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Hypoglycemia in Type 2 Diabetes Mellitus: Patterns, Predictors, Prevention and Management: A Narrative Review

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Abstract

Hypoglycemia is a clinically important complication of type 2 diabetes mellitus (T2DM), particularly in patients treated with insulin or insulin secretagogues. This narrative review synthesizes evidence on the prevalence, temporal patterns, predictors, consequences, prevention and management of hypoglycemia in T2DM, drawing on observational studies, clinical trials and guidelines identified through PubMed/MEDLINE, Scopus and Google Scholar. Risk is consistently associated with older age, longer diabetes duration, insulin exposure, intensive glycemic control with lower HbA1c, elevated diastolic blood pressure, renal disease, comorbidity, treatment complexity and impaired symptom recognition. Nocturnal and asymptomatic episodes often go undetected without structured glucose monitoring and severe events have been associated with cardiovascular events, hospitalization and mortality. Glycemic variability indices and continuous glucose monitoring (CGM) metrics provide predictive information beyond HbA1c and may support early identification of patients at risk. Preventing hypoglycemia comes down to everyday care rather than any single intervention. Glucose targets have to be set for the individual patient and medications and insulin adjusted carefully, with regular self-monitoring and routine review of meals, activity, injection technique, other medical conditions and drugs that might interact with treatment. The newer options look encouraging, but they still have to prove their worth in practice, since their value depends on how well they are validated, how sensibly clinicians read their output and whether patients can actually get access to them. In the end, hypoglycemia prevention works best as part of routine diabetes management, not as a problem dealt with separately after it occurs.

Keywords: Hypoglycemia, Type 2 diabetes mellitus, Predictors, Patterns, Continuous glucose monitoring, Prevention and management

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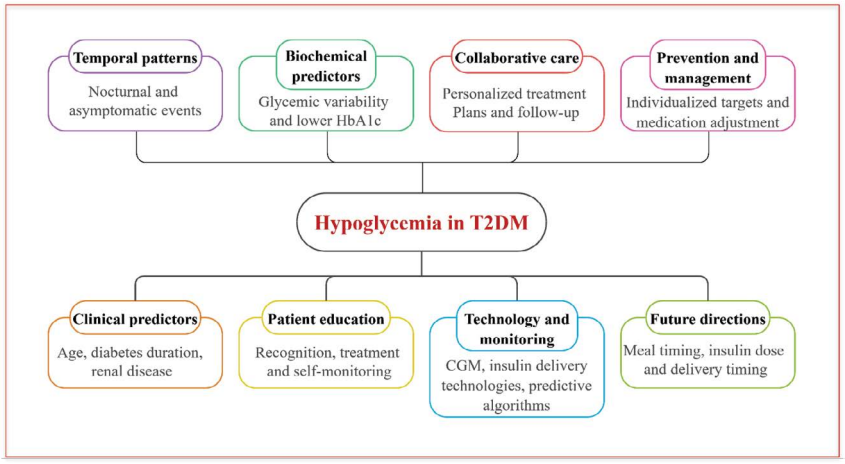
Graphical Abstract



Introduction

Hypoglycemia is an important treatment-related complication in type 2 diabetes mellitus (T2DM). It can interrupt daily activity, undermine confidence in treatment and make patients and clinicians reluctant to achieve glucose-lowering targets. Risk is especially relevant when insulin or insulin secretagogues are used, but a patient's vulnerability also reflects age, renal function, disease duration, prior episodes, food intake, activity, comorbidity, treatment complexity and the capacity to recognize and respond to falling glucose [1,2]. The clinical burden is not limited to a low glucose level, episodes may be unrecognized, recurrent, nocturnal or severe enough to require assistance. Severe events can affect the quality of life and treatment adherence, in addition to observational evidence have been associated with cardiovascular events, hospitalization and mortality. These relationships require cautious interpretation because comorbidity, frailty, treatment intensity and underlying illness may contribute to both hypoglycemia and adverse outcomes [3].

Hypoglycemia prevention is part of effective diabetes management, rather than a barrier to achieving optimal glucose control. The primary clinical goal is to select individualized targets and regimens that reduce symptomatic and severe events while maintaining meaningful glycemic benefit [4]. Therefore, this review carried out to highlight a comprehensive overview of the epidemiology, temporal patterns, predictors, treatment, technology, education, collaborative care, clinical trials and future directions. Routine care benefit from the measurement method, symptoms, need for assistance, timing and suspected precipitant together. This level of detail helps separate treatment safety from a single threshold-based outcome [5,6]. However, hypoglycemia management limitations are to avoid treating all patients with T2DM as one uniform group. A person using metformin alone has a different medication-related risk profile from someone using basal-bolus insulin and a stable outpatient differs from a hospitalized patient with acute illness. Interpretation should follow the actual population and treatment context reported by each study, especially when evidence is carried forward into recommendations for clinical practice [7]. To overcome

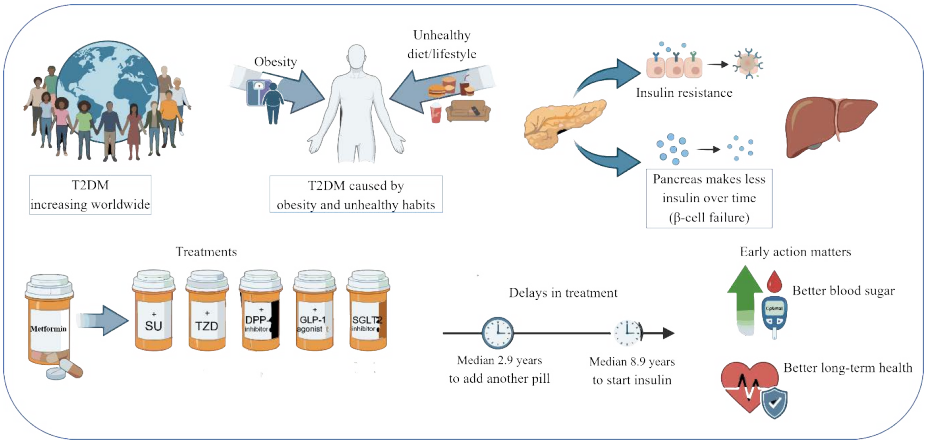


Figure 1: Conventional pharmacological management of type 2 diabetes mellitus and its therapeutic challenges

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these challenges the present review carried out based on the available literature, to organize the existing material into a concise clinical review **Figure 1**. The scope includes hypoglycemia occurs in T2DM, with particular emphasis on patients receiving insulin or insulinotropic therapies [8].

