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Beyond Insulin: Emerging Therapies for Type 1 Diabetes

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Abstract. Type 1 diabetes is a complex polygenetic disease that results from the immune system attacking and destroying the insulin-secreting β-cells in the pancreas. This irreversible destruction results in an absolute insulin deficiency, disrupting the body's ability to regulate blood glucose levels. The current standard treatment is exogenous insulin replacement therapy, where patients must administer it through multiple daily injections via a syringe or a pump. Although technological advances like continuous glucose monitors help to control blood glucose levels clearly, this traditional method still has several limitations. Consequently, a novel approach of using the growth differentiation factor 15 protein could be used alongside taking insulin injections, which stabilises blood glucose fluctuations better. Moreover, stem-cell therapies are being researched and developed due to their curative potential to regenerate β-cells. However, the new approaches lack clinical studies and still contain many risks, such as cancer development. The successful development of these therapies promises to restore the body's natural ability to produce insulin and reduce the dependence on insulin replacement.

Keywords: Insulin, insulin replacement therapy, stem cell therapy, GDF15

1. Introduction

Although Type 1 diabetes mellitus (T1DM) makes up just 5–10% of all diabetes cases, its prevalence is increasing worldwide, and it poses serious health risks both in the short and long term. [1]. The World Health Organisation (WHO) suggested that about 8.4 million people are living with type 1 diabetes and will increase by more than 100,000 per year if the trends continue. This disease is driven by the absence of insulin-producing β-cells [2]. The thought of using insulin replacement therapy was first proposed in 1921, and it remains the lifelong therapy for nearly 100% of the Type 1 diabetes patients. Afterwards, many artificial insulin analogues have been developed, and more new therapeutic approaches have been introduced to treat the disease from its causes. This review aims to summarise several advanced solutions for T1DM, providing a more comprehensive view for scholars and physicians.

2. Type 1 diabetes mellitus

T1DM is an autoimmune disorder due to the destruction of insulin-producing pancreatic β-cells within the pancreatic islets of Langerhans [2]. Its two major causes are genetic predisposition and environmental factors. Human leukocyte antigen (HLA), located on chromosome 6, represents the

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strongest genetic factor for T1DM, accounting for 40–50% of its heritable risk [3]. These genes encode major histocompatibility complex (MHC) proteins, whose primary functions are to distinguish self from non-self and to mediate immune protection against pathogens. The key determinants of T1DM are HLA class II genes, which encode for DQ and DR proteins. Certain haplotypes, such as DR3 and DR4, can significantly increase susceptibility, and the risk is even greater when both haplotypes are inherited [3]. In terms of environmental triggers, Dedrick et al. suggest that reduced microbial diversity due to overly hygienic environments may raise T1DM risks. Their study highlights that individuals with T1DM tend to have a less diverse gut microbiota, an increased abundance of Bacteroidetes taxa and an altered metabolite profile [4].

The development of T1DM requires three prerequisites: activation of T lymphocytes that target β-cells, a proinflammatory immune response, and a failure of immune regulation of self-reactive responses. In genetically predisposed individuals, Recognition of β-cell-specific antigens by T cells can be stimulated by environmental factors, thus initiating the autoimmune process. CD4+ T helper cells contribute to inflammation through the release of interferon-gamma (IFN-γ) and interleukin-17 (IL-17), thereby strengthening the immune response and drawing in CD8+ T cells and macrophages [5]. CD8+ T cells directly attack β-cells through the release of perforin and granzymes, inducing apoptosis. Macrophages further contribute by generating reactive oxygen species (ROS) and additional cytokines for the destruction of β-cells [5]. The cumulative effect of all the processes gradually destroys β-cells, leading to a deficiency in insulin.

3. Solutions for T1DM

3.1. GDF15

Growth Differentiation 15 (GDF15) has emerged as a novel, therapeutic solution for T1DM. As a cytokine secreted naturally in the body, GDF15 is a member of the TGF-β family and displays the characteristic cysteine knot. In most tissues, it occurs in the form of pre-pro-GDF15 with 308 amino acids [6]. To bind its receptor and perform functions, this pre-pro-protein forms a dimer through a disulfide bond at the C-terminal cysteines. Subsequently, a furin-like protease cuts the protein at the RXXR motif, allowing the 25 kDa GDF15 dimer to be secreted outside the cell. Under normal physiological states, GDF15 expression remains minimal but becomes strongly upregulated in terms of cellular stress, tissue injury and certain metabolic disorders, including T1DM [6]. This homeostatic and anti-inflammatory role illustrates its potential in T1DM therapy.

Growing evidence indicates that GDF15 is closely involved in the pathogenesis of T1DM. Notably, regulators of glucose metabolism, including peroxisome proliferator-activated receptor (PPAR) and AMP-protein kinase (AMPK), have been shown to reduce T1DM in NOD mice via activating GDF15 [7]. Furthermore, experiments in transgenic mice indicate that overexpressing GDF15 ameliorates insulin sensitivity and provides protection for the pancreatic β-cells. In human islets, β-cells exposed to pro-inflammatory cytokines produce less GDF15 by inhibiting its mRNA translation [8]. Consequently, treatments with recombinant mature GDF15 enhance β-cells survival and decrease inflammation in the pancreatic islets.

