REVIEW PAPER

Optimizing Glycemic Control Through Chronotherapy: A Review

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder with prolonged hyperglycemia due to irregular insulin production or action. It is a global health challenge, linked to cardiovascular disorders, neuropathy, nephropathy, and retinopathy, increasing morbidity, mortality, and healthcare costs. Managing diabetes involves oral hypoglycemics, insulin therapy, and lifestyle changes. AI-assisted precision systems aid glucose monitoring, and smart insulin technologies enhance glycemic control and compliance.

Objective: This review aims to explore the pathophysiology of Diabetes Mellitus in relation to circadian rhythm disruption, assess recent and emerging therapeutic strategies, and highlight the potential of Chronotherapeutic drug delivery in enhancing diabetes management.

Concept of Chronotherapy: Chronotherapy is about timing medical treatment to match the body's natural rhythms. This helps give medicine at the best times of the day. It makes the treatment work better and reduces side effects. Chronotherapeutics are novel clock-based DDS.

Key finding and Implication: Human body works on rhythm which is called circadian rhythm. The disruption of these rhythms impacts the metabolism of carbohydrates, lipids, and proteins, as well as insulin sensitivity and hormonal cycles. Implementing chronotherapy-based strategies enhances better glycemic control, reduces side effects like hypoglycemia, and boosts patient adherence. The use of novel technologies such as AI, wearable devices, and personalized medicine further strengthens the potential of time-based therapies. Nonetheless, patient variability and the absence of large-scale clinical trials pose challenges that need to be addressed for wider clinical adoption.

Keywords: Diabetes Mellitus, hyperglycaemia, glycemic control, Biological rhythm

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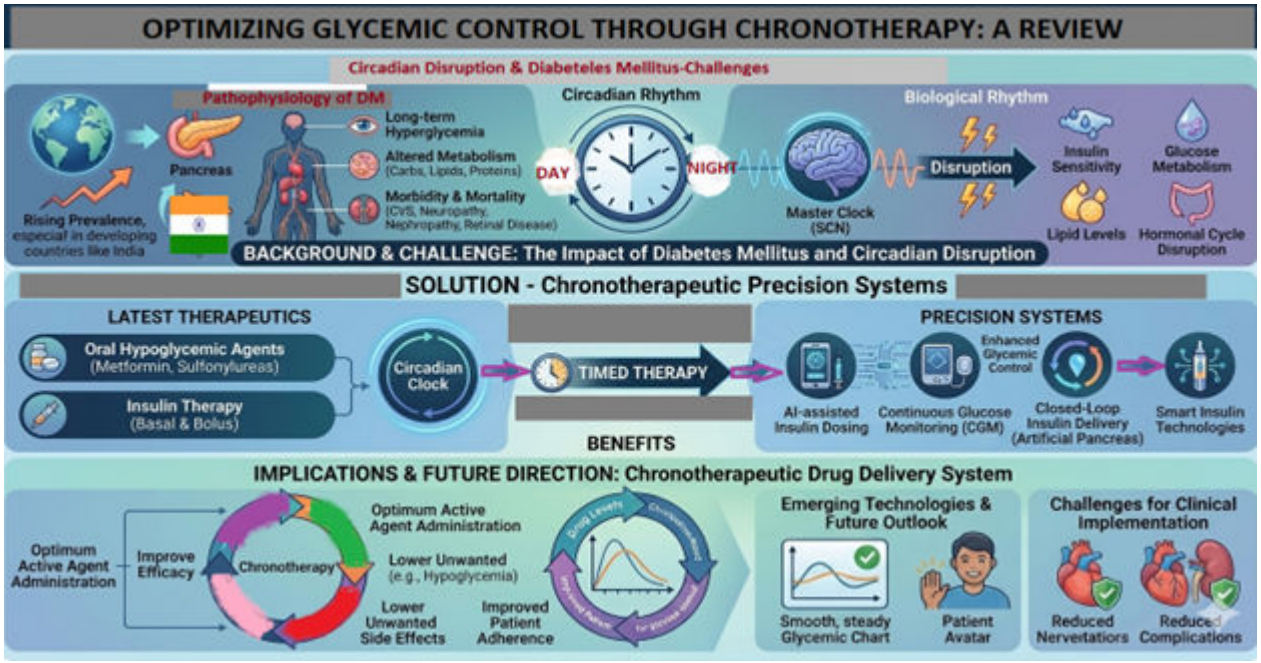
Graphical Representation



1. INTRODUCTION

Diabetes mellitus is a polygenic chronic metabolic disorder marked by elevated blood glucose levels, stemming from issues in insulin production, insulin action, or both. Globally, approximately 537 million individuals are affected by diabetes, with this number projected to rise to around 700 million by 2045 (IDF Diabetes Atlas 2025). Insulin is a hormone responsible for transporting glucose into cells for energy production. When this hormone malfunctions, cells cannot access glucose for energy, leading to diabetes mellitus a condition marked by high blood sugar (hyperglycemia) that can result in severe health complications. Diabetes mellitus (DM) presents in two forms: Type 1, which is insulin-dependent, and Type 2, which is non-insulin-dependent. Type 1 DM is an autoimmune condition characterized by a complete lack of insulin, typically seen in children due to the immune system attacking pancreatic beta cells. In contrast, Type 2 DM is more common in adults and involves either insufficient insulin production or insulin resistance. (Unai G.G. et.al. 2020). In Diabetes mellitus (DM), glycemic control involves regulating blood glucose levels to keep them as close as possible to those found in healthy individuals. Conventional approaches for glycemic control include oral hypoglycemics, insulin therapy, monitoring blood sugar levels and lifestyle modifications in Type 2 diabetes, whereas Type 1 DM relies solely on insulin therapy. Current strategies for managing blood glucose often fall short in maintaining stable long-term control, can cause adverse effects, and heavily depend on patient compliance. Both pharmacological and behavioral approaches to regulating blood glucose levels present significant scientific and practical challenges, primarily because they fail to consider the body's intrinsic 24-hour biological clock, leading to chronodisruption.