The study collected different types of evidence, such as observational studies, reviews, clinical guidelines and prediction studies. The main topics covered were what hypoglycemia is and its symptoms, insulin and other treatments, how common it is, when it happens, what predicts it, patient education, glucose monitoring and CGM, new technologies, treatment guidance and future prediction methods [9,10]. The inclusion scope is deliberately patient and outcome centered. The principal outcomes are biochemical, symptomatic, nocturnal, recurrent or severe hypoglycemia, along with patient experience, treatment safety and care utilization [11]. Evidence about prediction or technology is relevant when it measures or addresses low glucose in a population that can inform T2DM care. Findings from type 2 diabetes, gestational diabetes, non-diabetic cohorts or unrelated clinical questions are used only for limited context and should be labeled as indirect evidence [12]. This narrative review was conducted to provide a comprehensive overview of hypoglycemia in patients with T2DM, with particular emphasis. Relevant published literature addressing hypoglycemia in T2DM was identified through searches of major biomedical databases, including PubMed/MEDLINE, Scopus and Google Scholar. The search included combinations of keywords such as (hypoglycemia, type 2 diabetes mellitus, risk factors, predictors, prevention, management, patient education, self-management and clinical trials.

Epidemiology, Symptoms and Burden of Hypoglycemia

Hypoglycemia is a major complication of T2DM management and the risk grows as the disease progresses and insulin therapy becomes necessary. Patients are usually treated first with lifestyle changes and oral agents such as sulfonylureas and glinides, but prolonged use of these drugs can exhaust beta cells and lead to insulin therapy [13]. With increasing disease duration and prolonged exposure to insulin therapy, the risk of hypoglycemia increases substantially in insulin-treated patients. Hypoglycemia is defined as a blood glucose level at or below 70 mg/dL, with or without symptoms [14]. Older adults carry the highest risk, especially when comorbidities such as arrhythmias are present and glucose variability predicts nocturnal hypoglycemia in elderly patients on insulin [15]. As shown in **Figure 2**, reported risk factors include insulin therapy, advanced age and longer disease duration, lower HbA1c, elevated diastolic blood pressure and rural residence.

Hypoglycemic symptoms vary widely and are often missed, especially asymptomatic episodes detected only by

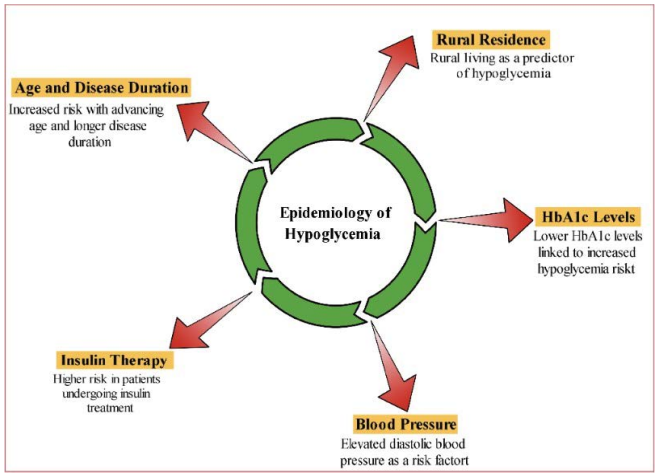

Figure 2: Epidemiology of hypoglycemia in T2DM: prevalence, risk factors and temporal patterns

CGM or routine measurement. Accurate event definitions must specify the glucose threshold, symptoms, the need for assistance as well as measurement method and the timing of detection, since definitions that mix these concepts conflate different types of episodes and complicate comparisons of prevalence and predictors [6]. In addition, the depth and duration of hypoglycemia with the patient's ability to recognize falling glucose. While Mild events cause tremor, weakness, impaired coordination, sweating or anxiety, while severe events progress to confusion, seizure or unconsciousness. Recurrent episodes reduce symptom awareness and delay detection of future events [16].

However, the risks depend on the treatment regimen and the patient's clinical profile. Insulin-treated patients are particular concern because insulin exposure and dosing errors can lower glucose beyond physiologic need and sulfonylureas add risk by stimulating insulin secretion, when combined with insulin or used in renal or hepatic impairment [17]. Reported studies across countries, care settings and study designs, because self-report, routine clinical records, emergency visits and CGM do not identify the same events. Whereas mild episodes are often underreported and severe-event datasets record in episodes that reach healthcare services. While a single prevalence not be generalized across all adults with T2DM or across treatment regimens [18].

However, older adults need particular attention because age often coexists with frailty, chronic kidney disease, cognitive limitations, polypharmacy and a reduced counter-regulatory response. In addition, insulin-treated older people show nocturnal hypoglycemia with rates that vary by treatment duration and patient characteristics [19]. Severe episodes of hypoglycemia can lead to emergency care and hospitalization, but health-system rates miss the burden of non-severe and unrecognized events. These events admissions persisted

or increased in some populations despite improvements in treatment, monitoring population age, medication exposure, access to care and event definitions limit direct comparison across settings [20]. Schematic representation of glucose homeostasis involving insulin-mediated glucose uptake in peripheral tissues, hepatic glucose regulation, pancreatic β-cell dysfunction and hypoglycemia associated with antidiabetic therapy as illustrated in **Figure 3**.

Prevalence and Patterns of Hypoglycemia in T2DM

Prevalence

Hypoglycemia is more common in insulin-treated T1DM, but the progressive decline of insulin secretion in T2DM eventually requires more complex regimens such as insulin therapy, making hypoglycemia a growing concern in insulin-treated patients with type 2 diabetes [21]. Patient-reported rates of hypoglycemic events in real-world settings have been assessed and reported events were correlated with glucose readings at the time each event occurred [22]. Nocturnal hypoglycemia often goes unrecognized, so its risk factors need further study. When patients self-report events, it is important to test how well their own assessment agrees with commonly used severity classifications and alert and alarm features were developed as a means of validation and evaluated in an observational setting. Because T2DM treatment places less emphasis on rapid mealtime insulin coverage and tight glycemic control, out of range glucose events are fewer than

