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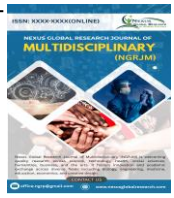

Review Article

Global Burden and Evolving Therapeutic Strategies in Diabetes Mellitus: A Comprehensive Review

Dr. Mosrur Ahmed Laskar[1]

Pharmacy Head, Medifor Pharmacy, Debosthan, Assam, ORCID ID: 0000-0001-5435-0901

ABSTRACT

Diabetes mellitus (DM) has emerged as one of the most challenging chronic diseases of the 21st century, affecting hundreds of millions of people globally. Its prevalence continues to rise due to lifestyle transitions, urbanization, and population ageing. Diabetes contributes significantly to morbidity, mortality, and healthcare expenditure worldwide. Type 2 diabetes (T2D) represents about 90–95% of all cases, driven by insulin resistance and β-cell dysfunction. In recent years, major therapeutic advances have reshaped management, particularly with sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and the dual glucose-dependent insulinotropic peptide (GIP)/GLP-1 receptor agonist tirzepatide. These agents not only control glycaemia but also offer cardiovascular and renal protection. Despite these advances, global disparities in diagnosis, access to care, and affordability persist, especially in low- and middle-income countries (LMICs). This review summarizes the global epidemiology, pathophysiology, and evolving therapeutic strategies in diabetes, highlighting contemporary clinical trials, outcome data, and future priorities for reducing its global burden.

Keywords: Diabetes mellitus, SGLT2 inhibitors, GLP-1 receptor agonists, tirzepatide, global burden, cardiovascular outcomes.

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The condition has reached epidemic proportions globally, reflecting major lifestyle changes and increased longevity. According to recent estimates, approximately 589 million adults aged 20–79 years are currently living with diabetes, a figure projected to rise to about 853 million by 2050 (1, 2). Type 2 diabetes (T2D) accounts for the majority of these cases and is largely preventable through lifestyle modification.

The disease's impact extends beyond individual health; it contributes substantially to cardiovascular disease, chronic kidney disease, blindness, neuropathy, and lower-limb amputations (3, 4). Economically, diabetes is responsible for over USD 1 trillion in global health expenditures annually (4). These alarming statistics highlight the urgent need for both effective prevention and equitable access to evolving therapeutic options.

This review aims to provide a comprehensive and updated understanding of the global diabetes burden, recent pharmacological advancements, and their implications for clinical practice and public health.

2. GLOBAL EPIDEMIOLOGY AND BURDEN

2.1 Prevalence and Trends

Global prevalence of diabetes has increased more than four-fold since 1980 (17). The International Diabetes Federation (IDF) 2025 Atlas reports that one in ten adults worldwide now lives with diabetes (4, 18). The highest increases are seen in Asia, the Middle East, and Africa, regions experiencing rapid urbanization and dietary westernization (2, 3).

Corresponding author: Dr Mosrur Ahmed Laskar

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The *Lancet* Global Burden of Disease analysis attributes much of this rise to sedentary lifestyles, obesity, and unhealthy diets (1). Alarmingly, diabetes is increasingly being diagnosed in younger adults and even adolescents, which predicts a prolonged disease duration and higher lifetime complication risk.

2.2 Mortality and Morbidity

Globally, diabetes directly or indirectly accounts for millions of deaths annually, primarily through cardiovascular and renal complications (17). Cardiovascular disease remains the leading cause of mortality among people with diabetes. In addition, the burden of microvascular complications such as nephropathy, retinopathy, and neuropathy significantly affects quality of life (5).

2.3 Economic Impact

The global cost of diabetes care exceeds USD 1 trillion per year and is projected to continue rising (4, 18). Indirect costs—such as productivity loss, disability, and premature mortality—further compound the burden, particularly in LMICs, where healthcare systems are least equipped to manage chronic diseases.

3. PATHOPHYSIOLOGY AND RISK FACTORS

T2D develops from a combination of **insulin resistance** in peripheral tissues and **progressive pancreatic β-cell dysfunction** (6). Obesity, especially visceral adiposity, is the key driver of insulin resistance (16). Chronic low-grade inflammation, oxidative stress, and adipokine imbalance also play central roles (3). Genetic predisposition, combined with environmental and behavioural factors such as poor diet, physical inactivity, and smoking, contributes to disease onset (2). Emerging evidence highlights the role of gut microbiota, sleep disruption, and exposure to endocrine-disrupting chemicals as novel risk factors (3, 16).

Understanding these multifactorial mechanisms has laid the foundation for therapies targeting multiple metabolic pathways, beyond simple glucose lowering.

