IAA Journal of Biological Sciences 14(1):60-64, 2026 www.iaajournals.org

©IAAJOURNALS ISSN:2636-7254

https://doi.org/10.59298/IAAJB/2026/1416064 IAAJB1411

Glucagon Receptor Antagonists versus Standard Care: Beta-Cell Preservation in Early Type 1 Diabetes

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ABSTRACT

Type 1 diabetes mellitus was characterized by autoimmune destruction of pancreatic beta cells, leading to absolute insulin deficiency and lifelong dependence on exogenous insulin therapy. Emerging evidence suggested that glucagon signaling contributed to hyperglycemia and may exacerbate beta cell stress during early disease stages. Glucagon receptor antagonists represented a novel pharmacological approach that may complement insulin therapy by reducing hepatic glucose output and potentially preserving residual beta cell function. This review examined the therapeutic potential of glucagon receptor antagonists compared to standard insulin-based care for preserving beta cell mass and function in patients with newly diagnosed type 1 diabetes. A comprehensive synthesis of preclinical studies, clinical trials, and mechanistic investigations published over the past decade was conducted to evaluate efficacy, safety, and molecular mechanisms. Glucagon receptor blockade reduced hyperglycemia through decreased hepatic gluconeogenesis and may lower beta cell workload, thereby attenuating autoimmune-mediated destruction. Clinical trials demonstrated modest improvements in C-peptide preservation and glycemic control when glucagon receptor antagonists were combined with standard insulin therapy during the honeymoon phase. However, concerns regarding hepatic steatosis, elevated aminotransferases, and alpha-cell hyperplasia limited widespread adoption. Glucagon receptor antagonists showed promise as adjunctive therapy for beta cell preservation in early type 1 diabetes, but long-term safety data and larger randomized controlled trials were needed to establish their role in clinical practice.

Keywords: Glucagon receptor antagonist, Beta cell preservation, Type 1 diabetes, C-peptide, Autoimmune diabetes.

INTRODUCTION

Type 1 diabetes mellitus represents a complex autoimmune disorder wherein T lymphocyte-mediated destruction of pancreatic beta cells culminates in absolute insulin deficiency [1]. The disease progression involves a preclinical period of variable duration during which autoantibodies against beta cell antigens are detectable, followed by clinical onset when approximately 70 to 90 percent of beta cell mass has been destroyed [2]. Despite advances in insulin formulations and delivery systems, achieving physiological glucose homeostasis remains elusive for most patients, and chronic hyperglycemia drives the development of microvascular and macrovascular complications. The recognition that a subset of beta cells persists even years after diagnosis has catalyzed research into disease-modifying therapies aimed at preserving residual insulin secretion. Preservation of endogenous C-peptide production, even at low levels, correlates with improved glycemic control, reduced hypoglycemia risk, and decreased incidence of long term complications [3].

Glucagon, a 29-amino acid peptide hormone secreted by pancreatic alpha cells, plays a central role in glucose counterregulation by stimulating hepatic glycogenolysis and gluconeogenesis. In type 1 diabetes, dysregulated glucagon secretion persists despite profound beta cell loss, contributing to fasting and postprandial hyperglycemia [4]. The bihormonal model of diabetes posits that hyperglycemia results not solely from insulin deficiency but from the dual abnormality of insufficient insulin coupled with excessive or inadequately suppressed glucagon secretion [5]. Glucagon receptor antagonists inhibit glucagon action at the hepatocyte level, thereby reducing hepatic glucose

output independent of insulin availability [6]. Beyond their direct metabolic effects, these agents may indirectly benefit beta cells by reducing glucotoxicity and decreasing the secretory burden imposed by chronic hyperglycemia. Furthermore, preclinical models suggest that glucagon signaling may modulate immune cell activity within the islet microenvironment, raising the possibility that glucagon receptor blockade could attenuate autoimmune-mediated beta cell destruction. This review is to critically evaluate the efficacy and safety of glucagon receptor antagonists compared to standard insulin-based care for preserving beta cell function in individuals with newly diagnosed type 1 diabetes, with emphasis on molecular mechanisms, clinical trial outcomes, and translational implications for disease modification.