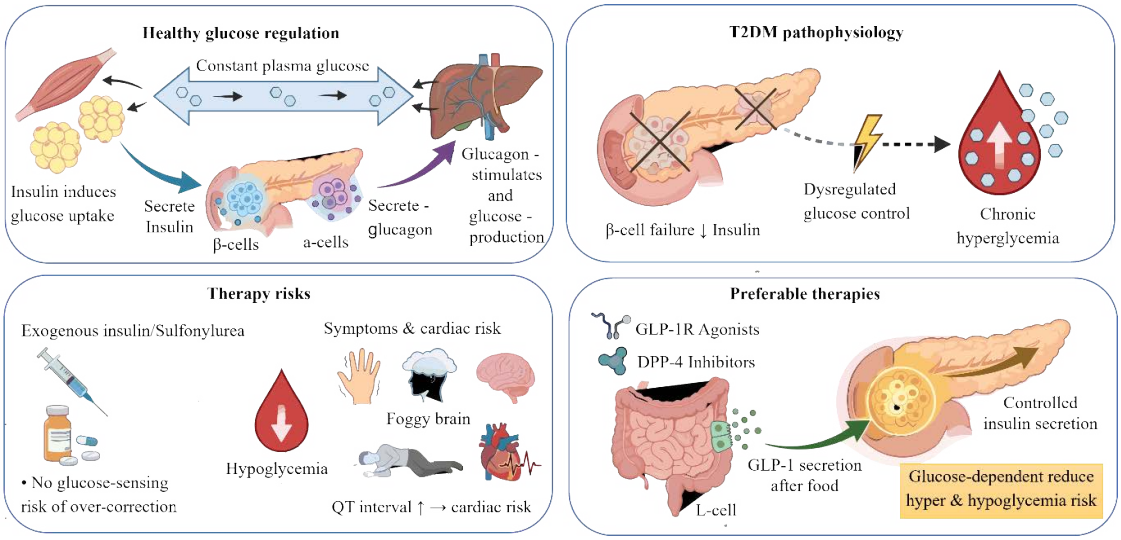

Figure 3: Integrated mechanisms of glucose homeostasis and hypoglycemia in T2DM

in T1DM [23]. Compared with daily self-monitored blood glucose, patients report higher hypoglycemic rates and lower hyperglycemic rates and agreement between patient-assessed severity and standard classifications is negative for both hypo and hyperglycemia. This disagreement has been addressed by focusing management on extreme events, which are over-represented and educational and management tools have been developed to improve CGM as a comparative resource.

The prevalence of hypoglycemia in T2DM varies with age, body composition, sex, antidiabetic treatment and glycemic control. Risk is greatest in older or clinically vulnerable patients and in those using insulin or other glucose-lowering drugs that carry hypoglycemia potential. Nocturnal hypoglycemia, glycemic parameters and cardiovascular and neurological consequences require particular attention and risk appears highest within 3 to 6 months after an HbA1c test, supporting continued monitoring over this period [6,24]. Highlights a potentially increased risk of hypoglycemia during the 3–6 months following an HbA1c assessment, underscoring the importance of ongoing glycemic monitoring and treatment reassessment (**Figure 4**).

Patterns

Hypoglycemia is a crucial limiting factor in the treatment of patients with T2DM. It is more common in patients treated with insulin or sulfonylureas and in those with poor glycemic control [21]. Severe hypoglycemia can cause neurologic impairment, altered mental status, seizures or death and two recent large studies reported that it increases the incidence of stroke up to fourfold in patients with long-standing T2DM. A recent population-based study examined changes in the incidence and predictors of hypoglycemia leading to emergency department visits and hospital admissions, although in patients with T1DM [25]. Reported studies of hypoglycemia have been inconsistent and the focus has been mostly on large critical cohorts or healthcare claims data. Similarly, the incidence of severe hypoglycemia was not

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substantially reduced in a population-based cohort studies showed reductions in the rates of treated hypoglycemia [26]. Together, these findings underline the need to look beyond common clinical characteristics toward the original patterns and predictors of hypoglycemia, as illustrated in **Figure 5**.

Temporal Patterns

Temporal patterns in reported studies were analyzed using the nadir-MIG index to assess minimum interstitial glucose likelihood across time periods. Patients with T2DM show distinct temporal patterns of hypoglycemia events may accumulate gradually before midnight, whereas in other glycemic profiles events cluster in the early morning hours and peak around mid-morning, a distinction that disappears in patients with marked glycemic variability [27,28]. A daily hypoglycemia likelihood measure derived from the difference

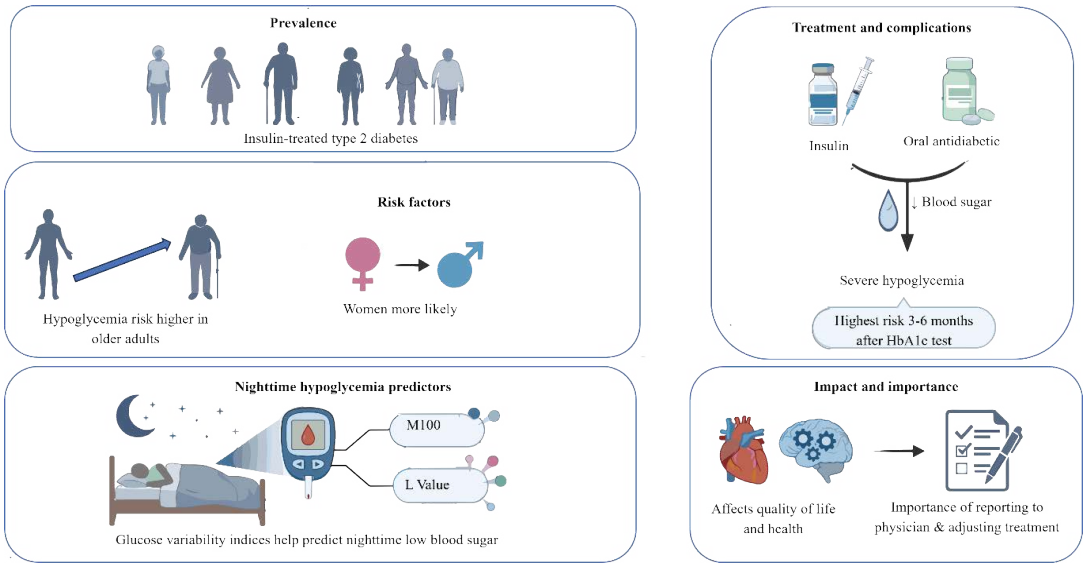

Figure 4: Key prevalence of hypoglycemia in T2DM

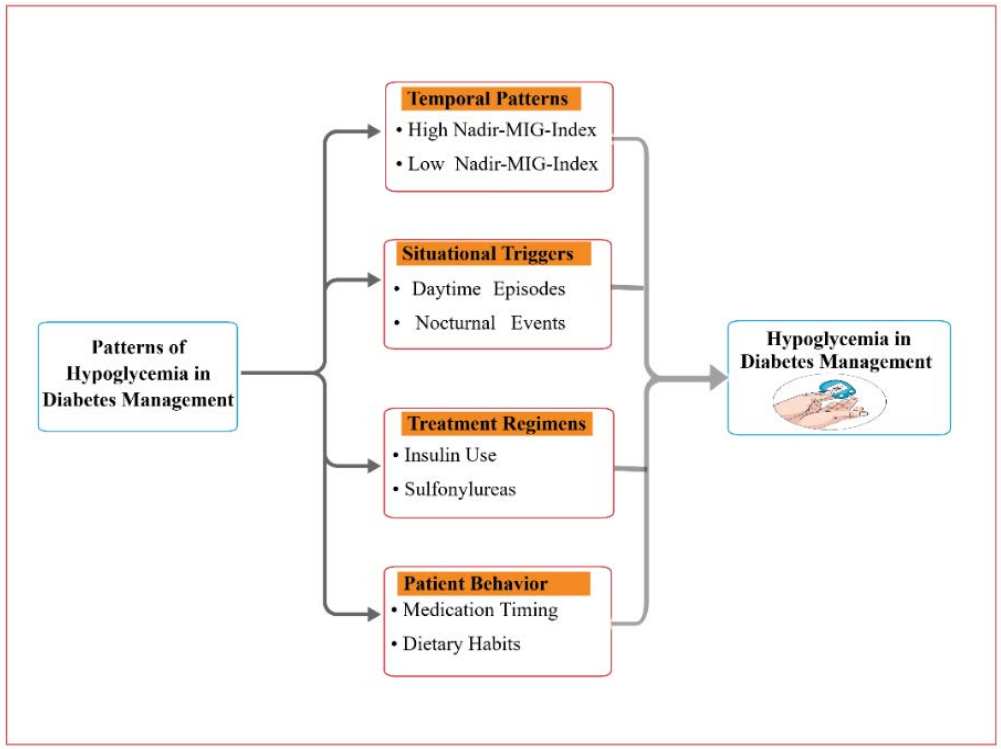

Figure 5: Patterns of hypoglycemia in T2DM by situation, treatment class and patient behavior