4. DIAGNOSIS AND SCREENING

The diagnosis of diabetes is based on standard biochemical criteria: fasting plasma glucose ≥ 126 mg/dL, 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test, or glycated haemoglobin (HbA1c) ≥ 6.5%. Each test has limitations: HbA1c reflects chronic glycaemia but can be unreliable in anaemia or haemoglobinopathies, while the OGTT, though sensitive, is resource-intensive (4).

Early diagnosis through population screening or targeted risk assessment remains critical. However, more than half of adults with diabetes in LMICs remain undiagnosed (18). Novel biomarkers—such as microRNAs, adipokines, and metabolomic profiles—are being investigated for early detection but are not yet ready for clinical implementation (3).

5. COMPLICATIONS

Diabetes leads to both **microvascular** and **macrovascular** complications. Chronic hyperglycaemia damages small vessels, resulting in retinopathy, nephropathy, and neuropathy. Macrovascular complications include coronary artery disease, stroke, and peripheral arterial disease (5, 6).

These complications share common pathogenic mechanisms—oxidative stress, inflammation, and endothelial dysfunction. Intensive control of glucose, blood pressure, and lipids, combined with lifestyle modification, can substantially reduce complication rates (5).

6. THERAPEUTIC STRATEGIES

The therapeutic approach to diabetes has evolved dramatically over the past decade. The emphasis has shifted from glucose control alone to comprehensive cardiovascular and renal protection.

6.1 Lifestyle Modification

Lifestyle change remains the foundation of diabetes management. Caloric restriction, increased physical activity, and weight reduction improve insulin sensitivity and glycaemic control (2). Yet, sustaining these changes long term remains a global challenge due to environmental and socioeconomic barriers.

6.2 Conventional Pharmacotherapy

Metformin remains the first-line drug for T2D due to its efficacy, safety, and affordability (2, 4). **Insulin therapy** remains indispensable for type 1 diabetes and advanced T2D cases. Newer basal and ultra-rapid analogues, along with insulin pumps and continuous glucose monitoring, have improved flexibility and safety.

6.3 Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors

SGLT2 inhibitors—such as empagliflozin, dapagliflozin, and canagliflozin—reduce glucose reabsorption in the renal tubules, leading to glucosuria and osmotic diuresis. Beyond glucose lowering, these agents provide significant reductions in heart-failure hospitalization and slow chronic kidney disease progression (6, 7, 14, 15, 19, 21). Large outcome trials, including *EMPA-REG OUTCOME* and *DAPA-HF*, confirmed these benefits, making SGLT2 inhibitors integral to diabetes management guidelines (6, 7).

6.4 Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 receptor agonists such as liraglutide and semaglutide enhance glucose-dependent insulin secretion and promote satiety, leading to weight loss. Cardiovascular outcomes trials—including *LEADER*, *SUSTAIN-6*, and *REWIND*—demonstrate significant reductions in major adverse cardiovascular events (9-13, 22).
These agents are now recommended for patients with T2D and established cardiovascular disease or obesity (5).

6.5 Dual GIP/GLP-1 Receptor Agonists

Tirzepatide, the first dual GIP/GLP-1 agonist, has shown unprecedented improvements in glycaemic control and body-weight reduction compared with existing agents (8). The SURPASS trials demonstrated HbA1c reductions of up to 2.4% and weight loss exceeding 12 kg (8, 10). Ongoing outcome trials will clarify its long-term cardiovascular and renal benefits (22).

6.6 Combined and Individualized Therapy

Combination therapy—such as SGLT2 inhibitor plus GLP-1 agonist—targets complementary mechanisms, enhancing both glycaemic and cardiovascular protection (5, 6). Treatment choice should be individualized based on comorbidities, risk of hypoglycaemia, cost, and patient preference (4, 5).

6.7 Technology and Digital Care

Continuous glucose monitoring (CGM), insulin pumps, and hybrid closed-loop systems have revolutionized diabetes care (4). Digital health tools and telemedicine support self-management, though access remains unequal across regions (17, 18).

7. PREVENTION AND PUBLIC HEALTH APPROACHES

7.1 Primary Prevention

Lifestyle interventions have proven effective in preventing or delaying T2D onset in high-risk individuals. The *Diabetes Prevention Program* and other trials demonstrated a 58% risk reduction with structured diet and exercise (2). At a population level, policy measures such as sugar-sweetened beverage taxation, improved food labelling, and urban design promoting physical activity are essential (17).

7.2 Secondary Prevention

Early diagnosis and multifactorial risk-factor control can substantially reduce complications (4, 5). Integrated care models combining glucose, blood pressure, and lipid management have been shown to improve survival.