Molecular Mechanisms of Glucagon Receptor Antagonism in Beta Cell Protection

Glucagon receptor antagonists exert their primary pharmacological effects by competitively or noncompetitively blocking the glucagon receptor, a class B G protein-coupled receptor predominantly expressed on hepatocytes [7]. Upon antagonist binding, the receptor fails to activate adenylyl cyclase, resulting in decreased intracellular cyclic adenosine monophosphate accumulation and subsequent inhibition of protein kinase A-mediated phosphorylation cascades that drive gluconeogenic enzyme expression. This reduction in hepatic glucose production directly lowers circulating glucose concentrations, thereby diminishing glucotoxicity, a pathological state in which chronic hyperglycemia impairs beta cell function through oxidative stress, endoplasmic reticulum stress, and increased apoptosis [8]. By alleviating glucotoxicity, glucagon receptor antagonists may create a metabolic environment more conducive to beta cell survival during the critical early phase of type 1 diabetes when residual beta cell mass is still appreciable.

Beyond glucose-lowering, glucagon receptor blockade may reduce the functional demand placed on surviving beta cells. In the setting of type 1 diabetes, remaining beta cells operate under chronic stress as they attempt to compensate for the loss of neighboring cells, leading to hyperactivity, increased antigen presentation, and enhanced visibility to autoreactive T lymphocytes. Preclinical studies in nonobese diabetic mice have demonstrated that pharmacological reduction of beta cell workload through intensive insulin therapy or somatostatin analogs can delay disease onset and preserve islet architecture [9]. Glucagon receptor antagonists similarly reduce the glucose excursion amplitude that beta cells must counteract, potentially decreasing their metabolic and immunological burden. Additionally, emerging evidence suggests that glucagon may have direct effects on immune cell populations within pancreatic islets, including modulation of dendritic cell maturation and T cell activation, although these pathways remain incompletely characterized in the context of type 1 diabetes. The interplay between metabolic and immunological mechanisms positions glucagon receptor antagonism as a multifaceted intervention with potential disease-modifying properties beyond simple glucose control.

Preclinical Evidence and Animal Models

Animal studies have provided foundational insights into the potential of glucagon receptor antagonism for beta cell preservation in autoimmune diabetes. In nonobese diabetic mice, the most widely used spontaneous model of type 1 diabetes, administration of glucagon receptor antagonists during the prediabetic phase resulted in delayed onset of hyperglycemia, reduced insulitis severity, and increased C-peptide levels compared to vehicle-treated controls [10]. Histological analyses revealed preservation of islet architecture with decreased immune cell infiltration and reduced apoptotic beta cell counts. These effects were most pronounced when treatment was initiated early in the disease process, before extensive beta cell loss, supporting the rationale for early intervention in human subjects. Mechanistic studies employing knockout mice deficient in the glucagon receptor have corroborated these findings, demonstrating resistance to streptozotocin-induced diabetes and improved glucose tolerance following partial beta cell ablation [11].

However, translating these preclinical observations to human type 1 diabetes presents several challenges. The autoimmune pathogenesis in nonobese diabetic mice differs from human disease in terms of genetic architecture, environmental triggers, and T cell epitope specificity [12]. Additionally, the compensatory alpha cell hyperplasia and glucagon hypersecretion observed with chronic glucagon receptor blockade in rodents raise concerns about pancreatic remodeling that may not be immediately apparent in short term studies [13]. Hepatic steatosis, characterized by excessive triglyceride accumulation in hepatocytes, has been consistently documented in multiple animal models treated with glucagon receptor antagonists, reflecting the critical role of glucagon in hepatic lipid oxidation and very low density lipoprotein secretion [14]. While metabolically adaptive in the short term, prolonged hepatic fat accumulation carries risks for nonalcoholic steatohepatitis and hepatic fibrosis. These safety signals necessitate careful monitoring in human trials and underscore the importance of identifying therapeutic windows that maximize beta cell preservation while minimizing adverse metabolic consequences.

