetes mellitus (T2DM) is a metabolic condition defined by insulin resistance, a relative lack of insulin, and elevated blood sugar levels. The worldwide incidence of T2DM has surged significantly over the past few decades, accompanied by a concerning rise in CVD among those impacted. Cardiovascular difficulties are the main reason for morbidity and mortality in T2DM, driven by an interplay of hyperglycemia, dyslipidemia, hypertension, and chronic inflammation. These factors contribute to accelerated atherosclerosis, endothelial dysfunction, and cardiomyopathy. Emerging evidence highlights the role of advanced glycation end products (AGEs), oxidative stress, and subclinical inflammation in the pathogenesis of cardiovascular complications in T2DM. Furthermore, traditional risk factors like obesity, smoking, and sedentary lifestyle synergize with diabetes-specific mechanisms, compounding the risk of CVD. This review explores the multifactorial mechanisms underlying the increased cardiovascular risk in T2DM and examines contemporary strategies for risk mitigation, including pharmacological therapies such as sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1RAs), and statins, as well as lifestyle interventions. Despite advancements in treatment, the burden of cardiovascular complications remains substantial, necessitating a comprehensive and individualized approach to management. Future research must focus on unraveling novel therapeutic targets and optimizing integrated care to reduce the cardiovascular burden in T2DM.

KEYWORDS

Type 2 Diabetes Mellitus (T2DM); Cardiovascular Disease (CVD); Insulin Resistance; Atherosclerosis; SGLT2 Inhibitors

ARTICLE HISTORY

Received 13 January 2025;
Revised 04 February 2025;
Accepted 11 February 2025

Introduction

T2DM is a worldwide health challenge, with an estimated 537 million adults affected worldwide in 2021. The condition is characterized by chronic hyperglycemia resulting from a combination of insulin resistance and inadequate compensatory insulin secretion. While diabetes management has traditionally focused on glycemic control to prevent microvascular complications such as retinopathy, nephropathy, and neuropathy, the macrovascular complications, particularly cardiovascular disease (CVD), have emerged as a dominant concern. CVD encompasses a spectrum of disorders, including coronary artery disease (CAD), stroke, heart failure, and peripheral artery disease (PAD), which collectively account for the majority of diabetes-related deaths [1].

The link between T2DM and cardiovascular complications is well-established. Epidemiological studies indicate that persons with T2DM have a two- to fourfold increased chance of CVD compared to their non-diabetic counterparts [2]. This risk continues even after adjustment for traditional risk factors such as hypertension, dyslipidemia, and smoking. Hyperglycemia, the hallmark of diabetes—exerts direct and indirect effects on the cardiovascular system, promoting atherogenesis, endothelial dysfunction, and myocardial damage [3]. Moreover, diabetes-specific mechanisms, including the development of progressive glycation end products (AGEs), chronic low-grade inflammation, and oxidative stress, further exacerbate cardiovascular risk [4].

Despite advances in pharmacotherapy and interventional cardiology, cardiovascular difficulties remain the main cause of mortality in T2DM [5]. This underscores the necessity for a deeper understanding of the pathophysiological mechanisms driving these complications and the development of more effective preventive and therapeutic strategies. The complexity of managing cardiovascular risk in T2DM is compounded by the heterogeneity of the disease, variations in patient profiles, and the coexistence of multiple comorbidities [6].

This review has provided a complete overview of the mechanisms underlying cardiovascular diseases in T2DM, with a focus on both traditional and diabetes-specific risk factors. It also discusses current and emerging strategies for risk reduction, emphasizing the importance of individualized care in mitigating the cardiovascular burden in this high-risk population. By highlighting the latest advances and gaps in knowledge, this article seeks to inform clinical trials and stimulate further study in this critical area.