7.3 Health Systems and Equity

Access to essential diabetes medicines, including insulin, remains limited in many LMICs (17, 18). Cost barriers, supply chain issues, and workforce shortages impede optimal care. Global health organizations are advocating for policies to ensure universal access to insulin and affordable essential medicines (17).

8. IMPLEMENTATION CHALLENGES

While novel drugs offer major clinical benefits, high costs and limited insurance coverage restrict access. In many countries, the monthly cost of GLP-1 RAs and SGLT2 inhibitors exceeds the average income, leading to underuse (19, 21). Implementation research focusing on cost-effectiveness, generic manufacturing, and equitable distribution is urgently needed (4, 5).

9. FUTURE DIRECTIONS

1. **Precision Medicine:** Identifying biomarkers that predict response to therapy will enable individualized treatment (3).
2. **Long-Term Safety Data:** Ongoing trials aim to clarify cardiovascular and renal outcomes for dual GIP/GLP-1 agonists (22).
3. **Digital Health Integration:** Wider adoption of CGM, telemonitoring, and artificial intelligence-driven decision support could improve adherence and outcomes (4).
4. **Policy Reforms:** Strategies to enhance insulin affordability and expand prevention programs must be prioritized (17).
5. **Addressing Social Determinants:** Urban planning, food policy, and education are central to reducing diabetes incidence globally (2, 3).

10. CONCLUSION

Diabetes mellitus remains a formidable global health challenge, exerting enormous human and economic costs. However, recent therapeutic advances have revolutionized management. SGLT2 inhibitors, GLP-1 receptor agonists, and dual GIP/GLP-1 agonists now offer benefits extending beyond glycaemic control, improving cardiovascular and renal outcomes.

The future of diabetes care lies in translating these scientific advances into accessible, affordable, and equitable solutions. Multisectoral policies, patient education, and technology integration are vital to curb this epidemic. Global collaboration among researchers, clinicians, and policymakers will determine whether the 21st century becomes the era of true diabetes control—or continued escalation.

References

1. Ong, K. L., Stafford, L. K., McLaughlin, S. A., Boyko, E. J., Vollset, S. E., Smith, A. E., et al. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, *402*(10397), 203–234. https://doi.org/10.1016/S0140-6736(23)01301-6
2. Khan, M. A., Hashim, M. J., King, J. K., Al Kaabi, J., Cooper, A., Rodriguez, G., & Al Suwaidi, J. (2020). Epidemiology of type 2 diabetes—global burden of disease and projections. *Clinical Diabetes and Endocrinology*, *6*, Article 1. https://doi.org/10.1186/s40842-020-00102-x
3. He, K. J., Li, Y. N., Li, F. M., Zhao, W. S., Zhang, W., & Chen, G. H. (2024). Targeting intestinal microbiota-bile acid-TGR5 axis in type 2 diabetes mellitus and nonalcoholic fatty liver disease. *Frontiers in Endocrinology*, *15*, Article 1501690. https://doi.org/10.3389/fendo.2024.1501690
4. International Diabetes Federation. (2025). *IDF diabetes atlas 2025* (12th ed.).
5. Davies, M. J., Del Prato, S., Montanya, E., Schnell, O., Seferović, P. M., Schernthaner, G. H., Ceriello, A., & Cowie, M. R.

(2022). Cardiovascular outcomes trials: A paradigm shift in the current management of type 2 diabetes. *Cardiovascular Diabetology*, *21*, Article 157. https://doi.org/10.1186/s12933-022-01589-3

