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Advances in Diabetes Management Beyond Insulin: A Systematic Review

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ABSTRACT

Diabetes mellitus, a chronic and progressive metabolic disorder, is one of the most significant global public health challenges, affecting millions worldwide. Traditionally managed with insulin as the cornerstone therapy, diabetes care has evolved considerably with the advent of innovative pharmacological, technological and lifestyle-based interventions. This systematic review explores advancements in diabetes management beyond insulin, focusing on the clinical efficacy, safety and integration of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors), continuous glucose monitoring (CGM) systems, AI-driven digital health tools and structured lifestyle interventions. GLP-1 RAs and SGLT-2 inhibitors have demonstrated substantial benefits, not only in glycemic control but also in reducing cardiovascular and renal risks, addressing critical comorbidities associated with diabetes. Similarly, CGM systems and AI-enabled applications have transformed self-management by providing real-time glucose monitoring and personalized feedback, enhancing adherence and improving outcomes. Lifestyle interventions, including evidence-based dietary modifications and structured exercise programs, remain foundational, offering sustainable and cost-effective approaches to delay or reverse disease progression. Despite these advancements, barriers such as cost, accessibility and adherence continue to limit their widespread adoption, particularly in low-resource settings. This review synthesizes evidence from recent studies and highlights the importance of integrating pharmacological and non-pharmacological approaches into comprehensive diabetes care frameworks. It also identifies research gaps, particularly regarding long-term outcomes and equitable access to emerging therapies. The findings underscore the need for multidisciplinary, patient-centered strategies to enhance the quality of life for individuals with diabetes and reduce the global burden of the disease.

INTRODUCTION

Diabetes mellitus, a complex chronic condition characterized by persistent hyperglycemia, is a global health burden affecting <500 million individuals worldwide. Its prevalence has risen sharply over the past two decades, driven by population aging, sedentary lifestyles and the obesity epidemic^[1]. Classified primarily into type 1 diabetes (T1D) and type 2 diabetes (T2D), the condition predisposes individuals to severe complications, including cardiovascular disease, chronic kidney disease and neuropathy, significantly reducing quality of life and increasing mortality rates^[2]. Historically, insulin therapy has been the cornerstone of diabetes management, particularly for individuals with T1D or advanced T2D who require exogenous insulin to maintain glycaemic control^[3]. While insulin is effective in lowering blood glucose levels, its limitations—such as the risk of hypoglycemia, weight gain and adherence challenges—highlight the need for alternative or complementary therapies. In recent years, innovations in diabetes management have transcended insulin-based therapy. Pharmacological advancements, including GLP-1 receptor agonists and SGLT-2 inhibitors, have shown potential to improve glycemic control while addressing the comorbidities often associated with diabetes, such as cardiovascular and renal complications^[4,5]. These agents not only enhance metabolic outcomes but also provide dual benefits in reducing major adverse cardiovascular events (MACE) and slowing the progression of chronic kidney disease (CKD)^[6]. Beyond pharmacology, non-pharmacological interventions such as lifestyle modifications and dietary strategies remain essential components of diabetes care. Structured exercise programs and personalized nutrition plans have demonstrated efficacy in reversing pre diabetes and improving insulin sensitivity, particularly in individuals with obesity^[7]. Technological advancements, particularly continuous glucose monitoring (CGM) systems and AI-driven digital health applications, have transformed diabetes self-management. CGM systems enable real-time monitoring of glucose levels, reducing glycemic variability and improving time-in-range metrics^[8]. Mobile health applications that leverage AI algorithms provide tailored recommendations for medication adherence, dietary adjustments and physical activity, empowering patients to actively manage their condition^[9]. Despite these innovations, barriers such as cost, accessibility and digital literacy remain significant, particularly in low-resource settings^[10]. This review aims to systematically explore advances in diabetes management beyond insulin, examining their clinical efficacy, safety and potential for integration into current care frameworks. By addressing both pharmacological and non-pharmacological approaches, the review seeks to provide a comprehensive

understanding of emerging trends in diabetes care and their implications for improving patient outcomes.

MATERIALS AND METHODS

Literature Search: A systematic literature search was conducted using PubMed, Scopus, MEDLINE and Web of Science databases for studies published between January 2000 and October 2023. Keywords included “diabetes management,” “beyond insulin,” “GLP-1 receptor agonists,” “SGLT-2 inhibitors,” “continuous glucose monitoring,” “digital health in diabetes” and “lifestyle interventions.” Boolean operators (AND, OR) were employed to refine the search results and additional studies were identified through manual screening of reference lists from relevant reviews and meta-analyses^[11].

