

## Noninsulin pharmacological management of type 1 diabetes mellitus

Vishvas Garg

Department of Pharmacy Practice, College of Pharmacy, University of New Mexico, USA

### ABSTRACT

The injectable nature and other shortcomings of insulin have stimulated interest in studying the noninsulin pharmacological therapies to manage type 1 diabetes mellitus (T1DM). The purpose of this study is to conduct a systematic literature review of noninsulin pharmacological therapies for the management of T1DM. For this, the following PubMed search was conducted: Diabetes Mellitus, Type 1/therapy"[Mesh] Limits: Review Sort by: Publication Date. After applying various inclusion and exclusion criteria, a total of 63 studies were reviewed. Based on this review, noninsulin pharmacological therapies can be divided into following classes: (1) Insulin-sensitizing agents (biguanides and thiazolidinediones), (2) gastrointestinal nutrient absorption modulators ( $\alpha$ -Glucosidase inhibitors and amylin), (3) immunotherapeutic agents, (4) incretin-based therapies, (5) recombinant human insulin-like growth factors, and (6) other promising therapeutics. Some of these are already used either as monotherapy or adjuvant to insulin, whereas, to manage T1DM, the benefits and risks of the others are still under evaluation. Nonetheless, insulin still remains the cornerstone to manage the T1DM.

**Key words:** Amylin, biguanides, incretin-based therapies, insulin-like growth factors, immunotherapeutic agents, thiazolidinediones, type 1 diabetes mellitus,  $\alpha$ -glucosidase inhibitors

### INTRODUCTION AND BACKGROUND

The global prevalence of diabetes is increasing due to factors such as population growth, aging, urbanization, and increased prevalence of obesity and physical inactivity. In this regards, currently, India has the largest number of diabetes patients (50.8 million people) in the world. Furthermore, the World Health Organization (WHO) estimates that, between the years 2000 and 2030, the prevalence of diabetes in India will increase by 151%.<sup>[1]</sup> The WHO also estimates that, in India, between the years 2006 and 2015, the predicted loss of national income from diabetes will be 336.6 billion International Dollars.<sup>[2]</sup>

Diabetes mellitus (DM) is generally of three main types: type 1 diabetes mellitus (T1DM, insulin-dependent diabetes), type 2 DM (noninsulin-dependent diabetes), and gestational DM.<sup>[3]</sup> About 10% of all the diabetes patients are of the T1DM.<sup>[3]</sup> In India, the prevalence of T1DM is variable. A study by Kalra *et al.* in 2010 found that the overall prevalence of T1DM in Karnal, Haryana, India, is 10.20 cases of T1DM per 100 000 population.<sup>[4]</sup> As per the two other studies, one conducted in Chennai and other in Karnataka, India, the overall prevalence of T1DM was found to be 3.8/100 000 persons in Karnataka and 17.93/100 000 persons in Chennai.<sup>[5,6]</sup>

Although extensive work has been conducted to examine type 2 DM, comparatively less attention has focused on T1DM, especially in developing countries.<sup>[4]</sup> Since the Diabetes Control and Complications Trial, intensive therapy has been directed at using insulin to achieve glucose and glycated hemoglobin (HBA1c) values as close to normal as possible. Nonetheless, this approach has several drawbacks. First, some patients may develop insulin resistance.<sup>[7]</sup> Second, despite the advances and various currently available insulin formulations, often the

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Corresponding Author: Mr. V Garg, 402 Cornell Dr. SE, Apt # 2, Albuquerque, NM 87106, USA. E-mail: vishvas4588@gmail.com

goals of excellent/good glycemic control is not achieved. Third, using the insulin therapies, hyperglycemia (especially postprandial hyperglycemia), and hypoglycemia continue to be problematic in the T1DM management. Fourth, the discomfort to the patients due to the injectable nature of the insulin.

These shortcomings of insulin therapies have stimulated interest in studying the noninsulin pharmacological therapies to manage T1DM. Recently, to our knowledge, there has been no published study to conduct a systematic literature review of noninsulin pharmacological therapies to manage T1DM. Therefore, the purpose of this study is to provide a systematic review of the published studies of the noninsulin pharmacological management of T1DM.