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between the lowest and second-lowest glucose values has been proposed, with risk rising substantially as this gap narrows. Consistent with these observations, CGM-derived glycemic patterns indicate that hypoglycemia risk in T2DM is additionally modulated by postural changes, particularly those affecting morning glycemia [29].

However, studies indicate that asymptomatic nocturnal hypoglycemia can be identified through large pre-to-post-breakfast glucose increments recorded in home CGM data. In insulin-dependent patients with T2DM treated with basal-supported oral therapy, studies have shown that a considerable proportion experience unrecognized nocturnal events. The MinAUC1 metric, which integrates glucose values over the early morning hours, has been reported to correspond with a pronounced pre-breakfast glucose rise in patients who experience hypoglycemia. On this basis, home CGM monitoring that tracks glucose dynamics around breakfast appears to predict nocturnal hypoglycemic risk more reliably than isolated pre-breakfast measurements [30].

Situational Triggers

Modeling studies suggest that CGM-based prediction algorithms with acceptable accuracy can serve as early warning systems for nocturnal hypoglycemia and may strengthen follow-up strategies in elderly, insulin-treated patients with T2DM [31]. Anticipating individual nocturnal episodes would allow countermeasures to be applied in time and this appears feasible even for patients who remain conscious during their most severe events [32]. In one reported model built on a set of CGM glucose metrics, nocturnal hypoglycemia episodes were identified an average of about one and a half days in advance, with performance improving as training data accumulated; however, continued model updating is necessary, as accuracy declines when the initial model is trained on data older than eight weeks. For very severe episodes associated with daytime hypoglycemia, supplementary safety measures such as direct monitoring have been proposed, including the presence of night-time personnel able to intervene in the event of unconsciousness [33].

A scoring system has also been developed to identify individuals at high risk of recurrent severe hypoglycemia for closer follow-up and most individuals with nocturnal events had high-risk scores. In such patients, clinicians should examine disordered insulin-omitting behavior or other contributing issues and establish preventive measures. Three or more nocturnal antecedent symptoms also indicate the need to analyze possible interventions [34]. Diarrhea, a long interval between the last meal and bedtime and older age can reduce awareness of nocturnal hypoglycemia. For patients worried about nocturnal events, clinicians should discuss evening eating habits, especially differences on weekends, when nocturnal events are more frequent [35]. Patients with advanced disease at risk of falling asleep while watching television in bed or after taking evening medications should be warned about the danger of hypoglycemia, since overt hypoglycemia can trigger situational symptoms before the first CGM reading confirms [31].

Predictors of Hypoglycemia

Reported predictors of hypoglycemia in insulin-treated T2DM a cross-sectional study found that improper insulin injection technique was significantly linked to an increased risk of hypoglycemia [36]. Socioeconomic factors, including rural residence and low monthly income, were also associated with higher risk, as were clinical conditions such as a history of diabetic ketoacidosis, hypertension, elevated total cholesterol, high low-density lipoprotein cholesterol (LDL-C), increased triglycerides, chronic kidney disease, depression and higher body weight. Elevated diastolic blood pressure doubled the likelihood of hypoglycemic events, a relationship potentially influenced by antihypertensive medications, particularly angiotensin-converting enzyme inhibitors (ACE-I) [37]. Self-monitoring of blood glucose (SMBG) was noted as a relevant factor and after controlling for confounding variables, lower glycated hemoglobin (HbA1c) was associated with a threefold increase in risk. The detailed predictors are summarized below [38]. Hypoglycemia in T2DM is associated with increasing disease burden, glucose variability, antidiabetic medications and strenuous physical activity, which may increase the risk of hypoglycemic events. Severe hypoglycemia can result in cardiovascular complications, hospitalization and increased morbidity and mortality, highlighting the importance of appropriate monitoring and individualized management (**Figure 6**).

Clinical Predictors

In a study of insulin-treated patients with T2DM no significant association was found between body mass index and hypoglycemia, while risk rose as diastolic blood pressure increased, an association possibly related to the antihypertensive drugs those patients used. Hypoglycemia is more prevalent among hypertensive than non-hypertensive patients, although antihypertensive treatment itself has shown contradictory findings [39]. Patient perceptions of symptomatic and asymptomatic hypoglycemia shape how hypoglycemia is understood, managed and acted upon and they highlight how common and frequently unnoticed hypoglycemia. Fear of hypoglycemia can also lead patients to change their treatment and peripheral neuropathy (PNP), by impairing sensory and autonomic function in the extremities, further contributes to the development of hypoglycemia [40]. Lower HbA1c levels predict higher risk intensive glycemic control targeting HbA1c below 7% is associated

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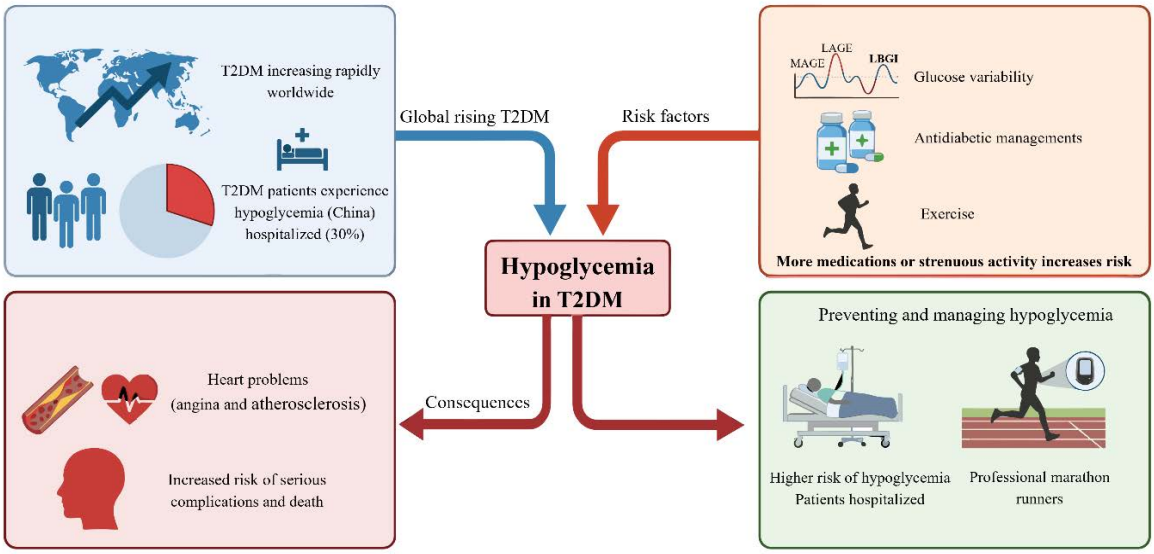