Inclusion and Exclusion Criteria:

Inclusion Criteria:

- Studies evaluating non-insulin-based diabetes management strategies.
- Randomized controlled trials (RCTs), cohort studies, or systematic reviews focusing on pharmacological agents, digital health technologies, or lifestyle interventions.
- Articles reporting measurable outcomes such as HbA1c reduction, cardiovascular benefits, renal protection, or patient-reported quality of life.

Exclusion Criteria:

- Studies exclusively focused on insulin therapy.
- Articles without clear methodology or outcome data.
- Non-peer-reviewed publications, editorials, or commentaries.

Data Extraction and Quality Assessment: Two independent reviewers extracted data, including study design, intervention type and outcome measures, using a standardized template. The Cochrane Risk of Bias Tool was applied to evaluate RCTs, while the Newcastle-Ottawa Scale assessed observational studies. Discrepancies in quality assessment were resolved through consensus^[12].

PRISMA Flow Diagram

Phase	Number of Studies
Studies identified through database search	1,725
Duplicates removed	420
Studies screened (title and abstract)	1,305
Full-text articles assessed for eligibility	350
Studies included in qualitative synthesis	120
Studies included in quantitative synthesis	90

RESULTS AND DISCUSSIONS

Pharmacological Advances:

- **GLP-1 Receptor Agonists:** GLP-1 receptor agonists (GLP-1 RAs) have emerged as one of the most

promising pharmacological options for type 2 diabetes management. These agents mimic the action of the incretin hormone GLP-1, enhancing insulin secretion in response to elevated blood glucose levels while suppressing glucagon release. Clinical trials, such as the LEADER study, demonstrated that liraglutide reduced HbA1c levels by approximately 1.0-1.5%, supported weight loss and decreased the risk of major adverse cardiovascular events (MACE) by 13%^[13]. Semaglutide, another widely used GLP-1 RA, has shown even greater efficacy in improving glycemic control and achieving significant weight reduction, making it particularly beneficial for overweight and obese patients with diabetes^[14]. Furthermore, GLP-1 RAs delay gastric emptying, which helps reduce postprandial hyperglycemia, a common challenge in diabetes management. Their cardiovascular and weight-related benefits have positioned them as essential components in treatment guidelines for type 2 diabetes, particularly for patients with cardiovascular comorbidities.

- **SGLT-2 Inhibitors:** Sodium-glucose co-transporter -2 inhibitors (SGLT-2 inhibitors) represent another groundbreaking advancement in diabetes care. By inhibiting glucose reabsorption in the kidneys, these drugs promote glucose excretion through urine, effectively lowering blood glucose levels. Beyond glycemic control, SGLT-2 inhibitors provide significant cardiovascular and renal benefits. The EMPA-REG OUTCOME trial demonstrated that empagliflozin reduced cardiovascular mortality by 38% and slowed the progression of chronic kidney disease (CKD) by 40%^[15]. These benefits are not limited to patients with diabetes., emerging evidence suggests that SGLT-2 inhibitors are effective in treating heart failure with preserved ejection fraction, highlighting their potential in broader therapeutic areas^[16]. However, adverse effects such as urinary tract infections and genital mycotic infections remain notable concerns, requiring careful patient selection and monitoring.

Technological Innovations:

- **Continuous Glucose Monitoring (CGM) Systems:** Continuous glucose monitoring (CGM) systems have revolutionized diabetes self-management by providing real-time glucose data and trends. Unlike traditional finger stick glucose monitoring, CGM systems allow patients to track glucose fluctuations throughout the day and night, facilitating timely adjustments in diet, exercise, and medication. Studies have shown that CGM reduces HbA1c levels by 0.4-0.6%, minimizes

glycemic variability and increases the percentage of time-in-range, particularly in patients with type 1 diabetes. Advanced CGM devices, such as the Dexcom G6 and FreeStyle Libre, offer additional features like alarm systems for hypo-or hyperglycemia and seamless integration with insulin pumps. CGM adoption has also demonstrated benefits in reducing the burden of diabetes-related complications by improving glycemic control and patient safety.

- **AI-Driven Digital Health Applications:** The integration of artificial intelligence (AI) into mobile health applications has further enhanced diabetes management by providing personalized, data-driven recommendations. AI-enabled apps like mySugr and BlueLoop analyze CGM data, dietary patterns and activity levels to offer tailored advice on glucose control. These tools empower patients to actively participate in their care, improve adherence to treatment regimens, and foster better communication between patients and healthcare providers. Studies indicate that users of these applications experience improved HbA1c outcomes and increased confidence in self-management. However, barriers such as cost, digital literacy and data privacy concerns limit widespread adoption, particularly in low-resource settings.