## RESEARCH DESIGN AND METHODS

PubMed was queried using the following search strategy: “Diabetes Mellitus, Type 1/therapy”[Mesh] Limits: Review Sort by: Publication Date.” In order to obtain the data on the latest advances in the field of the noninsulin pharmacological management of T1DM, the following inclusion criteria were applied: (1) articles published after 2007 and (2) only studies describing the therapies used in T1DM management. The following exclusion criteria were then applied to the abstracts of the studies remained after applying the inclusion criteria: (1) articles describing insulin therapies, (2) non-pharmacological therapies, (3) epidemiology of T1DM, (4) economics of T1DM, (5) studies whose primary focus was not T1DM, (5) studies describing the complications of T1DM, (6) studies describing the perioperative management of T1DM, and (7) studies describing prevention and risk factors of T1DM. The full-text articles of these remaining studies were then retrieved and reviewed. The references cited in all the above retrieved publications were also reviewed for relevance and were obtained when applicable.

## RESULTS AND DISCUSSION

A total of 526 articles were retrieved from the original PubMed search. After applying various inclusion and exclusion criteria, a total of 63 articles remained [Figure 1]. The results of the study of the full text of these articles are described below.

### Etiology of type 1 diabetes mellitus

T1DM is an autoimmune disorder of the pancreatic beta cells, which are responsible to produce insulin in the body. In T1DM, over the period of time, the body progressively destroys these beta cells creating insulin deficiency in the body. The exact etiology of T1DM is currently unknown;

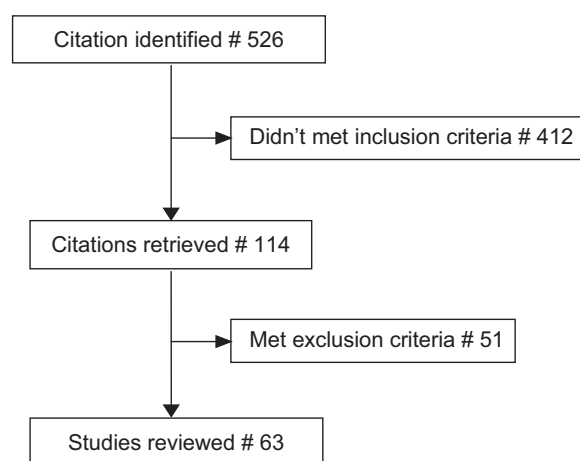


Figure 1: Roadmap for the PubMed literature search

however, several factors that may be responsible for the development of T1DM have been identified. These factors include genes (for e.g., human leukocyte antigen class II alleles, PTPN22, IL2RA, and CTLA-4), increase risk of T1DM due to cow's milk in genetically susceptible individuals, viruses (for e.g., Coxsackie B virus, Rubella virus, Epstein-Barr Virus, and cytomegalovirus), and environmental factors (for e.g., zinc and magnesium).<sup>[8-11]</sup>

### Noninsulin pharmacological management of type 1 diabetes mellitus

The noninsulin pharmacological agents can be divided into the following classes: (1) Insulin-sensitizing agents, (2) gastrointestinal nutrient absorption modulators, (3) immunotherapeutic agents, (4) incretin-based therapies, (5), recombinant human insulin-like growth factors, and (6) other promising therapeutics.

#### Insulin sensitizing agents

##### Biguanides

In 2010, a systematic review of 197 published clinical trials and clinical trial databases studies was conducted to assess the effects of metformin on HbA1c, weight, insulin-dose requirement, and adverse effects.<sup>[12]</sup> Nine studies involving randomization with informed consent of patients with type 1 diabetes to metformin (*vs* placebo or comparator) in either a parallel or crossover design for at least 1 week were identified. Authors further found marked heterogeneity in study design, drug dose, age of participants, and length of follow-up. After an exhaustive review, it was demonstrated that metformin is associated with reductions in: (1) insulin-dose requirement (5.7-10.1 U/day in six of seven studies); (2) HbA1c (0.6-0.9% in four of seven studies); (3) weight (1.7-6.0 kg in three of six studies); and (4) total cholesterol (0.3-0.41 mmol/l in three of seven studies). It was also found that the metformin is well tolerated, albeit with a

trend toward increased hypoglycemia. Furthermore, formal estimates of combined effects from the five trials which reported appropriate data indicated a significant reduction in insulin dose (6.6 U/day,  $P < 0.001$ ) but no significant reduction in HbA<sub>1c</sub> (absolute reduction 0.11%,  $P = 0.42$ ) levels. In addition, no reported clinical trials included cardiovascular outcomes. Therefore, the authors concluded that the metformin reduces insulin-dose requirement in type 1 diabetes, but it is unclear whether this is sustained beyond 1 year and whether there are benefits for cardiovascular and other key clinical outcomes.