Figure 6: Predictors along with their consequences of hypoglycemia in T2DM

with increased risk and a goal below 6% raises it further. In multivariate analysis, the only statistically significant and independent predictors of hypoglycemia were rural residence, knowledge of hypoglycemia symptoms, the availability and increasing frequency of SMBG, the presence of PNP, high diastolic blood pressure and low HbA1c [41].

In an American study, predictors of hypoglycemia included a history of hypoglycemia in the 12 months before enrollment, lower HbA1c, sex, use of statins and diuretics and self-measurement of blood glucose in the 3 months before the study. Chronic kidney disease roughly doubled the frequency of hypoglycemia, since reduced renal function prolongs insulin action and patients with diabetes carry a higher prevalence of microvascular complications and metabolic disease [42]. Hypoglycemia may also promote arterial damage and act as a secondary factor in the development of macrovascular complications, increasing the frequency of medical interventions for arterial lesions [43].

Biochemical Predictors

Glycemic variability measured in hospital predicts hypoglycemia, variation of blood glucose (CVBG) on the index day, compared with the lowest quintile, was independently associated with increased risk and each 10% increase in admission CVBG beyond 18% raised the adjusted odds of hypoglycemia by 19%. This effect was seen across a range of patient characteristics, admission glucose levels, diabetes history and insulin therapy, as indicated by interactions between CVBG and key clinical variables [44]. Across the quartile distribution of nadir glucose, CVBG and mean glucose on the index day, the adjusted odds of hypoglycemia were significantly elevated compared with the lowest quartile [45].

To improve detection of what is commonly considered sliding-scale insulin-induced hypoglycemia, models were developed and validated to predict biochemical (BG < 70 mg/dL) and clinically significant hypoglycemia (BG < 54 mg/dL or use of glucose-lowering interventions) in hospitalized patients treated with sliding-scale insulin [46]. Internal validation showed how many true hypoglycemic events would be detected at a given sensitivity cut-point; among insulin-treated patients, about 46% of clinically significant hypoglycemic events were detected at an 80% sensitivity threshold [47]. The models drew on extensive hospital record data, but clinically important predictors were frequently missing or recorded only as provider orders or actions. The conclusions are limited to newly admitted in patients treated with sliding-scale insulin, the study population was restricted to adults at a single hospital and CGM was not used [33].

Patient Education, Self-Management and Role of Healthcare Providers

Patient education is the foundation of hypoglycemia in T2DM management, generally patients should receive detailed counseling and health education about diabetes, the symptoms and management of hypoglycemia [48]. Patients should also receive continuing self-care education and proper training in self-monitoring of blood glucose (SMBG), including how to control the situation. For this, a diabetes self-care handbook should be developed to guide patients in managing blood glucose and in responding to hypoglycemia symptoms; when symptoms appear, patients should be advised to take a sugary drink or snack such as orange juice, cola or sweetened yogurt and then retest their blood glucose after 10 to 15 minutes. Also counseled to carry candy or sugar in their pocket together with a chart of their diabetes treatment [49]. Such hypoglycemia reminds patients of their

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daily management routine and helps them recognize when a problem arises. Proper training by health professionals is needed to help patients maintain an appropriate lifestyle and a sound understanding of the disease. Other measures emphasized include regular exercise, proper nutrition therapy, constant self-monitoring of blood glucose and strict adherence to treatment without changing doses before consulting a healthcare provider [50].

Importance of Education

In a shared decision-making approach, clinicians and patients act as partners and patients take part in treatment decisions. Individualized, interactive and reinforced diabetes education is therefore likely more helpful than simple group lessons. Hypoglycemia is a well-known acute complication of diabetes treatment and a main barrier to achieving glycemic goals in type 2 diabetes [51]. Early identification of high-risk populations and targeted diabetes education may reduce the incidence of hypoglycemic events and clinical studies support this effect of education [52]. One education program for patients with hypoglycemia problems aimed to prevent hypoglycemia by optimizing insulin therapy in type 2 diabetes and blood glucose awareness training, a psycho-educational intervention, was designed to improve the accuracy with which patients detect and interpret relevant symptoms. Diabetes education is thus an effective tool for managing hypoglycemia in type 2 diabetes [53].

However, the effect of structured education on hypoglycemia prevention in type 2 diabetes still limit. In one randomized study, a specialized individualized reinforcement program on hypoglycemia management was delivered after structured group education for patients with T2DM [54]. The structured group education covered the pathophysiology of diabetes and meal planning, while the additional individualized reinforcement education, delivered by phone calls or short messages four times weekly, covered the mechanism and management of hypoglycemia. To evaluate the effect of the reinforcement education, structured group education plus reinforcement was compared with structured group education alone and it was observed that proper outcome of the patient's improvements [51].

Self-Monitoring Techniques

Diabetes is a chronic condition that requires permanent control of blood glucose through a healthy diet, physical activity and medication. Hypoglycemia in T2DM, poor glucose regulation can lead to severe complications, including impaired wound healing, susceptibility to infection, kidney and heart failure, stroke and blindness, together with polyuria, dehydration and severe weight loss. These problems arise because the immune system destroys the insulin-producing pancreatic beta cells [55]. Treatment requires injected insulin and insulin therapy carries a hypoglycemia risk, with severe hypoglycemia potentially leading to coma. Fear of severe hypoglycemia is a major barrier to the strict glycemic control this therapy demands. Patients must therefore receive early, comprehensive education and counseling that enable them to recognize, prevent and treat hypoglycemia and technological approaches such as continuous subcutaneous insulin infusion, continuous glucose monitoring and hypoglycemia-prediction algorithms could further reduce severe episodes [56,57].

Conventional self-monitoring of blood glucose also has limitations. It requires samples after at least 8 hours of fasting and 2 hours after each meal, as well as overnight hourly samples and all daily capillary samples must be analyzed in a whole-blood glucose meter. Over the years, this classic procedure has proven insufficient [49,58]. To overcome this issue algorithms for the early identification and prevention of hypoglycemia, applied mainly to patients with type 2 diabetes, describes hypoglycemia monitoring chiefly through wearable devices operating with non-invasive methods [59]. Accurate blood glucose predictions can be obtained without a contemporaneous glucose measurement and non-invasive methods combined with dedicated wearables could estimate glucose accurately, gain acceptance among patients and potentially support industrial production of predictive wearables [60]. In addition, nocturnal devices, such as bed-based and wearable sensors, for preventing nocturnal hypoglycemia and shows that applying accurate, non-invasive prediction models to T2DM can considerably reduce slow blood glucose declines [31]. Also, it addresses implementing the developed algorithms as a smart database, a secondary prediction approach capable of the early identification and prevention of nocturnal hypoglycemic episodes [61].