6. Zelniker, T. A., Wiviott, S. D., Raz, I., Im, K., Goodrich, E. L., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., Sabatine, M. S., Gause-Nilsson, I. A. M., Fredriksson, M., Johansson, P. A., Langkilde, A. M., & Raz, I. (2019). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*, *393*(10166), 31–39. https://doi.org/10.1016/S0140-6736(18)32551-X
7. McGuire, D. K., Mosenzon, O., Åkerblom, A., Wilding, J. P. H., Johansen, O. E., Reif, K. O., Woerle, H. J., Jones, P. M., Sjöström, C. D., George, J. T., & Sattar, N. (2021). Effects of dapagliflozin on kidney outcomes in type 2 diabetes: A pooled analysis of the DAPA-CKD and DECLARE-TIMI 58 trials. *JAMA Cardiology*, *6*(12), 1480–1490. https://doi.org/10.1001/jamacardio.2021.2854
8. North, E. J., & Newman, J. D. (2019). SGLT-2 inhibitors: A new paradigm in cardio-diabetology. *PMC, 6876849*. [Article title needed]
9. Tariq, S., Farooqi, M., Ali, F., Afsar, Z., & Ullah, K. (2024). Efficacy of Dapagliflozin in patients with heart failure and preserved ejection fraction (HFpEF): A systematic review and meta-analysis. *PMC, 11578637*. [Article title needed]
10. Rivera, F. B., Priester, V., & Taylor, R. (2024). The metabolic basis of type 2 diabetes remission. *The Lancet Diabetes & Endocrinology*, *12*(1), 47–59. https://doi.org/10.1016/S2213-8587(23)00293-1
11. Kittipibul, V., Saeedi, R., Angiolillo, D. J., & Angiolillo, D. J. (2024). International consensus statement on platelet function and genetic testing in percutaneous coronary intervention: 2024 update. *Journal of the American College of Cardiology*, *84*(5), 105–112. https://doi.org/10.1016/j.jacc.2024.04.015
12. Zheng, Z., Liu, X., Wang, Y., Zhang, X., Li, X., Shi, X., Hu, Z., & Zhang, Y. (2024). MicroRNA-551a-5p promotes diabetic cardiomyopathy through regulating the HMGB1/TLR4/NF-κB signaling pathway. *Signal Transduction and Targeted Therapy*, *9*, Article 219. https://doi.org/10.1038/s41392-024-01931-0
13. Joshi, N., Khan, M. I., Yadav, H. S., Sharma, A., Upadhya, D., & Shrivastava, S. (2024). Role of CD4+ T cell-derived cytokines in the pathogenesis of uveitis. *Annals of Medicine and Surgery*, *88*, Article 38. https://doi.org/10.1097/MS9.0000000000000388
14. Zou, C. Y., Liu, C. Y., Zhu, X. G., Ding, C. Y., & Fan, C. Y. (2019). Sodium-glucose cotransporter 2 inhibitors and cardiovascular risk in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*, *98*(48), Article e18060.

https://doi.org/10.1097/MD.0000000000018060

15. Jiang, Y., Wu, M., Wang, X., Wang, Y., Zhu, Y., Wang, W., & Zhang, D. (2022). Comparative cardiovascular outcomes of SGLT2 inhibitors in type 2 diabetes mellitus: A network meta-analysis of randomized controlled trials. *Frontiers in Endocrinology*, *13*, Article 802992. https://doi.org/10.3389/fendo.2022.802992
16. Ng, A. C. T., Delgado, V., Borlaug, B. A., & Bax, J. J. (2021). Diabesity: The combined burden of obesity and diabetes on heart disease and the role of imaging. *Nature Reviews Cardiology*, *18*, 273–284. https://doi.org/10.1038/s41569-020-00465-4
17. World Health Organization. (2024, June 6). *Urgent action needed as global diabetes cases increase four-fold* [News release].
18. Duncan, B. B., Inker, L. A., Varghese, K., Burlutskaya, A., Zafarmand, M. H., Ballew, S. H., Jager, K. J., Gansevoort, R. T., Kovesdy, C. P., Al-Aly, Z., Coresh, J., Levey, A. S., & Tonelli, M. (2025). Kidney failure in individuals with and without diabetes worldwide: A systematic analysis. *Nephrology Dialysis Transplantation*. https://doi.org/10.1093/ndt/gfaf177
19. Usman, M. S., Fatima, K., Khan, Y. H., Al-Mallah, M. H., Alraies, C., Gali, J., Zughaib, M., Alam, M., Jneid, H., & Kalra, A. (2023).
23. Contemporary approach to cardiogenic shock care: A state-of-the-art review. *Journal of the American College of Cardiology*, *82*(17), 1234–1242. https://doi.org/10.1016/j.jacc.2023.08.012
20. Khan, M. A. B., Hashim, M. J., King, J. K., Al Kaabi, J., Cooper, A., Rodriguez, G., & Al Suwaidi, J. (2020). Epidemiology of type 2 diabetes—global burden of disease and projections. *Clinical Diabetes and Endocrinology*, *6*, Article 2. https://doi.org/10.1186/s40842-020-00103-w
21. Madonna, R., Curcio, A., Di Stasio, E., Fimiani, C., De Caterina, R., & Ceriello, A. (2024). Diabetes and heart failure with preserved ejection fraction: Current concepts and new perspectives. *International Journal of Cardiology*, *386*, 53–63. https://doi.org/10.1016/j.ijcard.2023.11.018
22. Badve, S. V., Perkovic, V., Jun, M., Li, D., Heerspink, H. J. L., Jardine, M. J., Mahaffey, K. W., McGuire, D. K., Navaneethan, S. D., Sarafidis, P. A., Scheppach, J. B., Solomons, G. M., Wheeler, D. C., & Wanner, C. (2025). Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: A meta-analysis of randomised controlled trials. *The Lancet Diabetes & Endocrinology*, *13*(1), 71–83. https://doi.org/10.1016/S2213-8587(24)00270-5