### Thiazolidinediones

In 2005, a study of noninsulin pharmacological therapies for the treatment of T1DM recommended that the use of thiazolidinediones (TZDs) in the treatment of T1DM requires further research.<sup>[13]</sup> In this regard, in a recently concluded randomized, double-blind, placebo-controlled crossover clinical trial of rosiglitazone *vs* placebo (24-week each, with a 4-week washout period), rosiglitazone resulted in decreased insulin dose (5.8% decrease *vs* 9.4% increase,  $P = 0.02$ ), but no significant change in HbA<sub>1c</sub> (-0.3 *vs* -0.1,  $P = 0.57$ ).<sup>[14]</sup> In congruence with this finding, currently, the United States Food and Drug Administration (US FDA) explicitly mentions in the rosiglitazone package insert that the rosiglitazone should not be used in the treatment of T1DM.<sup>[15]</sup>

Nonetheless, the benefits of TZDs on beta-cell functions in the latent autoimmune diabetes (LADA) patients have been demonstrated in several well-designed studies. In a 3-year follow-up study of LADA patients, to observe the beneficial effects on beta-cell function in the LADA patients treated with rosiglitazone, it was found that the Phencyclidine (PCP) level (after the 12<sup>th</sup> month) and delta C-Peptide (CP) level (after the 18<sup>th</sup> month) in insulin +/- rosiglitazone group were higher than those in insulin group.<sup>[16]</sup> In another randomized, double-blind clinical trial study of 50 adults, to evaluate the safety and effectiveness of rosiglitazone in the treatment of overweight subjects with type 1 diabetes, to take either insulin and placebo ( $n = 25$ ) or insulin and rosiglitazone 4 mg twice daily ( $n = 25$ ) for a period of 8 months, rosiglitazone in combination with insulin resulted in improved glycemic control and blood pressure without an increase in insulin requirements, compared with insulin- and placebo-treated subjects, with the greatest effect of rosiglitazone occurring in subjects with more pronounced markers of insulin resistance.

At the same time, rosiglitazone as well as pioglitazone have boxed warnings (the most serious type of warning issued by US FDA for those drugs, which have potential of serious injuries or fatalities associated with them) issued

to them for potential of causing congestive heart failure when administered.<sup>[15]</sup>

### Gastrointestinal nutrient absorption modulators

#### $\alpha$ -Glucosidase inhibitors

Acarbose is a reversible inhibitor of the intestinal alpha-glucosidases. The efficacy and safety of  $\alpha$ -Glucosidase inhibitors (acarbose) in the treatment of T1DM patients have been evaluated in several well-designed randomized controlled clinical trials. It has been consistently found that the use of acarbose in combination with insulin reduces postprandial plasma glucose levels in the T1DM patients who are not satisfactorily controlled with insulin alone. It has also been found that acarbose decreases insulin requirement in patients with T1DM. However, acarbose was shown to have no significant effect on HbA<sub>1c</sub> levels.<sup>[17-25]</sup> For instance, in one multicenter, double-blind, randomized, placebo-controlled, 6-week run-in study, 121 patients were randomized to acarbose or placebo and to high- or low-fiber diet for 24 weeks. At the end of 24 weeks of treatment, the intention to treat analysis showed that acarbose compared with placebo decreased 2 hours postprandial plasma glucose levels (12.23 +/- 0.83 *vs* 14.93 +/- 0.87 mmol/l;  $F = 6.1$ ,  $P < 0.02$ ) (least square means +/- SEM). Furthermore, no significant effect of acarbose was recorded on HbA<sub>1c</sub> levels or on the number of hypoglycemic episodes.