Diabetes mellitus is marked by notable circadian fluctuations in glucose regulation, insulin secretion, and insulin sensitivity. This metabolic disorder is characterized by prolonged hyperglycemia and disrupted carbohydrate and lipid metabolism, resulting from irregularities in insulin production, action, or both. These factors lead to predictable periods of heightened risk for hyperglycemia, particularly in the early morning and around meal times, making time-targeted delivery scientifically pertinent.

Current research suggests that the circadian clock controls the secretion of insulin, as well as the process of glucose metabolism, energy expenditure, and lipid metabolism. Even in healthy individual insulin sensitivity and glucose tolerance change a lot during the day. The hierarchical network of the biological timing system comprises a central control center, the suprachiasmatic nucleus (SCN), along with peripheral clocks located in the liver, pancreas, muscle, and fat. Additionally, it includes a molecular clock consisting of intracellular genetic machinery. Together, these components coordinate 24-hour circadian rhythms to optimize metabolic equilibrium and energy balance. Disruptions or dysregulation of this circadian clock may result in sever metabolic diseases like diabetes and obesity. (Mason et al., 2020). Scientific reports suggest disruptions in these cycles have a 20 to 40% increased risk of Type 2 diabetes. Current diabetes treatments only focus on stabilizing blood sugar and often overlook the body's 24-hour clock and result significant drawbacks.

Chronotherapy is an innovative approach of timing treatment at optimal times to align with biological rhythms and physiological processes. (Mason et al., 2020). This method helps control blood sugar in diabetes by timing drugs, meals, and lifestyle changes with the body's natural cycles.This review seeks to emphasize the advancements in chronobiology and chronotherapeutics for managing Type 2 DM through personalized strategies. It outlines the current understanding of chronobiology in diabetes and utilizes clinical evidence to highlight the potential of chronobiological interventions.

2. Pathophysiology of Diabetes Mellitus

Diabetes mellitus is a disease of persistent hyperglycemia with strong related to variation in circadian of glucose regulation, insulin secretion, and insulin sensitivity. Type 1 DM accounts 5–10% of cases, where the immune system attacks pancreatic cells, stopping insulin production. Managing it requires lifelong insulin replacement to prevent tissue catabolism and life-threatening conditions like diabetic ketoacidosis. In type 2 DM, the fundamental defect is either delayed insulin secretion in response to load or peripheral tissue's failure to respond to insulin. T2DM is a heterogeneous disorder with complex etiology involving genetics, lifestyle, insulin resistance, impaired insulin secretion, and increased hepatic glucose synthesis. Insulin resistance and insulin secretion both are interlinked to each other in T2DM. The failure of insulin secretion is due to impaired function of beta cells. Normally insulin is to promote hepatic storage of glucose in the form glycogen and reduce gluconeogenesis. In T2DM, the liver also shows insulin resistance as part of the resistance in peripheral tissue. This means at early stage liver shows insulin resistance i.e. in spite of hyperinsulinemia, gluconeogenesis process is not suppressed result increase synthesis of glucose from non-carbohydrate resources cause hyperglycaemia.

Type 1 Diabetes primarily arises from genetic predisposition and environmental factors that trigger the autoimmune destruction of pancreatic β-cells, resulting in an absolute deficiency of insulin. Conversely, Type 2 Diabetes is influenced by genetic and lifestyle factors, including obesity, hypertension, and physical inactivity, which contribute to insulin resistance, diminished insulin secretion, increased hepatic glucose production, and ultimately hyperglycemia as shown in Figure 1.

3. Current Treatment Strategies for Diabetes Mellitus

Current approaches to maintain diabetes involves using better medications, and delivery methods to get the best controlled blood sugar levels. The HbA1c test, measures average blood glucose levels of over the past two to three months, is a reliable indicator for diagnosing non-diabetes (below 5.7%), prediabetes (between 5.7-6.5%), or diabetes (more than 6.5%). The current treatment involves administration of oral antidiabetics, insulin shots and innovative treatment.

3.1. Oral Hypoglycemic Agents

The oral hypoglycemic drugs are used for managing type 2 diabetes mellitus. The classes of oral hypoglycemic drugs include Biguanides, Sulfonylureas, Meglitinides, Thiazolidinediones, Dipeptidyl Peptidase-4 (DPP-4) inhibitors, Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors, Alpha-glucosidase inhibitors, oral GLP-1 receptor agonists, and other emerging oral agents as depicted in Figure No. 2 and 3. These chemicals lower blood sugar level, increase sensivity of insulin and enhance the secretion of insulin by different mechanism as discussed in table No 1 . The timing of drug delivery, particularly in relation to circadian rhythm is crucial for their optimal action.