Despite there are hundreds of clinical studies on GDF15 as a biomarker, none currently focus on T1DM. Experts have pointed out the future perspectives of using GDF15 for T1DM. It is known as the first anti-inflammatory cytokine that can regulate chemokine-triggered leukocyte integrin activation, so future work should pay attention to it as a selective immunosuppressant to delay or prevent T1DM [8].

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3.2. Insulin replacement therapy

One of the most prevalent treatments today is exogenous insulin replacement therapy, which was first discovered in 1921 using crude animal extracts [9]. Nevertheless, early forms of insulin had poor absorption and inconsistent glucose-lowering effects, which may cause hypoglycemia. With time, insulin analogues have been engineered to be more humanised, improving their pharmacokinetics and enabling them to more accurately mimic physiological insulin.

Insulin is a dipeptide hormone composed of two chains linked by disulfide bonds, with 51 amino acids (A chain 21 amino acids, B chain 30 amino acids) and a molecular weight of 5802. β-cells in the pancreatic islets of Langerhans synthesise their precursor, proinsulin, and it is further secreted by exocytosis in its mature form, insulin [10]. The fundamental mechanism of exogenous insulin analogues in T1DM is to replace the lost hormone and act on insulin receptors (IRs). The receptors can always be found on tissues such as the liver, and the binding to the IRs will phosphorylate the insulin receptor substrate (IRS) proteins. The process initiates the PI3K-Akt signalling pathway and promotes an increased glucose uptake due to the translocation of glucose transporter proteins. Moreover, this pathway can mediate insulin's metabolism by inhibiting hepatic glucose production and stimulating glycogen synthesis, respectively [10].

Current major therapies primarily rely on a combination of intensive dietary management and lifelong exogenous insulin administration. They can be delivered either through multiple daily injections or continuous infusion via insulin pumps. Blood glucose self-monitoring combined with HbA1c testing, which reflects non-enzymatic glycosylation measurements, is broadly adopted and has improved the clinical use of commercial insulin formulations. This progress enabled the creation of various insulin analogues, and the four main types are rapid-acting, short-acting, intermediate-acting and long-acting [11]. They vary by onset, duration of action and dose. Table 1 below will show a clear comparison.

Table 1. List of insulin categories [11]

Type	Brand Names	Onset and Peak	Duration	Dose
Rapid Acting	Insulin glulisine insulin Aspart, insulin lispro,	Onset 4-20 min after, peak at 20-30 min	3-5h	Three times a day
Short Acting	Actrapid, Humulin S, Insuman Rapid	Onset 30 min, peak at 2-4h	4-6h	Three times a day
Intermediate Acting	Insulatard, Insuman Basal	Onset 1-2h, peak at 4-8h	12-18h	Once or twice daily
Long Acting	Levemir, Toujeo, Tresiba	Onset 1-2h, peakless	20-36h	Once daily

Clinical practice is now shifting toward continuous subcutaneous insulin infusion (CSII) systems, which the National Institute for Health and Care Excellence (NICE) recommends, instead of traditional delivery systems that may fail to introduce long-term insulin independence. Nineteen randomised controlled trials by the REPOSE study group evaluated the effectiveness of insulin pumps versus multiple daily injections (MDI) in adults with T1DM. The results suggest a long-lasting reduction in HbA1c and a decrease in hypoglycemia incidence in participants using an insulin pump [12]. Another meta-analysis of 25 randomised controlled trials compared CSII with MDI in both adults and children with T1DM. Results demonstrated that CSII decreased nocturnal hypoglycemia episodes, without significantly affecting the frequency of severe or minor hypoglycemia.

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3.3. Stem cell therapy

Stem cells are of interest due to their potential to generate unlimited glucose-responsive, insulin-producing β-cells and improve the survival of transplanted islets. This new approach can overcome the shortage of donor islets and improve the islet transplantation success rates in T1DM patients.

Human embryonic stem cells (hESCs) derived from early embryos are pluripotent, able to produce any cell type, and can self-renew indefinitely while preserving the ability to become various somatic cells, thus having the potential to regenerate new β-cells to treat T1DM patients [13]. Methods have been developed to differentiate hESCs into insulin-producing β-cells through endocrine and pancreatic progenitors, requiring activation of crucial pancreatic transcription factors (TFs) to mirror the stages of β-cell growth, for instance, Pdx, Mafa, Neurod1, Neurog3, and Pax4 [13]. Schulz et al. established an integrated manufacturing system that includes cell banking on a large scale, suspension-based differentiation, and controlled expansion methods by using the CyT49 cell line. Consequently, they reliably produced pancreatic cell populations that are enriched for β-cells, which can be further derived into functional islet-like structures when implanted into mice. This study also underlines that the mice restored normal glucose regulation within 4-5 months, which provides a scalable insight for potential T1DM therapy [14].