The pooled data from clinical trials also show that acarbose has a good general safety profile.<sup>[17-25]</sup> For example, in one of the clinical trials, the incidence of adverse events were 75% and 39% in acarbose and placebo groups, respectively, and were mild and confined to the gastrointestinal tract.<sup>[20]</sup> In another clinical trial, the most frequent reported adverse events were flatulence (43%), diarrhea (27%), and abdominal pain (11%).<sup>[21]</sup>

#### Amylin

In 2010, Lee *et al.* conducted a systematic literature review of the safety and efficacy of pramlintide (amylin analogue) in the treatment of T1DM.<sup>[26]</sup> A total of three placebo-controlled randomized controlled trials (RCTs), which compared pramlintide with placebo as adjuncts to either intensive insulin therapy<sup>[27]</sup> or to therapy with short- and long-acting insulin, were found.<sup>[28,29]</sup> The trial using intensive insulin therapy reported no significant difference in the reduction in HbA<sub>1c</sub> levels when comparing pramlintide with placebo at week 29.<sup>[27]</sup> The other two trials showed significantly greater improvement in HbA<sub>1c</sub> levels with pramlintide than placebo at 26 and 52 weeks, with between-group differences in HbA<sub>1c</sub> of 0.2% and 0.3%, respectively.<sup>[28,29]</sup>

Mild-to-moderate nausea, vomiting, and anorexia or reduced appetite were the most commonly reported adverse events and were more common with pramlintide than placebo in these clinical trials. Furthermore, severe hypoglycemia was generally reported more frequently with pramlintide than with placebo in these trials, with severe hypoglycemia occurring more often during the first 4 weeks of treatment as pramlintide doses were being adjusted.<sup>[27-29]</sup>

One of these trials also measured the patient-reported outcomes. It was found that the satisfaction was significantly greater with pramlintide treatment than placebo at 29 weeks of follow-up on 12 of 14 patient-reported outcome measures using a questionnaire developed specifically for this trial.<sup>[30]</sup>

### Immunotherapeutic agents

T1DM is caused by immune-mediated destruction of insulin-secreting beta-cells. Therefore, the ideal immunotherapy for T1DM would preserve beta-cell function with limited or few side-effects. Since last 30 years, various non-antigen-based immunotherapeutic agents have been used in the treatment of T1DM. Agents like cyclosporin showed early efficacy,<sup>[31-33]</sup> but in addition to side-effects like nephrotoxicity that made further use of this therapy inadvisable, the benefits disappeared once treatment stopped.<sup>[34]</sup> Other agents such as methotrexate<sup>[35]</sup> and antithymocyte globulin<sup>[36]</sup> did not show any benefit. Nonetheless, recently, various preclinical studies and clinical trials have demonstrated the efficacy of different types of anti-CD3 monoclonal antibodies<sup>[33,37]</sup> that have been tested in subjects with new onset T1DM. Teplizumab<sup>[38]</sup> and oteplizumab<sup>[39]</sup> (anti-CD3 antibodies) have both shown, in randomized clinical trials, an ability to reduce the loss of insulin production over the first 2 years of the disease. In addition, the need for exogenous insulin to maintain glucose control has been reduced. However, these agents alone do not restore normal glucose control, and future approaches will likely require combinations of agents with complementary immune or metabolic activity.<sup>[37]</sup>

Recently, Gandhi *et al.* conducted a systematic literature review and meta-analysis of immunotherapeutic agents to determine the efficacy of non-antigen-based immunotherapeutic approaches for preservation of beta-cell function in patients with type 1 diabetes.<sup>[33]</sup> Eligible studies were RCTs of antiproliferative agents (methotrexate, azathioprine), monoclonal antibodies (CD3, CD4), T-cell inhibitors (cyclosporin), and other immunotherapeutic agents (photopheresis, linomide, fucidin, buffy coat, intravenous immunoglobulin, BCG, nicotinamide) in patients with newly diagnosed type 1 diabetes followed for  $>$  or  $=$  6 months. Meta-analysis of 20 trials ( $n = 1187$

patients) found a small to moderate improvement in beta-cell function with immunotherapy (*vs* placebo, effect size 0.37, 95% confidence interval [CI]: 0.14-0.6) but there was moderate inconsistency in results across trials ( $I(2)$  65%, 95% CI: 39-77%). Sub-group analysis suggested a greater effect of cyclosporin and antiproliferative agents on beta-cell function when used for  $>$  or  $=$  6 months (pooled effect size 0.77 *vs* -0.11, respectively;  $P$  [interaction] = 0.002). Therefore, it was concluded that the non-antigen-based immunotherapy may preserve beta-cell function in patients newly diagnosed with T1DM. From the planned subgroup analyses, it was suggested that treatment administration for  $\geq 6$  months may be more efficacious than briefer courses.