Metformin, a first-line drug, inhibits hepatic gluconeogenesis, enhances insulin sensitivity, and reduces glucose production (Goel et al., 2022) (Bailey, 2024) (Baker et al., 2021). Traditionally taken in the morning, research now suggests that evening dosing is more effective. Studies show that taking metformin in the evening can reduce HbA1c levels by 0.4% more than taking it in the morning, as evening dosing helps control blood sugar levels after meals. This is because our bodies become less sensitive to insulin from late afternoon to early evening. Metformin is particularly effective in addressing the nighttime increase in liver glucose production, which significantly contributes to fasting hyperglycemia and the "dawn phenomenon." Administering metformin in alignment with the body's natural circadian rhythms can enhance glycemic control.

Sulfonylureas, including glipizide, glimepiride, and glibenclamide, enhance insulin release and contribute to lowering HbA1c levels, yet they are considered insufficient for addressing the dawn phenomenon.(Seino et al., 2017)(Pop & Lingvay, 2017). For optimal glycemic management, it is important to align the timing of sulfonylurea administration with the body's natural circadian rhythms of insulin sensitivity and glucose tolerance. The molecular clock within pancreatic β-cells regulates both the timing and amount of insulin release. To maximize the effectiveness of sulfonylureas in managing blood sugar levels, they should be administered in sync with the body's natural rhythm. This means taking them with the main meal or splitting the dose between the two largest meals of the day, which helps reduce the risk by ensuring the medication is available when it is most needed.

Meglitinides, including repaglinide and nateglinide, promote the release of insulin from pancreatic β-cells independently of glucose levels and are effective in controlling postprandial glucose. These drugs have a distinct binding site, act for a shorter period, and moderately lower blood sugar levels.(Distefano &. Watanabe, 2010)(Xie et al., 2023). Chronotherapy seeks to synchronize the administration of these medications, delivering them in higher doses during times of peak insulin sensitivity and glucose demand, thereby reducing the risk of prolonged hypoglycemia and enhancing their efficacy in controlling blood sugar levels.

Thiazolidinediones work as insulin sensitizers such as Pioglitazone, Rosiglitazone, and Lobeglitazone act by activating PPAR-γ to regulate glucose and lipid metabolism, thereby improving insulin sensitivity in liver, fat, and muscle, and are used as add-on therapy in type 2 diabetes with high efficacy, though limited by weight gain, fluid retention, and increased risks of heart failure and fractures. (Hauner, 2002; Quinn et al., 2008)(Davidson et al., 2017; Martens et al., 2002). According to sources, this category of medication plays a crucial role in enhancing insulin sensitivity, yet there is currently a scarcity of research specifically examining chronotherapeutic protocols.

DPP-4 (Dipeptidyl peptidase-4) suppressor, for example Sitagliptin, Linagliptin, Alogliptin, Sexagliptin and Vildagliptin enhance incretin activity via action against DPP-4 enzyme, leading to rises glucose dependent insulin secretion and reduced glucagon levels. Their application in type 2 diabetes is due to their efficacy, minimal risk of hypoglycaemia and weight management benefits, with a low risk of unwanted effects such as joint pain, pancreatitis and rare bullous

pemphigoid.(Davidson et al., 2017; Quinn et al., 2008; Vasudevan & Balasubramanyam, 2004).

SGLT2(Sodium–glucose co-transporter-2) inhibitors (gliflozins) like dapagliflozin, empagliflozin and canagliflozin stop renal glucose reabsorption, resulting in urinary glucose excretion. They help the heart and kidneys in type 2 diabetes mellitus due to cardioprotective and renoprotective effects, but they have drawbacks because of infection risk and no working as well when the kidneys are badly damaged. (Bjornstad et al., 2021; Kashihara et al., 2020).(Kashihara et al., 2020; Kim & Kim, 2022; Rastogi & Januzzi, 2023)

Alpha- glucosidase inhibitors, such as acarbose, miglitol, and voglibose, block intestinal enzymes to slow carbohydrate absorption and control blood sugar after meals. They are often used in combination with other medications, but their use is decreasing due to stomach side effects such as bloating, gas, and diarrhea. (Khan et al., 2024; Reuser & Wisselaar, 1994; Toeller, 1994)(Hedrington & Davis, 2019; Patel et al., 2024; Toeller, 1994). Semaglutide (Rybelsus) is an example of Oral GLP-1 receptor agonists increases liberation of insulin, boost weight loss and provide greatest glucose lowering with cardioprotective benefits in T2DM by copying the GLP-1 hormones, though they are expensive and often associated with problems like upset stomach, vomiting and diarrhoea. (Choe & Cho, 2021)(Wen et al., 2021; Zhao et al., 2021)(Nauck et al., 2026; Yang, 2025).Bromocriptine-QR put down insulin sensitivity result decrease hepatic glucose production. (Chikara et al., 2017; Mittermayer et al., 2015)(Feng et al., 2025; Frąk et al., 2023). Table No 1 outlines the various classes of oral hypoglycemic agents, their mechanisms, clinical roles, and limitations.