Pathophysiological Mechanisms of Cardiovascular Complications in T2DM

Role of hyperglycemia

Chronic hyperglycemia has a pivotal character in the growth of cardiovascular complications in T2DM. Sustained raised glucose levels contribute to endothelial dysfunction, a key early event in atherogenesis. Endothelial cells exposed to high glucose

***Correspondence:** Dr. Gary Hongoro, Department of Health Sciences, University of Pretoria, Pretoria, South Africa, email: gary.hongoro@up.ac.za

undergo metabolic and structural changes, help in impairing nitric oxide (NO) production, increase vascular permeability, and improve leukocyte bond. Hyperglycemia also drives the formation of advanced AGEs, which cross-link with proteins and receptors, triggering inflammatory and pro-thrombotic pathways [7].

Recent research has identified specific molecular pathways linking hyperglycemia to cardiovascular damage. Studies have shown that hyperglycemia-induced activation of protein kinase C (PKC) isoforms contributes to vascular permeability and pro-inflammatory cytokine expression [8]. Additionally, hyperglycemia-induced epigenetic changes, including histone modifications and non-coding RNA expression, have emerged as novel contributors to vascular dysfunction in diabetes [9].

Dyslipidemia and atherogenesis

Diabetes-associated dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, and small, dense low-density lipoprotein (LDL) particles. These abnormalities accelerate atherogenesis by promoting LDL oxidation, foam cell formation, and plaque instability. The pro-inflammatory milieu in T2DM further exacerbates lipid deposition in arterial walls, contributing to coronary artery disease and stroke [10].

Emerging data suggest that targeting residual lipid risk beyond LDL cholesterol can further reduce cardiovascular events. For instance, therapies targeting apolipoprotein B (apoB) and lipoprotein(a) [Lp(a)] are under investigation for their potential to mitigate atherosclerotic risk in T2DM. Ongoing clinical trials, such as those evaluating antisense oligonucleotides for Lp(a) reduction, hold promise for addressing unmet needs in lipid management.

Hypertension and vascular stiffness

Hypertension frequently coexists with T2DM, amplifying cardiovascular risk. Mechanistically, insulin resistance and hyperglycemia induce vascular stiffness through increased collagen deposition and reduced elastin in arterial walls [11]. Activation of the renin-angiotensin-aldosterone system (RAAS) in T2DM also promotes vasoconstriction, sodium retention, and oxidative stress, contributing to elevated blood pressure and end-organ damage.

Recent investigations have highlighted the role of endothelial glycocalyx degradation in hypertension and vascular stiffness in diabetes. The glycocalyx, a protective layer on the endothelial surface, is disrupted in hyperglycemic states, leading to impaired mechanotransduction and heightened vascular tone [12]. Novel therapies aimed at glycocalyx restoration are being explored as potential strategies for improving vascular health in T2DM.

Oxidative stress and inflammation

Oxidative stress is a hallmark of T2DM and plays a central role in cardiovascular pathology. Excessive production of reactive oxygen species (ROS) in hyperglycemic states overwhelms endogenous antioxidant defenses, damaging cellular components such as lipids, proteins, and DNA [13]. Concurrently, chronic low-grade inflammation—characterized by elevated levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)—contributes to endothelial dysfunction, plaque formation, and myocardial injury [14].

Recent advances in understanding the interplay between oxidative stress and inflammation have revealed the potential of targeting mitochondrial dysfunction to alleviate cardiovascular complications. Mitochondria-targeted antioxidants, such as mitoquinone (MitoQ), are being investigated for their ability to attenuate ROS production and protect against cardiovascular damage in T2DM.

Clinical Manifestations of Cardiovascular Complications

Coronary Artery Disease (CAD)

CAD is the most common cardiovascular complication in T2DM, manifesting as stable angina, acute coronary syndromes, or silent ischemia. The latter is particularly prevalent in diabetes due to autonomic neuropathy, which blunts the perception of pain. Diabetic patients with CAD often present with extensive and diffuse coronary atherosclerosis, necessitating aggressive management.