Role of Healthcare Providers

Healthcare providers play a crucial role in managing diabetes, both during the index hypoglycemic event, through counseling on prevention and afterward, to encourage prompt and appropriate treatment of recurrent episodes. Patients may also avoid seeking care because of fear of stigma related to over-treatment, being labeled non-compliant or being perceived as failing to keep their diabetes under control [62]. In reported studies, education and psychological support have been found effective in reducing fear of hypoglycemia. Because diabetes is typically considered an ambulatory care-sensitive condition, preventing hospitalization for complications such as severe hypoglycemia is a key challenge for healthcare systems. The number of patients with diabetes is increasing in most countries, making diabetes management a cornerstone of healthcare and the financial burden of diabetes hospitalizations places further pressure on health insurance systems [63]. Patient-centered, structured counseling and psychological support are pivotal components

of treatment. Patients should understand the chronic nature and severity of the disease and the risk of its complications. Realistic goal setting and adherence to treatment protocols also influence clinical outcomes. Treatment adherence can be defined as the degree to which a patient continues the agreed treatment and better patient outcomes are associated with higher compliance [64].

Collaborative Care Approaches

High rates of hypoglycemia are observed in patients with T2DM, especially those on advanced glycemic therapy. To reduce the rate and severity of hypoglycemia effectively, more research is needed on its recognition, management and collaborative care in this population [11,21]. The impact factors and predictive factors of hypoglycemia in patients with T2DM, with particular attention to the medication reconciliation and structured follow-up should be considered. For example, a retrospective observational study patients with hypoglycemia examined their demographic characteristics, the occurrence of hypoglycemic events and blood glucose management patterns before and after hypoglycemia [65]. Patients with hypoglycemia had lower average HbA1c values and mostly received combination therapy. The rates of dual or triple oral therapy exceeded national guideline recommendations, patients used traditional Chinese medicine treatment and other patients used third-generation sulfonylureas [66]. Moreover, patients tested their blood glucose once and neither increased their testing frequency, took sugar promptly, nor received symptomatic treatment. These findings suggest that governments should strengthen the management of diabetes care institutions [67]. Another survey of registered diabetic patients using medical insurance information in province further showed that education level was negatively correlated with hypoglycemic events; the lower the education level, the higher the occurrence of hypoglycemia. Given patients' limited ability to judge their own condition, hospital-affiliated education may have a protective effect in preventing and treating hypoglycemia [68].

Monitoring and Follow-Up

In reported studies patients used a median insulin dose of 86 IU/day at the index event, which fell to 74 IU/day at follow-up [69]. The risk of hypoglycemia was positively correlated with the use of sildenafil, diuretics, dihydropyridine calcium channel blockers, beta-blockers, night-shift work, longer insulin duration, basal-bolus regimens, inversely correlated with the use of glucose-lowering drugs, high fiber intake, metformin and sulfonylureas [70]. Variables linked to hypoglycemia analysis were then tested together in a multivariate model to find independent predictors. BMI was not significantly related to hypoglycemia, but the risk rose as diastolic blood pressure increased, a result also confirmed by event analysis. This association may be related to antihypertensive drugs, particularly ACE inhibitors, which have been suggested as a risk factor for hypoglycemia [71]. Similarly, study reported that insulin-treated patients with high diastolic blood pressure were significantly more likely to experience hypoglycemia [72]. However, this might be related to the number of medications, the concomitant use of antihypertensive medicines in T2DM increases the risk of hypoglycemic events. Lower HbA1c levels also predicted higher risk, so diastolic blood pressure and HbA1c may be important parameters for predicting hypoglycemia [73].

Technological Advances in Diabetes Management

Since the discovery of insulin a century ago, developed tools and technologies have made diabetes easier to manage effectively [74]. Fasting blood glucose tests, continuous glucose monitoring devices, insulin pumps and apps can support medication adherence, accurately define carbohydrate intake, detect hypoglycemia before symptoms appear or show the risk of hypoglycemia at a given time of day [75]. New technology offers solutions to the main problems of diabetes management, such as timely adjustment of medication doses, understanding how lifestyle choices affect blood glucose and detecting emerging hyperglycemia or hypoglycemia directly [76]. Technologies providing real-time glucose readings support better glycemic control. However, it is important to recognize the potential limitations of new technology and the appropriate place for engineered interventions.[77] The conventional and technology-assisted glucose monitoring, including fasting glucose testing, CGM, insulin pumps and mobile applications, together with the role of CGM in identifying hypoglycemia risk and the importance of patient education and regular follow-up as illustrated in **figure 7**.

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) is increasingly used to assess glycemic variability and hypoglycemia risk in older adults with type 2 diabetes [78,79]. A recently described CGM-derived hypoglycemia index quantifies the area under the glucose curve below a defined threshold and the resulting risk score, based on the highest daily values, correlates with the likelihood of future hypoglycemic episodes [80]. Threshold selection through statistical optimization has further improved the index's predictive accuracy and patients classified as high risk by this measure experience more subsequent hypoglycemic events. These findings indicate that CGM metrics can help identify older patients at elevated risk early enough for timely preventive action and that linking continuous glucose data directly to hypoglycemia prediction marks a useful departure from earlier approaches [81].

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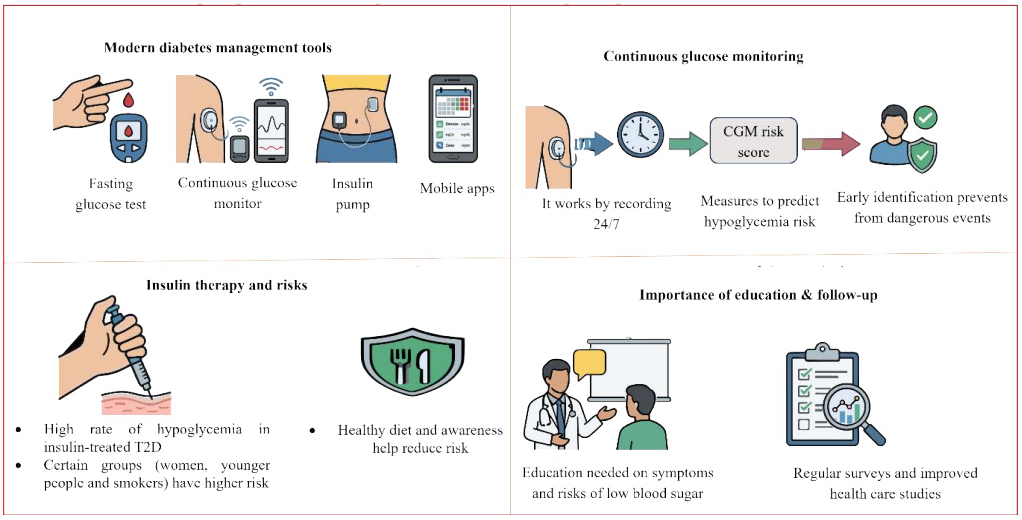