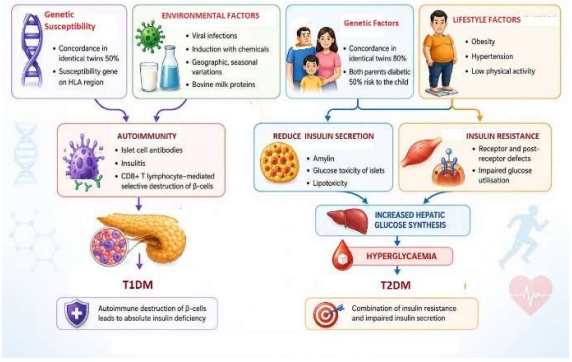


Figure 1: Schematic Mechanisms involved in Pathogenesis of Diabetes Mellitus.

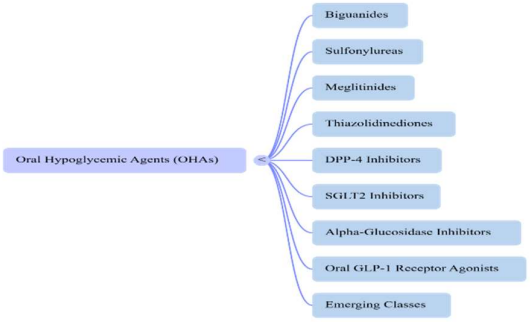


Figure 2: Oral Antidiabetic Drug Classes

Table No 1: Oral Hypoglycemic Agents for Diabetes Mellitus

Drug Class	Examples	Mechanism of Action	Clinical Role & Key Features	Limitations	Supporting Citations
Biguanides	Metformin	Reduces hepatic glucose production and increases insulin sensitivity via AMPK activation.	Foundational T2DM therapy; cardioprotective; no hypoglycemia risk.	Gastrointestinal issues; renal safety concerns; nutritional deficiencies.	(Goel et al., 2022; Bailey, 2024; Baker et al., 2021)
Sulfonylureas	Glimepiride, glipizide, glyburide	Closes ATP-sensitive potassium (KATP) channels to trigger	Potent blood glucose re1duction (HbA1c by 1–2%).	High risk of hypoglycemia and weight gain.	(Seino et al., 2017; Pop & Lingvay, 2017)

		insulin secretion.			
Meglitinides	Repaglinide, Nateglinide	Closes KATP channels to stimulate insulin release.	Fast onset; useful for mealtime glucose spikes.	Hypoglycemia; weight gain; risk of beta-cell exhaustion.	(Distefano & Watanabe, 2010; Xie et al., 2023)
Thiazolidinediones (TZDs)	Pioglitazone, Rosiglitazone	Binds to PPAR-gamma to regulate glucose and lipid metabolism.	High efficacy; improves insulin sensitivity in liver, fat, and muscle.	Weight gain; fluid retention; heart failure and fracture risk.	(Hauner, 2002; Quinn et al., 2008; Davidson et al., 2017; Martens et al., 2002)
DPP-4 Inhibitors	Sitagliptin, Linagliptin, Vildagliptin	Inhibits DPP-4 enzyme to prolong incretin (GLP-1/GIP) activity.	Weight-neutral; low hypoglycemia risk; often used with metformin.	Joint pain; pancreatitis; risk of bullous pemphigoid.	(Davidson et al., 2017; Quinn et al., 2008; Vasudevan & Balasubramanyam, 2004)
SGLT2 Inhibitors	Dapagliflozin, Empagliflozin, Canagliflozin	Blocks SGLT2 in renal tubules to promote glucose excretion in urine.	Recommended for patients with heart failure (HF) or chronic kidney disease (CKD).	Infection risks; reduced efficacy in advanced renal impairment.	(Bjornstad et al., 2021; Kashihara et al., 2020; Kim & Kim, 2022; Rastogi & Januzzi, 2023)
Alpha-Glucosidase Inhibitors	Acarbose, Miglitol, Voglibose	Inhibits small intestine enzymes to slow carbohydrate absorption.	Targets postprandial (after-meal) glucose levels.	Significant GI distress (bloating, flatulence, diarrhea).	(Khan et al., 2024; Reuser & Wisselaar, 1994; Toeller, 1994; Patel et al., 2024)
Oral GLP-1 Receptor Agonists	Oral Semaglutide (Rybelsus)	Mimics GLP-1 hormone to stimulate insulin and promote weight loss.	Metabolic and cardio-renal benefits; cardiovascular risk reduction.	High cost; gastrointestinal distress (nausea/vomiting).	(Choe & Cho, 2021; Wen et al., 2021; Zhao et al., 2021; Nauck et al., 2026; Yang, 2025)

Emerging Classes	Sotagliflozin, Colesevelam, Bromocriptine	Varies (e.g., dual SGLT1/2 inhibition; dopamine-2 agonism).	Emerging treatments for T2DM management.	Specific limitations depend on the individual agent.	(Chikara et al., 2017; Mittermayer et al., 2015; Feng et al., 2025; Frąk et al., 2023)

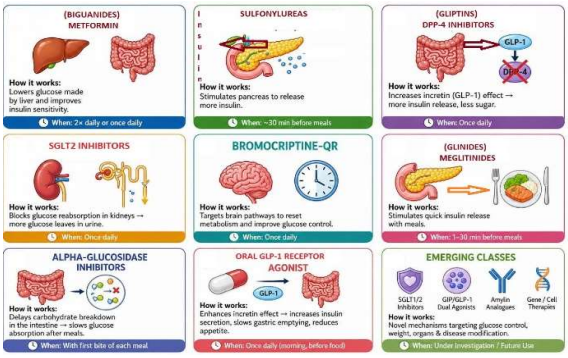


Figure 3: Oral Antidiabetic Drug Classes and Their Targets

3.2. Insulin Therapy

Insulin therapy is crucial for managing glycemic levels, being indispensable for all individuals with Type 1 diabetes and often necessary for those with Type 2 diabetes as the condition advances. This requirement becomes evident when HbA1c levels fall below 9.0%, oral medications prove ineffective, or when there are pronounced symptoms of high blood sugar.