Clinical Trial Evidence in Early Type 1 Diabetes

Clinical investigation of glucagon receptor antagonists in type 1 diabetes has been limited but informative. The majority of clinical trials have focused on type 2 diabetes, where these agents demonstrated robust glucose-lowering efficacy but were complicated by hepatic safety concerns that led to discontinuation of several drug development programs [15]. In type 1 diabetes, a small number of proof-of-concept studies have evaluated glucagon receptor

antagonists as adjunctive therapy to insulin during the honeymoon period, defined as the initial months to years after diagnosis when residual beta cell function remains detectable. These trials have enrolled patients within three to six months of diagnosis, a timeframe hypothesized to offer the greatest opportunity for disease modification before irreversible beta cell loss occurs.

Results from these early phase trials indicate that glucagon receptor antagonists, when added to standard intensive insulin therapy, produce modest reductions in glycated hemoglobin and decreased insulin dose requirements compared to insulin monotherapy [16]. More importantly, several studies have reported attenuated decline in stimulated C-peptide secretion over six to twelve month follow up periods, suggesting a potential beta-cell preserving effect [17]. Mixed meal tolerance tests, which assess endogenous insulin secretion in response to nutrient challenge, revealed higher area under the curve C-peptide values in antagonist-treated groups compared to controls. These differences, while statistically significant in some studies, have been of modest magnitude, and the durability of benefit beyond the initial treatment period remains uncertain. Subgroup analyses suggest that individuals with higher baseline C-peptide levels and shorter disease duration derive greater benefit, reinforcing the importance of early intervention.

Safety analyses from type 1 diabetes trials mirror findings from type 2 diabetes studies, with elevated hepatic aminotransferases and imaging evidence of hepatic steatosis observed in a subset of participants [18]. Most cases were asymptomatic and reversible upon drug discontinuation, but these findings necessitate regular hepatic monitoring and may limit long-term use. Hypoglycemia rates were not significantly increased compared to standard care, likely because glucagon receptor antagonists do not directly stimulate insulin secretion. Gastrointestinal side effects, including nausea and diarrhea, were reported more frequently in antagonist-treated groups. The modest clinical benefit, coupled with hepatic safety concerns, has tempered enthusiasm for widespread adoption pending completion of larger randomized controlled trials with extended follow-up and comprehensive safety assessments.

Comparative Effectiveness and Standard of Care Considerations

Standard care for newly diagnosed type 1 diabetes centers on intensive insulin therapy aimed at achieving near normoglycemia while minimizing hypoglycemia risk [19]. Multiple daily injection regimens or continuous subcutaneous insulin infusion, coupled with carbohydrate counting and continuous glucose monitoring, constitute the cornerstone of management. During the honeymoon phase, residual beta cell function contributes to glycemic control, and insulin requirements are typically lower than in established disease. Preservation of this residual function has been the target of numerous immunomodulatory interventions, including anti-CD3 monoclonal antibodies, which have demonstrated modest delays in C-peptide decline by inducing partial T cell tolerance [20]. Compared to these immunotherapies, glucagon receptor antagonists offer a fundamentally different mechanism that addresses metabolic rather than immunological pathology.

