Editorial

Adjunctive and Emerging Therapies in Type 1 Diabetes: Closing the Gaps in Care

Aisha Sheikh

Despite significant advancements in insulin delivery systems and glucose monitoring technologies, Type 1 Diabetes (T1D) remains a complex and burdensome condition, especially in resource-limited settings. The global burden of unmet needs in T1D is substantial and persistent.

Recent data suggest that more than 80% of individuals with T1D fail to achieve a glycated hemoglobin (HbA1c) target of <7%, with even poorer outcomes reported from low- and middle-income countries (LMICs), where barriers in access, availability, and affordability of insulin continue to challenge optimal care.[1]

Moreover, acute complications such as Diabetic Ketoacidosis (DKA) and severe hypoglycemia remain frequent and dangerous. Studies indicate that approximately 1 in 20 individuals with T1D are hospitalized annually due to DKA.[2] Similarly, nearly 12–20% experience one or more severe hypoglycemic events within a year, even among users of advanced technologies such as Automated Insulin Delivery (AID) systems or Continuous Glucose Monitors (CGMs).[2]

Beyond acute events, insulin resistance, weight gain, and elevated cardiovascular (CV) risk—2- to 4-fold higher even in well-controlled patients—pose long-term challenges. Recent estimates suggest that two-thirds of individuals with T1D are either overweight or obese, a stark contrast to historical perceptions of T1D phenotypes.[1]

While exogenous insulin remains the cornerstone of T1D management, it does not address all pathophysiological aspects of the disease. In fact, insulin therapy may exacerbate some issues such as weight gain, insulin resistance, and hypoglycemia. This highlights the need for adjunctive pharmacologic therapies that can improve glycemia without increasing the risk of hypoglycemia or ketosis.

Historically, agents such as metformin, thiazolidinediones, and pramlintide have been explored as adjuncts in T1D with variable success. In recent years, there has been increasing interest in the potential of SGLT2 inhibitors and incretin-based therapies, including Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA) and dual GLP-1 RA/Glucose-Dependent Insulinotropic Polypeptide (GLP-1/GIP analogues), to play a supportive role in T1D management.

SGLT2 Inhibitors: Promise and Precaution

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) have demonstrated multiple benefits in people with type 2 diabetes, and even in individuals without diabetes, particularly in relation to cardiorenal outcomes. In T1D, data are promising yet tempered by safety concerns. Phase 3 trials such as EASE-2 showed that empagliflozin resulted in HbA1c reductions of 0.5%, improvements in time-in-range (TIR), reduced insulin requirements, weight loss (~2.7 kg), and reductions in albuminuria and systolic blood pressure, without an increase in severe hypoglycemia (2.7% vs. 3.1% with placebo).[3]

However, the increased risk of DKA remains a major barrier. Regulatory authorities such as the US Food and Drug Administration (FDA) declined approval, whereas Japan and the European Medicines Agency (EMA) have allowed restricted use under strict guidelines—targeting patients with higher Body Mass Index (BMI), higher total daily dose (TDD) of insulin, and emphasizing patient education and sick-day management. Lower doses (e.g., empagliflozin 2.5 mg) are being explored in trials with more favorable safety profiles.

Ketone monitoring is key to mitigating risk. Emerging tools such as continuous ketone monitoring (CKM) and routine ketone checks at fasting state during well days

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(e.g., three times per week) are being investigated for SGLT2i users in T1D.[4]

Incretin-Based Therapies and GLP-1 Receptor Agonists

Hyperglucagonemia, particularly postprandial, is a well-recognized but under-addressed contributor to hyperglycemia in T1D. Studies show that glucagon levels paradoxically rise after meals in T1D patients, aggravating hepatic glucose output and glycemic instability.[5]

GLP-1 receptor agonists offer a dual benefit: suppression of inappropriate glucagon secretion and modest enhancement of insulin sensitivity. Trials of liraglutide and semaglutide in T1D demonstrate modest HbA1c reductions (0.2–0.3%), significant weight loss, and insulin dose reductions, albeit with a small increase in mild hypoglycemia.[6]

With the increasing use of automated insulin delivery newer data from semaglutide in T1D trials report up to 22% insulin dose reductions with no increased hypoglycemia.[7] Additional benefits may be more pronounced in individuals with preserved C-peptide, suggesting a possible role in β-cell protection.[8] Ongoing trials are exploring cardiorenal and hepatic (Metabolic dysfunction-Associated Steatotic Liver Disease or MASLD) outcomes in T1D populations, as well as optimal phenotype matching for these agents.

Glucagon Receptor Antagonists (GRAs): An Emerging Class

Targeting glucagon action through glucagon receptor antagonists (GRAs) represents a novel therapeutic approach.[9] Agents such as volagidemab, a once-weekly human monoclonal antibody, have shown significant reductions in insulin requirements (21–26%), improved TIR, and a placebo-corrected HbA1c reduction of 0.65% in Phase 2 trials—without increased hypoglycemia.[10]

Furthermore, GRAs may improve insulin sensitivity at the level of adipose and muscle tissues and increase lean body mass. In a small crossover trial, the combination of GRA with SGLT2i demonstrated additive benefits: reduced glycemic variability, improved TIR, and importantly, attenuated ketogenesis during insulin deficiency.[11] Safety concerns—particularly regarding hepatic fat accumulation, alpha-cell hyperplasia, and counter-regulatory responses—remain under investigation.

Glucokinase Activators

Glucokinase (GK) acts as a glucose sensor in both pancreatic and hepatic tissues. GK activators are currently under early-phase evaluation in T1D, with some studies reporting improved glycemic profiles, no excess DKA risk, and possible protection from hypoglycemia. These agents may contribute to reducing disease burden and improving patient confidence in glucose stability.[12]

While technological advances such as CGMs, CSII, and hybrid closed-loop systems are transforming care for many, they are largely inaccessible to individuals in LMICs. In these settings, the divide between those who can afford and those who cannot is growing.

For lower-middle-income countries (LMIC) like Pakistan, the most urgent priorities remain universal access to insulin, regular glucose monitoring, and structured diabetes education. While innovative adjunctive therapies hold promise, their incorporation into clinical practice must be cautious, evidence-driven, and equitable.

Policymakers, healthcare systems, and professional societies should prioritize strengthening existing diabetes services—ensuring reliable access to optimal insulin therapy, comprehensive/structured patient education, and tools like CGMs and advanced insulin delivery systems where feasible. Adjunctive therapies, when clinically indicated, can complement these efforts.

Ultimately, the goal must be to deliver person-centered, scalable, and sustainable care to all individuals living with T1D—particularly in underserved and vulnerable populations.

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