### Incretin-based therapies

Incretin-based therapies, i.e., Glucagon-Like Peptides-1 analogues and DiPhenyl Peptidyl-4 inhibitors, are newest classes of drugs for the treatment of type 2 diabetes. However, few studies have examined the effects of incretin-based agents in T1DM, none of them on long-term treatment. The rationale behind the possibility of using the incretin-based agents in T1DM is that these agents may preserve beta-cell integrity and function, as shown from the animal model studies. Both *in vitro* studies and animal models of non-autoimmune diabetes have shown that incretin-based agents have the potential to expand beta-cell mass, stimulation of islet neogenesis and beta-cell proliferation, differentiation of putative beta-cell precursors, and inhibition of beta-cell apoptosis.<sup>[40]</sup>

Several sources of data suggest that also human beta-cell may potentially respond to incretin-based agents. First, human islet regeneration persists a long time after the onset of T1DM.<sup>[41]</sup> This, in turn, suggest that even when almost the entire beta-cell mass is lost, the human pancreas may still respond to treatments capable of expanding beta-cell mass. Second, exenatide improves the function of transplanted islets in patients with T1DM.<sup>[42]</sup> Third, in patients with type 2 diabetes and being on metformin, those receiving exenatide had a 2.4-fold higher beta-cell function at 1 year compared with those receiving insulin.<sup>[43]</sup> Although data are still limited and the effect of incretin-based agents seems to disappear early after discontinuation of treatment, it is conceivable that this class of drugs may preserve beta-cell function in human beings, at least for up to 1 year of continuous treatment.<sup>[43]</sup>

Therefore, incretin-based therapies, if proven effective, would represent an entirely new approach to the treatment of T1DM, focused on protection and preservation of beta-cell. Nonetheless, the safety and efficacy of incretin-based agents is still under consideration as many of the agents in this drug class are yet not approved. For instance,

vildagliptin is although approved in European countries and Japan, it is still waiting for approval by the US FDA. Altogether, these observations suggest that the time for testing incretin-based agents for preservation of beta-cell mass in type 1 diabetes may have come. As a result, testing of incretin-based agents should be performed in well-designed and adequately powered randomized clinical trials.<sup>[44]</sup>

#### *Recombinant human insulin-like growth factors*

Insulin-like growth factor-1 (IGF-1) and its receptors share considerable homology with insulin and insulin receptors, and their respective signaling pathways interact at the post-receptor level.<sup>[45]</sup> Although the growth hormone (GH)-IGF-1 axis principally regulates tissue growth and differentiation, insulin exerts its primary effects on fuel metabolism. However, these two endocrine systems interact at multiple levels and in DM, the GH-IGF-1 axis is grossly disturbed, with increased secretion of GH, reduced plasma levels of IGF-1, and complex tissue-specific changes in IGF binding proteins (IGFBPs). Therefore, as a likely consequence of intraportal insulin deficiency, patients with type 1 DM also exhibit abnormalities of the growth GH/IGF/IGFBPs axis, including GH hypersecretion, reduced circulating levels of IGF-1 and IGFBP-3, and elevated levels of IGFBP-1. The availability of recombinant human IGF-1 (rhIGF-1; mecasermin),<sup>[46]</sup> which is currently approved in the US for the long-term treatment of growth failure in children with severe primary IGF-I deficiency or with GH gene deletion who have developed neutralizing antibodies to GH, and in the European Union for the long-term treatment of growth failure in children and adolescents with severe primary IGF-I deficiency,<sup>[47]</sup> used either alone or in combination with insulin, has led to experimental studies and clinical trials in human beings to test these hypotheses. These studies have examined the impact of subcutaneous rhIGF-1 injections on sensitivity and metabolic parameters. In patients with type 1 and 2 DM, insulin sensitivity is significantly improved, insulin requirements are reduced, and glycemic control of dyslipidemia is generally improved in short-term studies.<sup>[48]</sup> rhIGF-1 is a particularly attractive possibility in patients with type 2 DM, where insulin resistance is the fundamental problem. Some patients with genetic syndromes of severe insulin resistance also benefit from treatment with rhIGF-1, which can bypass blocks in the insulin signaling pathway.