Hypoglycemia is the main risk associated with insulin treatment. Therefore, it is crucial for all patients undergoing insulin therapy to have glucagon prescribed for emergencies. Basal Insulin manage blood glucose levels during fasting and put down hepatic glucose production. Bolus Insulin manage blood glucose levels after meal. The figure No 4 illustrates insulin management strategies for uncontrolled blood glucose in Type 2 Diabetes Mellitus (T2DM). Basal insulin is administered once daily, usually at bedtime or in the morning, to control fasting blood glucose, while rapid-acting bolus insulin is given before meals to manage postprandial glucose spikes.

3.3. Dawn Syndrome management

The dawn syndrome is the characteristics of Diabetes mellitus, which leads to high level of blood sugar, usually morning between 4 a.m. to 8 a.m. that is further aggravated due to in midnight counterregulatory hormones, such as glucagon, adrenaline, growth hormone, and cortisol, that increase the blood glucose production. Chronotherapy helps manage this condition by synchronizing antidiabetic treatment with the body's biological clock. Evening administration of Metformin, particularly around 8 PM, effectively reduces morning hyperglycemia and can lower HbA1c levels more than morning dosing. Other oral agents, such as meglitinides and α-glucosidase inhibitors, may also be timed to improve glycemic control while minimizing nocturnal hypoglycemia. The figure No 4 also highlights dawn phenomenon management using bedtime basal insulin dose adjustment or insulin pump therapy to achieve stable glycemic control, reduce complications, and improve patient outcomes.

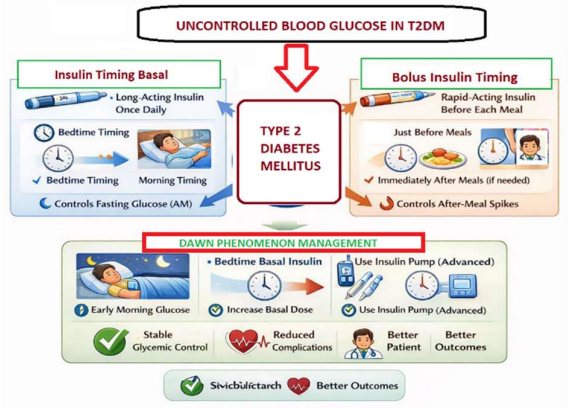


Figure 4: Insulin Timing and Dawn Phenomenon Management

4. Chronomodulated Drug Delivery Systems for Diabetes Mellitus

Chronotherapeutic systems for managing diabetes mellitus are based on the concept of chronopharmaceutics, which aims to deliver antidiabetic medications in synchronization with the body's circadian rhythms (CRs) to achieve optimal glycemic control and therapeutic outcomes (Jain N et al., 2016). CRs are natural 24-hour cycles that synchronize an organism's body and behavior with day and night while regulating key physiological functions such as metabolism, hormone secretion, and immune activity. Since blood glucose levels, insulin secretion, insulin sensitivity and glucose tolerance fluctuate throughout the day, designing drug delivery systems that release medication at specific times can improve treatment effectiveness and minimize adverse effects (Adepu S et al., 2021). This approach, known as chronotherapy, focuses on aligning antidiabetic therapy with the body's biological clock to

enhance efficacy, optimize glucose regulation, and reduce toxicity and complications (Ando H et al., 2012). Contemporary treatment approaches involve personalized patient care according to biological rhythms of the body. Factors such as artificial light, irregular sleep and eating patterns, and shift work misalign the circadian clock, leading to insulin resistance in muscle and liver tissues, reduce the glucose intake and impaired insulin secretion (Rane et al., 2009). Research indicates that glucose tolerance is greater in the morning and diminishes by the evening. Additionally, consuming more calories in the evening is linked to an increased risk of metabolic syndrome.

Chronotherapeutic systems are based on the notion of chronopharmaceutics, which involves delivery of medicine in a burst at circadian timing that is connected with a certain pathological issue in order to obtain maximal medicinal impact (Jain N et al. 2016). s (Zhao R et al. 2020).

The pulsatile drug delivery system releases the drug at desired time as per pathophysiological need of disease, resulting in improved patient therapeutic efficacy and compliance (Anusha V et al. 2023). The main objective of delivering drug through pulsatile drug delivery system at specific time of day or night will reducing the dosing frequency, minimizing adverse drug reaction and to improve patient compliance by enhancing the therapeutic efficacy of the drug. Chronotherapy will improve glucose metabolism and glycaemic control by aligning the administration time of diabetes medications with the circadian rhythms of the body (Mason I C et al. 2020). This will ensure that the medication works when it is needed the most, leading to better blood glucose control.

