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Effect of CRISPR-Cas9 Beta-Cell Editing versus Insulin Therapy on Glycemic Control in Type 1 Diabetic Adults: A Narrative Review

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder leading to beta-cell destruction and absolute insulin deficiency, necessitating lifelong insulin therapy. While insulin therapy remains the standard for glycaemic control, it does not address the underlying autoimmune pathology or restore endogenous insulin production. This review compared the effect of CRISPR-Cas9-mediated beta-cell editing with standard insulin therapy on glycaemic control in adults with type 1 diabetes. A narrative review approach was utilised to synthesise published evidence on mechanisms, efficacy, safety, translational feasibility, and ethical considerations of CRISPR-Cas9 beta-cell editing versus insulin therapy. Insulin therapy effectively reduced hyperglycaemia and prevents acute complications, but carries limitations such as hypoglycaemia risk, imperfect glycaemic control, and inability to replicate physiological insulin secretion. Conversely, CRISPR-Cas9 beta-cell editing demonstrates promise in preclinical studies, enabling restoration of insulin production through edited stem-cell-derived beta-like cells or immune modulation to prevent beta-cell destruction. Such editing offers potential durable remission or cure of T1DM. However, clinical translation is limited by challenges in delivery systems, off-target effects, immunogenicity, regulatory approvals, and ethical concerns. No human clinical trial data currently exist to validate safety and efficacy. CRISPR-Cas9 beta-cell editing offers a potential disease-modifying alternative to insulin therapy for type 1 diabetes, though significant translational research is required before clinical adoption. Integrating gene editing with existing insulin management may optimise future therapeutic strategies for durable glycaemic control and improved patient outcomes.

Keywords: CRISPR-Cas9 beta-cell editing, Type 1 diabetes mellitus, Insulin therapy, Glycaemic control, Gene editing therapy.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterised by destruction of pancreatic beta cells, leading to absolute insulin deficiency and persistent hyperglycaemia [1, 2]. Affecting millions globally, T1DM imposes significant disease burden, complications risk, and reduced quality of life due to lifelong dependence on exogenous insulin therapy. Insulin therapy remains the cornerstone of T1DM management, enabling glycaemic control, preventing acute complications such as diabetic ketoacidosis, and reducing microvascular and macrovascular risks [3, 4]. However, exogenous insulin administration faces major limitations, including suboptimal glucose regulation, risk of hypoglycaemia, and inability to replicate physiological insulin secretion patterns.

Recent advances in gene editing technology have opened new frontiers in T1DM treatment, with the CRISPR-Cas9 system emerging as a revolutionary tool for targeted genome modifications [5]. CRISPR-Cas9 enables precise editing of specific genes involved in beta-cell function and immune recognition [6]. Preclinical studies demonstrate the potential of CRISPR-based strategies to restore insulin production by editing stem cells to differentiate into insulin-secreting beta-like cells or correcting autoimmune targets to prevent beta-cell destruction. Unlike insulin therapy, which addresses only the metabolic consequences, CRISPR-Cas9 editing offers a disease-modifying approach aiming for durable glycaemic control and potential cure. This narrative review compares the effect of CRISPR-Cas9-mediated beta-cell editing with standard insulin therapy on glycaemic control in adults with type 1 diabetes. It synthesises evidence on mechanisms, efficacy, safety, translational feasibility, and ethical considerations

of these two contrasting therapeutic approaches. Understanding their comparative benefits and limitations is critical for guiding future clinical research and therapeutic development, as the quest for functional cures for T1DM progresses from experimental models to potential real-world applications.

Mechanisms of Action

i. **Insulin Therapy:** Insulin therapy replaces deficient endogenous insulin through subcutaneous injections or continuous subcutaneous insulin infusion (CSII) [7]. Exogenous insulin analogues are designed to mimic basal and prandial secretion patterns, modulating glucose uptake, glycogenesis, and inhibiting gluconeogenesis. However, peripheral insulin administration does not reproduce portal vein insulin concentrations, leading to imperfect metabolic control and potential hypoglycaemia due to pharmacokinetic variability.

ii. **CRISPR-Cas9 Beta-Cell Editing:** CRISPR-Cas9 allows genome editing, enabling gene knock-out, knock-in, or correction [8, 9]. Applications in T1DM include beta-cell regeneration, autoimmunity correction, and endogenous beta-cell gene correction, potentially restoring insulin production and immunological tolerance.

Efficacy in Glycaemic Control

i. **Evidence for Insulin Therapy:** Multiple studies and meta-analyses confirm that intensive insulin therapy achieves HbA1c reductions to near-normal levels, reducing microvascular complications [10]. However, despite technological advances in insulin analogues and delivery systems, only a minority of patients achieve optimal glycaemic targets consistently, and hypoglycaemia remains a persistent risk. Furthermore, exogenous insulin does not prevent disease progression or beta-cell loss.

ii. **Evidence for CRISPR-Cas9 Beta-Cell Editing:** Preclinical studies in murine models demonstrate that CRISPR-edited stem-cell-derived beta-like cells can normalise blood glucose upon transplantation, with sustained insulin secretion and reversal of hyperglycaemia [11]. Autoimmunity-targeted CRISPR editing strategies have shown success in preventing immune-mediated beta-cell destruction, prolonging graft survival. However, human clinical trial data are lacking, and long-term durability, scalability, and safety remain to be established.