Figure 7: Modern technology approaches to diabetes management and prevention of hypoglycemia

Hypoglycemia and Its Awareness in Insulin-Treated T2DM

Hypoglycemia is common among patients with insulin-treated type 2 diabetes mellitus (T2DM). Studies in this area have generally enrolled patients with established T2DM on insulin and excluded those with other forms of diabetes, pregnancy, malignancy or major uncontrolled comorbidities [82]. Assessment typically combines clinical interview with blood glucose and HbA1c measurement, blood pressure and pulse monitoring and screening for peripheral neuropathy and hypoglycemic symptoms [83]. Reported prevalence is high in this population and episodes may be accompanied by falls in blood pressure and pulse rate. Occurrence has been linked to demographic and socioeconomic factors, while healthy dietary practices appear protective. Both symptomatic and asymptomatic episodes occur and impaired hypoglycemia awareness may raise the risk of severe outcomes [84]. These findings support regular monitoring, dietary management and patient education on recognizing and treating hypoglycemia and such epidemiological studies can identify risk factors and inform preventive strategies [85]. Limitations include selection bias, examiner bias and variability in clinical assessment, so prospective studies are needed to confirm the findings and strengthen prevention in insulin-treated T2DM [86].

Clinical Trials of Hypoglycemia in T2DM

Clinical trials in patients with T2DM have clarified several aspects of hypoglycemia. In metformin-treated patients, hypoglycemia delayed platelet and coagulation activation, with flow-cytometry markers and fibrinogen, factor VIII and PAI-1 rising 24 hours after the event and the glycemic threshold rising (NCT03460899). Adding the MyHC-T2D psychoeducation program to proactive nurse-led care did not significantly reduce severe hypoglycemia over 14 months, although both arms improved from baseline and a possible CGM benefit for level 2 events appeared (NCT04863872). A pharmacist-led counselling intervention (SUGAR Handshake) nearly halved hypoglycemic attacks over three months (NCT04081766). In primary care, hypoglycemia incidence and severity were greatest with insulin and sulfonylureas compared with metformin and insulin carried the highest risk of severe episodes (NCT02666521). Once-weekly efsitora did not increase hypoglycemia versus glargine under standardized provocation (NCT04957914). Hypoglycemia reduced platelet prostacyclin sensitivity in T2DM, promoting platelet hyperactivity (NCT02205996). Mild hypoglycemia to about 3 mmol/L impaired executive function, attention and memory (NCT03014011) and endothelial microparticles peaked within 240 minutes of the event, suggesting a means of confirming that hypoglycemia occurred (NCT03102801). GIP infusion during insulin-induced hypoglycemia raised glucagon and lowered glucose infusion requirements (NCT01414556). Reduced awakening after nocturnal hypoglycemia, a pattern of clinical interest because impaired nocturnal awareness is associated with severe outcomes (NCT01780272). The details of several registered clinical trials are presented in the **Table 1**.

Emerging Challenges and Hypoglycemia Management in T2DM

Severe hypoglycemia has traditionally been viewed as a complication of long-standing insulin use in type 1 diabetes, yet it also occurs frequently in T2DM treated with newer agents alone, without insulin or secretagogue therapy. Research on whole-day glucose exposure is needed to define the patterns of hypoglycemia and identify susceptible individuals and phenotypic markers of nutrient sensitivity

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Table 1: Characteristics of clinical trials of hypoglycemia in type 2 diabetes mellitus (ClinicalTrials.gov)

NCT no.	Study focus	Design	Intervention	Primary outcome	Sponsor	Status; completion
NCT03460899	Hypoglycemia-induced platelet activation in T2DM (clamp study)	Interventional (randomized, single-group)	Euglycaemic vs hyperinsulinaemic/ hypoglycaemic clamp	Change in platelet activation (ADP-induced LTA)	Medical University of Graz	Completed; Jun 2018
NCT07887334	Hypoglycemia risk prediction in elderly women with T2DM (frailty/ sarcopenia)	Observational (cohort, cross-sectional)	Geriatric, sarcopenia and laboratory assessment	Frequency of hypoglycemic episodes (12 weeks)	Samara State Medical University	Completed; Dec 2025
NCT04863872	Prevention of severe hypoglycemia in T2DM: proactive care vs care + education (PHT2)	Interventional (randomized, parallel)	Proactive care management ± MyHC-T2D education	Self-reported severe hypoglycemia (14 months)	Kaiser Permanente	Completed; Jun 2024
NCT04081766	Pharmacist-led counselling to control hypoglycemia in older adults with T2DM (SUGAR Handshake)	Interventional (randomized, parallel)	Pharmacist-led counselling vs usual care	Frequency of total hypoglycemic episodes (12 weeks)	University of Lincoln	Completed; Dec 2020
NCT02666521	Hypoglycemia frequency and severity in T2DM managed in primary care	Observational (other, prospective)	None (observational)	Frequency of mild hypoglycaemic episodes (12 months)	University of Leicester	Completed; Jun 2017
NCT04957914	Hypoglycemia incidence with LY3209590 vs insulin glargine in T2DM	Interventional (non-randomized, parallel)	LY3209590; insulin glargine	Incidence of documented hypoglycaemia (to day 186)	Eli Lilly and Company	Completed; Oct 2022
NCT02205996	Acute hypoglycemia effects on platelets and endothelial function in T2DM	Interventional (non-randomized, parallel)	Insulin clamp (euglycaemic/ hypoglycaemic)	Platelet activation markers (P-selectin, fibrinogen binding)	University of Hull	Completed; May 2013
NCT01614769	Glimepiride effects on recovery from hypoglycemia in T2DM	Interventional (randomized, crossover)	Glimepiride 2/4 mg vs placebo; hypoglycaemic clamp	Recovery time from hypoglycemia to euglycemia	Merck Sharp & Dohme LLC	Completed; Jan 2013
NCT01523405	Hypoglycemia frequency, impact and QoL in T2DM (India, multicentre)	Observational (case-only, cross-sectional)	None (non-interventional)	Diabetes-related QoL (modified 15-item DQoL)	AstraZeneca	Completed; Feb 2013
NCT03014011	Mild hypoglycemia and cognitive function in T2DM	Interventional (randomized, crossover)	Hypoglycaemic vs euglycaemic clamp	Psychomotor speed (Symbol Digit Modalities Test)	Bispebjerg Hospital	Completed; Jul 2018
NCT03102801	Biomarkers for detecting hypoglycemia after the event in T2DM	Interventional (non-randomized, parallel)	Insulin infusion (Humulin S)	Endothelial microparticles after hypoglycaemia	University of Hull	Completed; Jan 2018
NCT06982846	Retatrutide effects on recovery from hypoglycemia in T2DM	Interventional (randomized, parallel)	Retatrutide vs placebo (16 wk)	Time to plasma glucose recovery (48 to 70 mg/dL)	Eli Lilly and Company	Completed; May 2026
NCT07314749	Hypoglycemia early-warning system + physician-nurse management in hospitalized T2DM	Interventional (non-randomized, parallel)	Collaborative intervention vs usual care (insulin pump)	Incidence of hypoglycemia (<3.9 mmol/L)	Third Affiliated Hospital, Sun Yat-Sen University	Completed; Feb 2025
NCT01414556	GIP effects during insulin-induced hypoglycemia in T2DM	Interventional (randomized, crossover)	GIP vs saline	Glucagon/insulin (C-peptide) response (AUC)	Mikkel Christensen	Completed; Nov 2012