As of early 2026, GLP-1 receptor agonist (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists (trizepatide) are the best available options for treating type 2 Diabetes with high levels of efficacy for reducing \(HbA1c\) and weight loss, and low risk of hypoglycaemia.There are several important studies that have compare the efficacy and safety of contemporary glucose lowering medications and insulin analogues for diabetes management. Table No. 2 summarizes major clinical trials evaluating antidiabetic therapies and their associated hypoglycemia outcomes.

Table No. 2: Clinical Trials on Antidiabetic Therapies and Hypoglycemia

Clinical Trials	Therapy Evaluated	Main Finding	Supporting Citation
GRADE Trial	In metformin. Liraglutide, sitagliptin, glargine and glimepiride were added	Comparison of sitagliptin or glimepiride found that severe hypoglycaemia was lowest with liraglutide and sitagliptin. HbA1c targets were maintained longer with liraglutide and insulin glargine.	**(Seaquist E.R. et.al. 2024)**
CONCLUDE Trials	Insulin glargine U300 VS Insulin degludec	Lower rates of nocturnal and severe hypoglycaemia with similar HbA1c reduction with degludec	**(Tsimikas A.P. et. al. 2023)**
EDITION Trials	Insulin glargine U300	It has been shown to achieve a similar HbA1c reduction to U100 glargine while reducing the number of hypoglycemic events that occur during the night.	**(Mohan V. et.al. 2025)**
BRIGHT Trial	Glargine U3000 VS degludec	Similar glycemic control, glargine U300 had lower hypoglycaemia while titrating.	**(Mohan V. et.al. 2025)**
EASE Trials	Empagliflozine in diabetes	Important HbA1c and weight loss with a relatively low risk of hypoglycaemia when used properly with insulin.	**(Evans M. et.al. 2020)**

Basal insulin analogs (insulin in glargine and insulin degludec) have been consistently shown to lower HbA1c by about 1-1.5% in people who have uncontrolled type 2 diabetes (Dehghani M et.al.2024). GLP-1 receptor

agonist like liraglutide and known to produce greater HbA1c reduction than DPP-4 inhibitors and to induce weight loss (Gilbert MP et.al. 2020). In general the SGLT2 inhibitors, including empagliflozin offer moderate improvements in HbA1c (Approx 0.5-1.0%) and further cardiovascular and renal advantages (Evans M. et.al. 2020).

4.1. HbA1c Control

Glycemic variability is reduced and fasting glucose is better and more consistently controlled using basal insulin analogs. GLP-1 receptor agonists have been linked to weight reduction and have been shown to improve postprandial and fasting glucose levels. Since SGLT2 inhibitors improve glycemic control without increasing insulin production, they can be taken at any stage of a diabetes diagnosis. With reduced increase in insulin dosage, combination treatment (basal insulin + GLP-1 RA or SGLT2 inhibitor) can often yield additive decrease in HbA1c.

4.2. Reduction in Hypoglycemia Risk

A big improvement with newer diabetes medications is the reduced risk of low blood sugar as opposed to old medications like sulfonylureas. Insulin and insulin secretagogues (sulfonylureas) are the drugs most likely to cause hypoglycaemia. In comparison, newer classes of drugs, such as GLP-1 receptor agonist and SGLT2 inhibitors, tend to have a lower risk of hypoglycaemia, unless they are used in combination with drugs that are also hypoglycemic. Table No. 3 presents the comparative risk of hypoglycemia associated with different antidiabetic therapies.

Table No. 3: Comparative Risk of Hypoglycemia Associated with Antidiabetic therapies

Therapy Class	Relative Hypoglycemia Risk	Evidence
Sylfonylureas	Higher	More likely to cause symptomatic and severe hypoglycemia
Basal insulin analogs	Sparingly but rises vs ancient insulin	Long acting analogues reduce nighttime hypoglycaemia compared to NPH insulin,
GLP-1 R A	Low	Minimal hypoglycaemia, unless used in combination with insulin or sulfonylureas
DPP-4 Inhibitors	Low	Lower risk of sulfonylureas (with moderate HbA1c reduction)
SGLT2 Inhibitors	Low	Not consistently significantly different from placebo in numerous studies (not used with insulin or SU therapy/0

5. Benefits of Chronotherapy in Diabetes

Chronotherapy is the practice of timing insulin, oral hypoglycemic drugs and even food to coincide with insulin sensitivity and glucose tolerance peaks throughout the day. The idea is that the secretion and action of insulin, the production of glucose by the liver, and the utilization of glucose by muscles all follow a circadian rhythm, indicating that timing is as important as the content (Hariri A. et.al. 2023). Chronotherapy offers a new and promising approach to management of diabetes mellitus by synchronizing the administration of medication with the body natural circadian rhythm. Among the key benefits of chronotherapy is better glycemic control, which is achieved by aligning the timings of taking medicines with daily variations in insulin sensitivity and glucose metabolism. The time-specific drug delivery system enables therapeutic compounds to be most effective when the body requires them the most as glucose tolerance tends to be high in the morning and low in the evening or night. The primary advantage of chronotherapy is that it minimizes side effects, such as hypoglycemia, which is a common side effect of conventional treatment of diabetes. To minimize the risk of injurious episodes of hypoglycemia it is vital to administer medications at the most suitable time to prevent the unnecessary exposure to the medication. It is of paramount importance during the night, when hypoglycemia has higher chances of remaining undiagnosed. Chronotherapy enhances the pharmacodynamics and pharmacokinetic responses of drugs and thus, increases the efficacies of drugs. Time-based medication administration increases the therapeutic effect by promoting improved drug absorption, distribution, metabolism, and excretion.