Safety Considerations

i. **Insulin Therapy:** While generally safe, insulin therapy is associated with risks such as hypoglycaemia, injection site reactions, lipodystrophy, and weight gain. Chronic hyperinsulinaemia may exacerbate cardiovascular risks in some patients.

ii. **CRISPR-Cas9 Beta-Cell Editing:** Safety concerns include off-target effects, immune responses, mutagenesis, and ethical issues [12]. Preclinical validation and safety monitoring are crucial before clinical translation. Current applications focus on somatic editing.

Translational Feasibility

i. **Insulin Therapy:** Insulin therapy is widely available, cost-effective relative to advanced genetic interventions, and supported by robust infrastructure for prescription, education, and monitoring [13]. However, it imposes a lifelong treatment burden, with economic and psychosocial implications.

ii. **CRISPR-Cas9 Beta-Cell Editing:** Successful translation of CRISPR beta-cell editing into clinical practice faces challenges such as efficient delivery systems, ensuring cell function, preventing immune rejection, obtaining regulatory approvals, and ensuring cost and manufacturing scalability [14].

iii. **Ethical and Social Implications:** CRISPR-Cas9 applications in T1DM raise ethical considerations surrounding gene editing safety, informed consent, equity of access, and potential misuse for germline modifications [15]. Ensuring that gene-editing therapies align with patient values, public health equity, and stringent ethical frameworks is critical for societal acceptance [16]. Insulin therapy, while ethically uncontroversial, poses equity challenges regarding availability and affordability in low-resource settings, contributing to preventable diabetes-related mortality globally.

iv. **Integration into Clinical Practice:** Future diabetes care may integrate CRISPR-based therapies alongside insulin management [16]. For example, patients receiving beta-cell replacement via gene editing may require transient insulin therapy until engraftment and functional insulin secretion are established. Successful integration will depend on multidisciplinary collaboration, patient-centred approaches, and updated clinical guidelines incorporating gene therapy innovations.

Current Research Gaps

Addressing these gaps through preclinical optimisation, phased clinical trials, and stakeholder engagement is essential for advancing CRISPR therapies for T1DM. Key research gaps include:

i. Long-term safety and off-target profiling of CRISPR-Cas9 edits in human beta cells [17].
ii. Scalable and efficient delivery systems for in vivo editing or stem cell-derived cell therapies [18, 19].
iii. Strategies to achieve immune tolerance and prevent recurrent autoimmunity post-editing.

iv. Robust clinical trial data evaluating efficacy, safety, and durability in humans.
v. Ethical, regulatory, and health systems readiness for clinical implementation.

Future Directives

The future of T1DM treatment lies in leveraging disease-modifying therapies such as CRISPR beta-cell editing to achieve durable glycaemic control or cure [20, 21]. Ongoing research exploring combination strategies, such as immune modulation alongside gene editing, may enhance outcomes. Meanwhile, advancements in insulin formulations, closed-loop insulin pumps, and continuous glucose monitoring continue to improve quality of life for patients reliant on insulin therapy.

Collaborative efforts among researchers, clinicians, regulators, and patients are vital to ensure safe, ethical, and effective translation of gene editing innovations from bench to bedside. Ensuring equitable access to such transformative therapies will be a central challenge and responsibility for the global diabetes community.

CONCLUSION

In conclusion, insulin therapy remains the cornerstone of glycaemic control in type 1 diabetic adults, offering life-sustaining treatment despite its limitations in replicating physiological insulin secretion and risks of hypoglycaemia. Conversely, CRISPR-Cas9-mediated beta-cell editing represents a promising disease-modifying approach by targeting the underlying pathophysiology of beta-cell destruction or dysfunction, offering prospects for durable remission or cure. Preclinical studies demonstrate the potential of CRISPR-edited stem-cell-derived beta-like cells to restore insulin production and normalise glucose levels, though translational barriers including delivery, safety, and immunogenicity must be overcome before clinical application. Ethical considerations, regulatory frameworks, and cost-effectiveness analyses will play pivotal roles in determining the feasibility of integrating gene editing into routine T1DM care. Ultimately, CRISPR-Cas9 beta-cell editing and insulin therapy represent complementary rather than competing modalities, with the former offering long-term solutions and the latter ensuring immediate metabolic control. Future diabetes management will likely integrate these approaches within personalised treatment paradigms, aiming to achieve optimal glycaemic outcomes, complication prevention, and improved quality of life for individuals living with type 1 diabetes.

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