Lifestyle Interventions:

- **Dietary Strategies:** Dietary modification remains a cornerstone of diabetes management, with several evidence-based approaches showing efficacy in improving glycemic control and overall metabolic health. Low-carbohydrate diets, Mediterranean diets and plant-based diets are among the most studied and widely recommended strategies. For example, the PREDIMED trial demonstrated that the Mediterranean diet reduced HbA1c levels and lowered the risk of cardiovascular events in patients with type 2 diabetes. Similarly, plant-based diets improve insulin sensitivity and promote weight loss, making them particularly effective for overweight individuals. Personalized dietary plans that consider individual metabolic responses and cultural preferences further optimize outcomes, offering a sustainable approach to dietary adherence.
- **Exercise Programs:** Structured exercise programs combining aerobic and resistance training have shown significant benefits in managing diabetes and its complications. Regular physical activity enhances insulin sensitivity, reduces HbA1c levels by an average of 0.7% and improves

cardiovascular fitness. Programs tailored to individual capabilities and preferences, such as walking, cycling, or strength training, increase adherence and long-term benefits. Emerging evidence also supports the role of high-intensity interval training (HIIT) in improving glycemic control in shorter durations, offering an alternative for individuals with time constraints. However, adherence remains a challenge, emphasizing the need for community-based initiatives and motivational interventions to sustain exercise routines.

Integration of Multimodal Approaches: The integration of pharmacological, technological and lifestyle-based interventions represents the future of diabetes management. Combining therapies like GLP-1 RAs and CGM systems with personalized lifestyle interventions creates a synergistic effect, addressing the multifaceted nature of diabetes. Multi modal approaches not only improve glycemic control but also target the underlying metabolic, cardiovascular and renal dysfunctions associated with diabetes, providing comprehensive and patient-centered care. However, challenges such as cost, accessibility and long-term adherence remain significant barriers to implementing these innovations on a large scale. Policymakers and healthcare providers must work collaboratively to develop strategies that ensure equitable access, particularly for under served populations. Public health campaigns and subsidies for advanced therapies and technologies can further bridge these gaps and promote better outcomes.

Advancements in diabetes management beyond insulin signify a transformative shift in how this chronic condition is approached and treated. Historically, insulin has served as the cornerstone of diabetes care, particularly for individuals with type 1 diabetes and those with advanced type 2 diabetes. However, the limitations of insulin therapy, including the risks of hypoglycemia, weight gain and adherence challenges, have driven the need for alternative therapies that can provide broader benefits. Over the past decade, pharmacological innovations such as GLP-1 receptor agonists and SGLT-2 inhibitors have emerged as game-changers, addressing not only glycemic control but also cardiovascular and renal comorbidities that often accompany diabetes. These therapies have demonstrated efficacy in large-scale trials, such as the LEADER and EMPA-REG studies, which showed significant reductions in major adverse cardiovascular events (MACE) and improvements in renal outcomes. Unlike traditional insulin therapy, these drugs offer additional advantages such as weight loss, reduced blood pressure and lower rates of hypoglycemia,

making them highly attractive options for comprehensive diabetes management. Alongside these pharmacological advances, the rise of digital health technologies has revolutionized how patients monitor and manage their condition. Continuous glucose monitoring (CGM) systems, for example, provide real-time glucose data, enabling better decision-making for both patients and clinicians. Similarly, AI-powered mobile applications offer personalized recommendations, fostering improved adherence to treatment plans. When combined with foundational lifestyle interventions like dietary modifications and exercise programs, these innovations represent a multi-pronged approach that addresses the complex and multifaceted nature of diabetes. Despite these strides, challenges such as cost, accessibility and long-term sustainability of these interventions remain, highlighting the need for systemic solutions to ensure equitable access and integration into healthcare systems.