The common adverse effects reported for rhIGF-1 are dose-related and include edema, jaw pain, arthralgia, myalgia, hypotension, injection site pain, and less commonly, Bell's palsy and raised intracranial pressure. Although disturbance of the GH-IGF-1 axis participates in the development of diabetic complications, the functional consequences of

the complex changes in IGFBP expression at the tissue level are uncertain, and it is not known whether systemic IGF-1 therapy or other manipulations of the GH-IGF-1 axis would be helpful or harmful. The potential benefits of IGF-1 therapy in DM have yet to be realized.<sup>[46-48]</sup>

#### *Other promising therapeutics*

##### **SmartInsulin**

Smartinsulin™ was developed in Massachusetts Institute of Technology. In 2003, SmartCells, Inc. filed base patent for the Smartinsulin™. SmartInsulin™ consists of a layered, biocompatible, and biodegradable polymer-therapeutic that is bound to an engineered glucose-binding molecule. Insulin is released from SmartInsulin only when the therapeutic is unbound by the presence of a specific glucose concentration.<sup>[49]</sup> Currently, the proof-of-concept studies have demonstrated the key capabilities of Smartinsulin™.<sup>[50]</sup>

##### **Islet Sheet Technology**

Islet Sheet Technology (IST) will provide stable blood glucose levels without injected insulin or immunosuppressive drugs. The technology is based on a removable, bio-invisible sheet called an Islet Sheet and research is ongoing now at the University of California, Irvine.<sup>[51]</sup> For the IST, the researchers have conducted large animal studies in 2009 and have determined dose and implant site for the same in 2010. The developers of the technology plan to start clinical trial studies from the year 2013.<sup>[52]</sup>

##### **Immune modulators and islet antigenic vaccines combined therapies**

It has been shown that the suboptimal doses of the FcR-nonbinding anti-CD3 F(ab')<sub>2</sub> in conjunction with intranasal administration of proinsulin peptide can reverse diabetes in two mouse models of diabetes.<sup>[53]</sup> During the follow-up experiments, it was found that the anti-CD3 in conjunction with a GAD65 plasmid vaccination could synergize strongly in a Rat Insulin Promoter-Lymphocytic Choriomeningitis Virus (RIP-LMCV) model of T1DM.<sup>[54]</sup>

##### **Immune modulators and compounds promoting beta-cells growth or decreasing beta-cells apoptosis combination therapies**

In a prospective open-label crossover trial of 20 individuals with long-standing T1DM, subjects were randomized to exenatide with or without daclizumab. Exenatide delayed gastric emptying, suppressed endogenous incretin levels, but did not increase C-peptide secretion. Furthermore, the combination of intensified insulin therapy, exenatide, and daclizumab did not induce improved function of these remaining beta-cells.<sup>[55]</sup> Nonetheless, future clinical trials are required to determine the appropriate efficacy and safety of this therapy.

### Cytokine-based therapeutics

Various clinical trials have demonstrated the efficacy of cytokines in the management of T1DM. In the trials, subjects (n = 63) with T1DM received Islet neogenesis-associated protein (INGAP) 300 or 600 mg/day of INGAP peptide in a 90-day, randomized, double-blind, placebo-controlled manner. It was found that INGAP peptide increases C-peptide secretion in T1DM.<sup>[56]</sup> In another clinical trial, the safety and efficacy of ingested human recombinant interferon-alpha (hrIFN-alpha) for preservation of beta-cell function in young patients with recent-onset type 1 diabetes was evaluated. It was found that the patients in the 5 000-unit hrIFN-alpha treatment group maintained more beta-cell function 1 year after study enrollment than individuals in the placebo group.<sup>[57]</sup>

## CONCLUSION

In the management of T1DM, various shortcomings of insulin therapies such as injectable nature of insulin, development of insulin resistance, inability to reach excellent glycemic control by insulin, and hyperglycemia and hypoglycemia caused by insulin have resulted in the stimulation of interest to develop noninsulin pharmacological therapies to manage T1DM. We conducted a systematic literature review and divided noninsulin pharmacological therapies into following classes: (1) Insulin-sensitizing agents, (2) gastrointestinal nutrient absorption modulators, (3) immunotherapeutic agents, (4) incretin-based therapies, (5) recombinant human insulin-like growth factors, and (6) other promising therapeutics. In these, some therapies, either independently or as adjuvant to insulin, are currently used to manage T1DM, whereas some others are currently in development stage. Nevertheless, the current ongoing research to develop noninsulin pharmacological therapies is promising and progressive. However, currently, insulin is the cornerstone therapy used to manage T1DM.

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