Besides enhancing patient compliance, simplified dosage schedules can also make the treatment plan easier, allowing the patient to be administered less frequently. The concept of chronotherapy gives credence to the specific and personalized therapy because of the distinctiveness of the circadian rhythm, food habits, and metabolic responses in each individual. It allows developing individualized treatment plans that can enhance the health outcomes and well-being of patients. This strategy can save healthcare spending in the long term by reducing the risks of complications and hospitalizations that happen due to the insufficient Glycemic Control. In general, chronotherapy denotes the shift of the conventional symptom treatment to a more physiological and time-conscious approach to treatment and offers substantial benefits to enhance the effectiveness, safety, and personalization of diabetes management.

Several studies have demonstrated that administering insulin or some oral diabetes medication at a time of maximum insulin sensitivity in the day (which is usually earlier) helps to lower the glucose level better than doing so at fixed times, regardless of the rhythm (Kashyap S. et.al. 2021). When insulin is given at the right time and/ or insulin sensitizers, the risk of low blood sugar and weight gain is reduced but the doses are not delivered in a one size fits all manner as they are based on the body's need (Chauhan V et.al. 2025).

Better insulin sensitivity and metabolic health is the result of synchronizing sleep, meal timing, and activity with the circadian signals, which helps to lower insulin resistance, night time glucose peaks, and cardiovascular risk factors. A 8-10-hour window during the "metabolically active period" of the day may positively impact fasting glucose, postprandial glycemia and β-cell function in T2DM. When cardiometabolic risk has been caused by a circadian misalignment, regular sleep-wake cycles and earlier meals can correct this and lower the risk of developing diabetes and cardiometabolic disease.

6. Challenges and Limitations of Chronotherapy

Despite its potential to enhance therapeutic results and minimize side effects, chronotherapy encounters several obstacles and constraints. Variations in circadian rhythms, which are influenced by factors such as age, lifestyle, genetics, and sleep habits, can impact how patients respond to treatment and complicate the standardization of dosing schedules. Additionally, patients often struggle to adhere to strict medication regimens, which can diminish the effectiveness of chronotherapeutic strategies. Figure No 5 highlights the primary challenges and limitations of using chronotherapy in managing diseases.

6.1. Patient Variability: People possess various internal clocks, with significant differences between those who are inclined to be active in the morning and those who prefer the evening (Gentry N.W. et.al. 2021). A consistent treatment period for all patients sometimes undermines the goal of chronotherapy, necessitating a tailored evaluation of the body clock. Systemic drug exposure can vary by more than tenfold in individual patients, independent of dose modification, making universal optimum time impossible to define (Colita C.I. et.al 2024). Circadian rhythmicity varies with age, gender, and comorbidities, hindering the formation of consistent.

6.2. Lifestyle Factors: The internal circadian clock is disrupted by exposure to light, work shifts and unpredictable sleep-wake cycles, leading to a mismatch of the internal clock with the external environment. It is challenging to patients to follow specific treatment regimens. The time of meals and physical activity disturbs peripheral clocks, and abnormal habits can counterbalance the benefit of regular pharmaceutical treatment.

6.3. Need for large-scale clinical trials: Since some studies have been positive, even systematic, randomized, pragmatic trials should be conducted to demonstrate the usefulness in a variety of types of health conditions. The lack of developed methods, regulatory resources, and long-term research to integrate circadian biomarkers into a routine clinical practice is limited.

Figure 5: Challenges and Limitations of Chronotherapy

7. Recent Advances & Future Perspectives

Chronotherapy have a bright future in diabetes treatment for new drugs delivery system based on cutting-edge technology, customized medicine, and the research of chronobiology (Ballesta A. et.al. 2017). Personalized medicine as a field is destined to have a tremendous impact by tailoring treatment regimens according to metabolic responses, genetic composition and circadian

cycles of individuals. The necessity of individual approaches to patients is supported by the fact that clock gene differences such as BMAL1, CLOCK, PER, and CRY have an effect on glucose metabolism and response to medications (Schrader L.A. et.al 2024). Doctors can design optimized treatment regimens that can improve glucose control and avoid side effects based on genetic and behavioral data. Care for diabetes based on chronotherapy is being further revolutionized by the fast development of artificial intelligence and wearable glucose monitoring devices. Artificial intelligence can be used in systems to analyze data provided by continuous glucose monitors, predict glycemic variations, and recommend precise schedules to administer drugs (Ji C. et.al. 2025). It is possible to administer insulin in a time-based and automated way using wearable devices such as smart insulin pumps and continuous glucose monitors that enable one to monitor glucose levels in real time. Such technological changes promote the degree of patient engagement and compliance and accuracy of treatment. In addition, another frontier in research is development of chronobiologically based drugs. Examples of chronomodulated drug delivery systems that are receiving much interest in the pharmaceutical industry are pulsatile release formulations and glucose-responsive insulin systems. The purpose of these systems is to synchronize the release of medications with changes in metabolic activity that take place during the day. Hopefully, these systems can make a tremendous improvement in treatment outcomes and minimize side effects. Finally, but certainly not the least, the successful implementation of chronotherapy into clinical practice requires clinical studies on a large scale and the development of clear clinical criteria. It is necessary to develop protocols based on evidence for the timing of drugs, patient selection, and treatment monitoring in order to guarantee chronotherapy's efficacy and safety. With the development of research, chronotherapy that offers a more efficient and patient-oriented method of diabetes management is expected to be part of a precision medicine. This involves the utilization of innovative drug delivery systems to improve pharmacological action. New therapies include smart insulin administration and artificial intelligence therapies. These technologies allow continuous glucose monitoring and self-administration of insulin. Figure 6 shows advanced techniques including AI-assisted dosing, closed-loop systems, and predictive monitoring are used in diabetes treatment and improving patients's conditions.