In addition to generating abundant insulin-producing β-cells from hESCs, stem cell strategies can support higher islet survival rates. During islet isolation and transplantation, from 5% to 47% of β-cells die soon after the procedure [15]. This is caused by various conditions, such as IBMIR (instant blood-mediated inflammatory reaction), where the immune system reacts immediately to transplanted islets; impaired vascularisation that results in the lack of oxygen for transplanted islets; as well as hypoxia that may stress and kill β-cells [15]. Research indicates that the survivability of islet cells is enhanced when co-transplanted with mesenchymal stem cells (MSCs). This is due to the MSCs' ability to provide protection to β-cells from death and further promote blood vessel formation, which can avoid the conditions mentioned above. MSCs are multipotent cells that can both become different cell types and pericytes that help stabilise blood vessels around the islets. Their potent immunomodulatory properties can affect T and B cells, lowering the risk of inflammation, while the paracrine factors they release promote the growth and function of surrounding cells [16].

4. Discussion

T1DM continues to be a leading cause of blindness, kidney failure and stroke, with a steadily rising number of cases over the past 40 years. Those therapeutic approaches that were introduced in this review need to be further evaluated for their efficacy.

GDF15 therapy is a new approach for treating T1DM. The biggest advantage of this novel solution is that it can act as a complement to insulin therapy, which has been shown to improve insulin sensitivity in various tissues, including the liver and adipose tissue. A study demonstrated GDF15's capacity to increase insulin action via β-adrenergic receptor-mediated mechanisms, highlighting its potential to magnify insulin therapy effectiveness in T1DM patients [17]. In this way, this therapy may reduce the total insulin dosage required to achieve glycemic control, which further mitigates the risk of insulin-related side effects. Moreover, GDF15 is a naturally secreted protein in the human body, so it also improves metabolic regulation, such as glucose intolerance and modulates immune responses that diminish the possibility for immune-mediated β-cell destruction. However, the lack of clinical trials suggests further development is still required to examine the efficacy of this protein. Some off-target effects since GDF15 can act on multiple tissues, and its

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short half-life are other major difficulties that slow down its development. Most importantly, it cannot fully replace insulin because it cannot independently regulate blood glucose, so insulin treatment is still needed.

Insulin replacement therapy is the standard and most common treatment in the twenty-first century for T1DM patients. They require lifelong insulin therapy because of the failure of their body to produce insulin. Therefore, the wide range of insulin analogues available allows treatment to be tailored to patients' needs (Table 1). Intensive insulin regimens help to keep blood glucose levels like non-diabetics. This method significantly lowered the risk of microvascular and macrovascular complications. Nathan et al. suggested it successfully reduced the risk of severe retinopathy by 47 % and a 39% reduction in microalbuminuria [18]. Additionally, the self-monitoring of blood glucose and HbA1c testing technologies optimise dosage, which promotes better effectiveness. Several novel delivery systems have been developed, such as a self-orienting millimetre applicator (SOMA), which positions itself in the stomach and delivers insulin through the stomach wall. In this way, it provides stable insulin levels in diabetic rodents like injections and could improve insulin therapy in the future. This brings one of the challenges in current insulin therapies – dependence on delivery systems. Traditional delivery systems (syringes, pens and pumps) are too. Invasive and can reduce adherence. This therapy can also lead to dangerously low blood sugar and contribute to a loss of weight.

In terms of stem cell therapies, the primary advantage would be their potential to restore endogenous insulin secretion. Unlike injecting insulin directly, it provides the ability to regenerate insulin-producing β-cells. Researchers have demonstrated the ability of hESCs to be differentiated into pancreatic progenitors. Furthermore, the method illustrates its unlimited growth potential so large number of cells can be produced for transplantation. As a result, this strategy could help overcome the severe shortage of compatible donor islets and enhance the success of islet transplantation in T1DM patients. One of the downsides of this method is ethical concerns. Using hESCs involves the destruction of human embryos, which some people consider to be the destruction of a potential human life. Moreover, the unlimited growth of cells could also lead to the development of a tumour after transplantation. There is also a possibility of immune rejection, where hESC-derived β-cells will be recognised as foreign by the immune system. This requires patients to undergo lifelong immunosuppression, which carries its own risks of infections.

5. Conclusion

Despite significant medical advances, T1DM continues to be the major contributor to blindness, kidney failure and stroke, and the global prevalence has risen steadily over the last 40 years. While modern fast-acting and long-acting insulin is still the most popular treatment, as also improves patients' quality of life. Nevertheless, the alternative, novel approaches, GDf15 and stem cell therapies, have the potential to help with traditional insulin replacement therapy and help to cure T1DM from its causes. However, these methods still have limitations to consider, and more clinical trials should be conducted to ensure optimum results.

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