Recent clinical trials, such as ISCHEMIA-CKD and THEMIS, have provided insights into optimizing CAD management in T2DM, emphasizing the need for personalized treatment approaches based on comorbidities and risk profiles [15].

Heart failure

Heart failure in T2DM is influenced by both ischemic and non-ischemic mechanisms. Diabetic cardiomyopathy, characterized by myocardial fibrosis, impaired contractility, and diastolic dysfunction, occurs independently of coronary artery disease [16]. Hyperglycemia-induced oxidative stress, RAAS activation, and advanced glycation contribute to myocardial remodeling and dysfunction.

Emerging evidence from studies like EMPEROR-Reduced and DAPA-HF highlights the efficacy of SGLT2 inhibitors in reducing heart failure hospitalizations and improving quality of life in diabetic patients [17]. These findings have expanded the therapeutic landscape for heart failure management in T2DM.

Stroke

T2DM significantly increases the risk of both ischemic and hemorrhagic stroke. Hyperglycemia exacerbates ischemic brain injury by impairing cerebral blood flow, promoting thrombogenesis, and inducing neuroinflammation [18]. The coexistence of hypertension, dyslipidemia, and atrial fibrillation further compounds stroke risk in diabetic individuals.

Recent advancements in stroke prevention include the development of anticoagulants with improved safety profiles and precision medicine approaches to identify high-risk patients based on genetic and biomarker data.

Peripheral Artery Disease (PAD)

PAD is a major macrovascular complication in T2DM, characterized by reduced blood flow to the extremities due to atherosclerosis. Symptoms range from intermittent claudication to critical limb ischemia, with a high risk of ulceration and

https://doi.org/10.61577/jdrm.2025.100002

amputation. The interplay of endothelial dysfunction, inflammation, and impaired angiogenesis underlies the pathogenesis of PAD in diabetes.

Innovative therapies, such as angiogenesis-stimulating agents and stem cell-based treatments, are under investigation for improving limb perfusion and reducing amputation rates in diabetic patients with PAD.

Emerging Risk Factors and Novel Insights

Gut microbiota and cardiovascular health

Recent research highlights the role of gut microbiota in modulating cardiovascular risk in T2DM. Dysbiosis, or imbalance in gut microbial composition, has been linked to systemic inflammation, insulin resistance, and atherogenesis [19]. Short-chain fatty acids (SCFAs) produced by gut microbes exert protective effects by reducing inflammation and improving endothelial function. Probiotics and prebiotics targeting gut health are being explored as adjunctive therapies for cardiovascular risk reduction.

Epigenetics and precision medicine

Epigenetic modifications, including DNA methylation, histone acetylation, and non-coding RNA regulation, are emerging as critical players in cardiovascular complications of T2DM [20]. Understanding these mechanisms offers opportunities for precision medicine approaches, enabling tailored interventions based on individual genetic and epigenetic profiles. Biomarkers derived from epigenetic studies are being developed for early detection and risk stratification.

Immune modulation

The immune system is a pivotal part of the inflammatory cascade contributing to cardiovascular damage in T2DM. By recent studies, it is known that definite immune cell subsets, like pro-inflammatory macrophages and Th17 cells, as key mediators of vascular inflammation. Therapies targeting these pathways, including monoclonal antibodies and immune checkpoint inhibitors, are being investigated for their potential to mitigate cardiovascular complications.

Risk Mitigation Strategies

Pharmacological interventions

Antihyperglycemic agents

SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have confirmed significant cardiovascular benefits in large-scale trials, reducing key adverse cardiovascular events (MACE) and heart attack hospitalizations [21].

Lipid-Lowering Therapies

Statins remain the foundation of lipid management in T2DM, with additional benefits observed with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Antihypertensive Medications

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are chosen for their cardioprotective effects in diabetic patients.

Lifestyle modifications

Lifestyle interventions, such as dietary changes, regular physical activity, and smoking cessation, are critical elements of cardiovascular risk reduction. Weight loss through calorie restriction and exercise improves insulin sensitivity, blood pressure, and lipid profiles, attenuating cardiovascular risk.