7.1. Smart insulin and AI-assisted dosing

The early diagnosis, management, and therapy of healthcare are in the sphere of AI application becoming more prevalent. The spheres of interest in diabetes care involve the use of AI wearable devices and mobile apps, AI-enabled insulin pumps, personalized care. AI-assisted dosage is symbolic of an alteration of response to violent treatment, especially in diabetes. They use AI and machine learning to process the information of Continuous Glucose Monitors (CGM) and automate insulin dosages.

7.2 Automation of Insulin Distribution (AID) / Implanted Pancreas: Closed-loop systems, such as the MiniMed 670G, adjust insulin infusion rates every few minutes based on real-time glucose measurements, reducing the risk of hypoglycaemia (Dermawan D. et.al. 2022).

7.3 Advanced Algorithms: The most recent ones are based on Reinforcement Learning (RL) to develop patient-specific "dynamic control policies" that learn the metabolic flexibility of an individual over time.

7.4 Predictive Analytics: The contemporary technology can forecast glucose fluctuations up to 120 minutes beforehand, which can be used to proactively regulate medication. Decreased patient burden: Type 2 diabetes Technologies such as SmartAdjust ® technology are legalized, and AI-powered intelligent pens (e.g., InPen) can assist in optimizing management of individuals who do not use pumps (Daly A. et.al.2021).

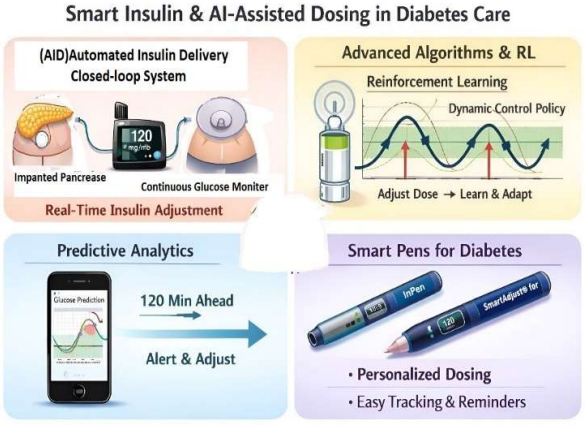


Figure 6: Advanced Techniques in Diabetes Treatment

CONCLUSION

Diabetes mellitus, especially Type-II, is a major global health challenge due to its multifactorial pathophysiology involving insulin resistance, β-cell dysfunction, chronic inflammation, and oxidative stress. Traditional treatments, like oral hypoglycemic drugs and insulin therapy, have improved disease management but

often fail to achieve ideal glycemic control or ensure long-term patient adherence. This is largely due to neglecting individual biological variability and the metabolic processes' dynamic nature governed by circadian rhythms. Emerging evidence highlights circadian biology's critical role in regulating glucose metabolism, hormonal secretion, and insulin sensitivity. Disruption of these rhythms significantly contributes to poor glycaemic control and increased metabolic complications. Chronotherapy has emerged as a promising approach aligning drug delivery with the body's internal clock, enhancing therapeutic efficacy while minimizing adverse effects. Advancements in chronomodulated drug delivery systems, along with artificial intelligence, continuous glucose monitoring, and smart insulin technologies, have strengthened time-based personalized therapy's potential. These approaches improve pharmacokinetic and pharmacodynamic outcomes and enhance patient adherence by simplifying treatment regimens and reducing dosing frequency. Despite its promise, chronotherapy's clinical application faces challenges, including inter-individual circadian rhythm variability, lifestyle influences, and lack of standardized clinical guidelines supported by large-scale trials. Addressing these through research, circadian biomarker development, and personalized treatment protocols is essential for successful translation into clinical practice. In conclusion, chronotherapy represents a shift from conventional symptom-based treatment toward a more physiological, precise, and patient-centered approach in diabetes management. Its integration with modern technologies and personalized medicine holds significant potential to improve clinical outcomes, reduce complications, and enhance quality of life for diabetes mellitus patients.

AUTHOR CONTRIBUTION

Raushan Kumar was responsible for conceptualizing the study, collection, analysis, and synthesis of relevant literature, citation and referencing, and drafting the initial version of the manuscript contributed to the, as well as assisting in manuscript revisions. Meenakshi Gupta provided overall supervision, offering valuable insights and intellectual guidance throughout the manuscript's development. As the corresponding author, Meenakshi Gupta oversaw the submission process and facilitated all communications with the journal. All authors have thoroughly reviewed and approved the final manuscript, ensuring its accuracy, coherence, and scholarly integrity.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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