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NCT01780272	Nocturnal hypoglycemia and sleep quality in T2DM	Interventional (randomized, crossover)	Glucose clamp	EEG-identified arousals (0-4 h after sleep stage N2)	Novo Nordisk A/S	Completed; Sep 2013
NCT06746714	Pharmacist-led hypoglycemia prevention with 'Hypoglycemia on a Page' (HOAP) in high-risk T2DM	Interventional (randomized, parallel)	Pharmacist-led HOAP care vs usual care	Safer-regimen discontinuation; excess hypoglycaemia (TBR <4%)	Kaiser Permanente	Recruiting; Dec 2027

could guide adjustments in insulin dose and delivery timing. Because dietary macronutrients have complex and dynamic effects on postprandial glycemia, how carbohydrates, fats and proteins interact within a meal and how meal timing and insulin modify these effects, still require comprehensive study [11].

The optimal timing of mealtime insulin injections also remains unresolved. The conventional advice to inject insulin about 15 minutes before a meal may not fit all circumstances; a post hoc analysis found little difference between injecting regular insulin 30 minutes before or at mealtime with rapid-acting analogue insulins many patients inject just before or immediately after eating, an approach that reduced postprandial hyperglycemia and hypoglycemia compared with premixed insulins. The assumption that a physiologic injection pattern should mimic meal-stimulated insulin secretion of the non-diabetic state has been neither supported nor contradicted by systematic examination of the evidence and as more patients receive intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion, defining the optimal injection timing is a pressing need [87].

Technological advances in diabetes management over the past two decades have not necessarily improved hypoglycemia control. In a population-based observational study of severe hypoglycemia trends, home visits and phone consultations declined or remained at a low, stable rate, yet severe events requiring hospitalization became an increasing burden in adults with T2DM [88].

Future Directions

Severe hypoglycemia is increasingly recognized in T2DM patients treated with newer agents alone, without insulin or secretagogue therapy and research on whole-day glucose exposure is needed to define its patterns and identify susceptible individuals; phenotypic markers of nutrient sensitivity could guide adjustments in insulin dose and delivery timing [89]. The interaction of dietary macronutrients within a meal and how meal timing and insulin modify postprandial glycemia, also require comprehensive study [90]. Optimal mealtime insulin injection timing remains unresolved and as more patients receive intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion, defining this timing is a pressing need [91].

Despite two decades of technological advances, severe hypoglycemia requiring hospitalization has become an increasing burden in adults with T2DM [92]. Technological approaches such as continuous subcutaneous insulin infusion, continuous glucose monitoring and hypoglycemia-prediction algorithms could further reduce severe episodes, though their integration into routine care requires further validation and accessibility [93]. Future research should use larger, more diverse cohorts and examine the dynamic interactions of treatment regimens, patient characteristics and lifestyle factors to optimize hypoglycemia prevention and improve overall diabetes care outcomes.

Conclusion

Hypoglycemia remains a difficult problem in type 2 diabetes, especially in patients on insulin. Despite wider therapeutic options and new technology, hypoglycemic events continue to carry risks of cardiovascular complications and mortality. Recognizing the clinical, biochemical and behavioral factors that predict these events is essential for individualizing treatment and limiting that risk. Patient education, self-monitoring and collaborative care improve awareness, prevention and management, while continuous glucose monitoring and predictive algorithms hold promise for early detection, although they still need validation and better accessibility before routine use. Future studies should include larger and more diverse populations and investigate the interplay between treatment regimens, patient characteristics and lifestyle factors, thereby enabling more targeted hypoglycemia prevention and improved outcomes in diabetes care.

Abbreviation:

ACE-I: Angiotensin-converting enzyme inhibitors; *AUC*: Area under the curve; *BG*: Blood glucose; *BMI*: Body mass index; CKD: Chronic kidney disease; *DM*: Diabetes mellitus; *FBS*: Fasting blood sugar; *GLD*: Glucose-lowering drug; *GLP-1*: Glucagon-like peptide-1 receptor; *GLP-1R*: Glucagon-like peptide-1 receptor; *HbA1c*: Glycated hemoglobin; *ICU*: Intensive care unit; *ITA*: Insulinotropic agent; *MAGE*: Mean amplitude of glycemic excursion; *ME*: Marathon experience; *MIG-index*: Minimum interstitial glucose index; *MDI*: Multiple daily injections; *NPH*: Neutral protamine Hagedorn insulin; *OAD*: Oral antidiabetic drug;

PNP: Peripheral neuropathy; *PPBS*: Post-prandial blood sugar; *QOL*: Quality of life; *SCIs*: Subcutaneous insulin injections; *SMBG*: Self-monitoring of blood glucose; *SMBG*: Self-monitoring of blood glucose; *SU*: Sulphonylurea; *VAS*: Visual analog scale; *CGM*: Continuous glucose monitoring; *CVBG*: Coefficient of variation of blood glucose.

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Author Contributions

Abdulkadir Abdu conceived the idea, prepared the manuscript and created the figures. Eithar Elshafie Mohamed Eltayib and Khalid Mohammed performed the literature search and data collection. Mohamed Ibrahim Arman Ali and Islam Rahama Imam Ahmed collected data and drafted the manuscript. Israa Abdelrahim drafted and critically reviewed the manuscript. Mohamedidris Hamed conceived the initial idea, drafted and reviewed the manuscript. Hossamaldeen Bakrey performed the literature search, collected data and critically reviewed the manuscript. All authors have read and approved the final version of the manuscript.

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The authors report no financial or any other conflicts of interest in this work.

Clinical trials

Not applicable

Consent to Participate

It is a review article; thus, it is not applicable

Ethical Approval

This study does not involve experiments on animals or human subjects.

Data Availability

The data that support the findings of this study are available in standard research databases such as PubMed, Science Direct or Google Scholar and/or on public domains that can be searched with either key words or DOI numbers.

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