Recent studies have emphasized the role of plant-based diets and time-restricted feeding in improving metabolic and cardiovascular outcomes in T2DM. These dietary patterns reduce systemic inflammation and enhance glycemic control, offering additional cardioprotective benefits [22].

Integrated care models

Comprehensive care models that integrate diabetes and cardiovascular management have shown promise in improving outcomes. Multidisciplinary approaches involving endocrinologists, cardiologists, and primary care providers ensure personalized and holistic care, addressing the multifaceted needs of diabetic patients.

Digital health tools, like continuous glucose monitoring (CGM) and mobile health applications, are increasingly being utilized to enhance patient engagement and optimize care delivery [23]. These technologies provide real-time data for personalized decision-making, facilitating better glycemic and cardiovascular risk management.

Conclusions

Cardiovascular complications remain a significant challenge in the organization of type 2 diabetes mellitus. The interplay of hyperglycemia, dyslipidemia, hypertension, oxidative stress, and inflammation underscores the complexity of CVD in this population. Advances in pharmacological therapies and lifestyle interventions have improved outcomes, yet the residual risk of cardiovascular events highlights the need for continued innovation. Future research should focus on elucidating novel mechanisms, identifying high-risk individuals, and optimizing integrated care strategies to reduce the cardiovascular burden in T2DM. A proactive and individualized approach to management is essential to mitigate the profound impact of cardiovascular complications on the lives of diabetic patients.

Disclosure Statement

No potential conflict of interest was reported by the authors.

References

1. Nesto RW. Correlation between cardiovascular disease and diabetes mellitus: current concepts. Am J Med. 2004;116(5):11-22. https://doi.org/10.1016/j.amjmed.2003.10.016
2. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13 000 men and women with 20 years of follow-up. Arch Intern Med. 2004;164(13): 1422-1426. https://doi.org/10.1001/archinte.164.13.1422
3. Funk SD, Yurdagul Jr A, Orr AW. Hyperglycemia and endothelial dysfunction in atherosclerosis: lessons from type 1 diabetes. Int J Vasc Med. 2012;2012(1):569654. https://doi.org/10.1155/2012/569654
4. Yang P, Feng J, Peng Q, Liu X, Fan Z. Advanced glycation end products: potential mechanism and therapeutic target in cardiovascular complications under diabetes. Oxid Med Cell Longev.