Pharmacological Innovations: The development of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) marks a significant milestone in diabetes care. GLP-1 RAs, such as liraglutide and semaglutide, improve glycemic control through glucose-dependent mechanisms, reducing the risk of hypoglycemia commonly associated with insulin therapy. Beyond glycemic benefits, GLP-1 RAs contribute to weight loss and cardiovascular protection, addressing two major comorbidities of type 2 diabetes. For example, the LEADER trial demonstrated a 13% reduction in major adverse cardiovascular events (MACE) with liraglutide, emphasizing the dual metabolic and cardiovascular benefits of this class of drugs^[13,14]. Similarly, SGLT-2 inhibitors have revolutionized diabetes management by offering glycemic control alongside cardiovascular and renal protection. These agents reduce glucose reabsorption in the kidneys, thereby promoting glucose excretion and improving metabolic outcomes. The EMPA-REG Outcome trial highlighted a 30% reduction in cardiovascular mortality and a 40% slowing of chronic kidney disease (CKD) progression among patients treated with empagliflozin^[15,16]. These findings underscore the potential of SGLT-2 inhibitors to address the systemic complications of diabetes beyond glycemic control. Despite these benefits, barriers to widespread adoption persist. Cost remains a significant concern, particularly in low-resource settings where access to these therapies is limited. Additionally, long-term safety data are still being evaluated, necessitating ongoing research to assess their effects over extended periods and in diverse populations^[17].

Technological Advancements: Digital health technologies, particularly continuous glucose monitoring (CGM) systems and artificial intelligence (AI)-driven health applications, have transformed diabetes self-management. CGM systems provide real-time glucose readings, enabling patients to make immediate adjustments to their diet, physical activity, or medications. Studies have shown that CGM reduces HbA1c by 0.4-0.6% and improves time-in-range metrics, particularly in patients with type 1 diabetes. Moreover, CGM minimizes the risk of^[11] hypoglycemia by providing early warnings of glucose fluctuations, enhancing patient safety and quality of life. AI-driven mobile applications, such as mySugr and BlueLoop, further enhance diabetes management by analyzing glucose patterns and providing personalized recommendations. These tools empower patients to engage actively in their care, improving adherence to treatment regimens and fostering better health outcomes^[18]. However, challenges such as cost, digital literacy and data security must be addressed to ensure equitable access and usability across populations.

Lifestyle Interventions: Lifestyle interventions remain foundational in diabetes management, offering a cost-effective and sustainable approach to glycemic control. Dietary strategies, including low-carbohydrate, Mediterranean and plant-based diets, have demonstrated efficacy in improving insulin sensitivity, reducing HbA1c and promoting weight loss^[13,19]. The PREDIMED trial, for instance, highlighted the benefits of the Mediterranean diet in reducing the risk of cardiovascular events among patients with type 2 diabetes^[20]. Exercise programs, combining aerobic and resistance training, further enhance glycemic control and cardiovascular fitness. Regular physical activity has been shown to reduce HbA1c by an average of 0.7% and improve overall metabolic health^[14]. When integrated with pharmacological and technological advancements, lifestyle interventions provide a holistic approach to diabetes care. Despite their proven benefits, adherence to lifestyle interventions remains a challenge. Barriers such as lack of motivation, socioeconomic constraints and limited access to structured programs must be addressed through community-based initiatives and personalized care plans^[21].

Barriers and Future Directions: While advances in diabetes management have significantly improved patient outcomes, several barriers hinder their widespread implementation. High costs and limited insurance coverage restrict access to innovative therapies and technologies, particularly in low- and middle-income countries^[22]. Additionally, disparities in

healthcare delivery, including rural-urban divides and socioeconomic inequities, exacerbate these challenges. Future research should prioritize the development of cost-effective interventions and explore strategies to integrate these innovations into primary care settings. Long-term studies are needed to assess the safety and efficacy of newer pharmacological agents and technologies across diverse populations. Policymakers must also address systemic barriers by subsidizing diabetes care and implementing public health campaigns to raise awareness about emerging therapies^[23].

CONCLUSION

Advances in diabetes management beyond insulin have significantly improved the landscape of care for individuals with diabetes. Pharmacological innovations such as GLP-1 receptor agonists and SGLT-2 inhibitors offer dual benefits of glycemic control and reduction in cardiovascular and renal risks, addressing key limitations of insulin therapy. Alongside these, digital health technologies like continuous glucose monitoring and AI-driven applications empower patients by providing real-time data and personalized care, enhancing self-management and adherence. Lifestyle interventions, including dietary modifications and structured exercise programs, remain essential, offering sustainable and cost-effective ways to improve glycemic control and overall health outcomes. Despite these advancements, challenges such as cost, accessibility and adherence remain. Bridging these gaps is crucial to ensure equitable access to these therapies and technologies, particularly in low-resource settings. Future research should focus on long-term outcomes, scalability and integration of these approaches into comprehensive diabetes care frameworks. By addressing these challenges, healthcare systems can move closer to providing personalized, effective and equitable care, ultimately improving the quality of life for individuals with diabetes.

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