https://doi.org/10.61577/jdrm.2025.100002

2019;2019(1):9570616. https://doi.org/10.1155/2019/9570616
5. Joseph JJ, Golden SH. Type 2 diabetes and cardiovascular disease: what next?. Curr Opin Endocrinol Diabetes Obes. 2014;21(2): 109-120. https://doi.org/10.1097/MED.0000000000000044
6. Martín-Timón I, Sevillano-Collantes C, Marfn-Penalver JJ, del Cañizo-Gómez FJ. Management of cardiovascular risk factors in type 2 diabetes mellitus patients. EmJ. 2016;1(4):89-97. Available at: https://www.emjreviews.com/wp-content/uploads/2018/01/Management-of-Cardiovascular-Risk-Factors-in-Type-2-Diabetes-Mellitus-Patients.pdf
7. Negre-Salvayre A, Salvayre R, Augé N, Pamplona R, Portero-Otin M. Hyperglycemia and glycation in diabetic complications. Antioxid Redox Signal. 2009;11(12):3071-3109. https://doi.org/10.1089/ars.2009.2484
8. Mapanga RF, Essop MF. Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways. Am J Physiol Heart Circ Physiol. 2016;310(2):H153-H173. https://doi.org/10.1152/ajpheart.00206.2015
9. Khullar M, Cheema BS, Raut SK. Emerging evidence of epigenetic modifications in vascular complication of diabetes. Front Endocrinol. 2017;8:237. https://doi.org/10.3389/fendo.2017.00237
10. Ray A, Huisman MV, Tamsma JT, Van Asten J, Bingen BO, Broeders EA, et al. The role of inflammation on atherosclerosis, intermediate and clinical cardiovascular endpoints in type 2 diabetes mellitus. Eur J Intern Med. 2009;20(3):253-260. https://doi.org/10.1016/j.ejim.2008.07.008
11. Hill MA, Yang Y, Sun Z, Zhang L, Sowers JR. Mechanisms underlying vascular stiffening in obesity, insulin resistance, and type 2 diabetes. InThe Science, Etiology and Mechanobiology of Diabetes and its Complications. 2021:63-88. Academic Press. https://doi.org/10.1016/B978-0-12-821070-3.00021-0
12. Sieve I, Münster-Kühnel AK, Hilfiker-Kleiner D. Regulation and function of endothelial glycocalyx layer in vascular diseases. Vascular pharmacology. 2018;100:26-33. https://doi.org/10.1016/j.vph.2017.09.002
13. Caturano A, Rocco M, Tagliaferri G, Piacevole A, Nilo D, Di Lorenzo G, etc. Oxidative Stress and Cardiovascular Complications in Type 2 Diabetes: From Pathophysiology to Lifestyle Modifications. Antioxidants. 2025;14(1):72. https://doi.org/10.3390/antiox14010072
14. Greig D, Castro P, Gabrielli L, Miranda R, Verdejo H, Alcaino H, et al. Inflammation and endothelial dysfunction in patients with chronic heart failure. Revista Médica de Chile. 2008;136(6): 687-693. https://doi.org//s0034-98872008000600001
15. Arnold SV, Bhatt DL, Barsness GW, Beatty AL, Deedwania PC, Inzucchi SE, et al. Clinical management of stable coronary artery disease in patients with type 2 diabetes mellitus: a scientific statement from the American Heart Association. Circulation. 2020; 141(19):e779-e806. https://doi.org/10.1161/CIR.0000000000000766
16. Aneja A, Tang WW, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. The American journal of medicine. 2008; 121(9):748-757. https://doi.org/10.1016/j.amjmed.2008.03.046
17. Raschi E, Fadini GP, Diemberger I, Poluzzi E, De Ponti F. SGLT2 inhibitors for heart failure with reduced ejection fraction: a real EMPEROR?. Expert Opin Pharmacother. 2021;22(5):647-650. https://doi.org/10.1080/14656566.2020.1846719
18. Desilles JP, Syvannarath V, Ollivier V, Journé C, Delbosc S, Ducroux C, et al. Exacerbation of thromboinflammation by hyperglycemia precipitates cerebral infarct growth and hemorrhagic transformation. Stroke. 2017;48(7):1932-1940. https://doi.org/10.1161/STROKEAHA.117.017080
19. Yoo JY, Sniffen S, McGill Percy KC, Pallaval VB, Chidipi B. Gut dysbiosis and immune system in atherosclerotic cardiovascular disease (ACVD). Microorganisms. 2022;10(1):108. https://doi.org/10.3390/microorganisms10010108
20. Khullar M, Cheema BS, Raut SK. Emerging evidence of epigenetic modifications in vascular complication of diabetes. Front Endocrinol. 2017;8:237. https://doi.org/10.3389/fendo.2017.00237
21. Goldman DM, Warbeck CB, Waterfall TJ, Sud A, Quarshie M, Craddock JC. Plant-based and early time-restricted eating for the prevention and treatment of type 2 diabetes in adults: A narrative review. Can J Diabetes. 2024. https://doi.org/10.1016/j.jcjd.2024.03.002
22. Shan R, Sarkar S, Martin SS. Digital health technology and mobile devices for the management of diabetes mellitus: state of the art. Diabetologia. 2019;62(6):877-887. https://doi.org/10.1007/s00125-019-4864-7

https://doi.org/10.61577/jdrm.2025.100002