The comparative effectiveness of glucagon receptor antagonists versus standard insulin therapy alone must be assessed not only through glycemic metrics and C-peptide preservation but also through patient-centered outcomes, including quality of life, treatment burden, and long-term complication risk. While C-peptide preservation is an established surrogate endpoint associated with improved outcomes, the magnitude of benefit conferred by glucagon receptor antagonists in published trials has been modest, typically preserving an additional 10 to 20 percent of baseline C-peptide secretion at one year. Whether this degree of preservation translates into clinically meaningful reductions in hypoglycemia or microvascular complications over decades of disease remains unknown. Furthermore, the addition of an oral medication to an already complex insulin regimen increases treatment complexity and cost, considerations that must be weighed against potential benefits. Head-to-head comparisons with emerging immunotherapies such as teplizumab, recently approved for delaying clinical onset in at risk individuals [21], will be essential for establishing the relative value of glucagon receptor antagonism in the therapeutic armamentarium.

Knowledge Gaps, Safety Concerns, and Future Research Directions

Despite promising preclinical and early clinical evidence, significant knowledge gaps impede the integration of glucagon receptor antagonists into routine clinical practice for type 1 diabetes. Long term safety data extending beyond two years are lacking, and the natural history of antagonist induced hepatic steatosis remains incompletely characterized. Whether prolonged glucagon receptor blockade increases risk for clinically significant liver disease, including nonalcoholic steatohepatitis with fibrosis, is unknown [22]. The development of noninvasive biomarkers and imaging modalities for hepatic monitoring will be critical for identifying at risk individuals and guiding treatment decisions. Additionally, the compensatory alpha cell hyperplasia observed in animal models raises theoretical concerns about pancreatic neoplasia, though no signal has emerged in human studies to date.

The optimal timing, duration, and patient selection criteria for glucagon receptor antagonist therapy require further investigation. Current trials have focused on the honeymoon period, but whether earlier intervention during the presymptomatic stage of autoimmunity could prevent or delay clinical onset is an open question that warrants exploration in high-risk individuals identified through autoantibody screening [23]. Combination strategies that pair glucagon receptor antagonists with immunomodulatory agents represent a rational next step, potentially addressing both the metabolic and autoimmune drivers of beta cell destruction. Preliminary preclinical data suggest

synergistic effects when glucagon receptor blockade is combined with anti-inflammatory or immunosuppressive therapies, but human trials are needed to validate these findings. The identification of biomarkers that predict treatment response would enable precision medicine approaches, targeting therapy to individuals most likely to benefit while sparing others from unnecessary exposure to potential adverse effects.

Mechanistic questions also remain. The relative contributions of reduced glucotoxicity, decreased beta cell workload, and potential immunomodulatory effects to the observed beta cell preservation are incompletely understood. Advanced imaging techniques, including positron emission tomography with beta cell-specific tracers, could provide a noninvasive assessment of beta cell mass changes over time [24]. Single-cell transcriptomic and proteomic profiling of islet cells and immune populations before and after glucagon receptor antagonist treatment may reveal molecular pathways that mediate therapeutic benefit or adverse effects [25]. Finally, the development of next-generation glucagon receptor antagonists with improved hepatic safety profiles, potentially through tissue-selective delivery or dual receptor targeting, represents an active area of pharmaceutical innovation that may overcome current limitations.

CONCLUSION

Glucagon receptor antagonists represent a mechanistically novel approach to beta cell preservation in early type 1 diabetes that diverges from traditional immunomodulatory strategies by targeting the metabolic abnormalities that exacerbate beta cell stress and dysfunction. Preclinical studies have demonstrated that glucagon receptor blockade can delay diabetes onset, reduce insulitis, and preserve islet architecture in autoimmune diabetes models through mechanisms including reduced glucotoxicity and decreased beta cell secretory burden. Early phase clinical trials in newly diagnosed type 1 diabetes patients have shown that adjunctive glucagon receptor antagonist therapy produces modest improvements in glycemic control and attenuates the decline in C-peptide secretion compared to intensive insulin therapy alone. However, the magnitude of clinical benefit has been limited, and the durability of beta cell preservation beyond the initial treatment period remains uncertain. Hepatic safety concerns, particularly the consistent observation of elevated aminotransferases and hepatic steatosis, constitute a significant barrier to widespread clinical adoption and necessitate careful patient selection and monitoring. The comparative effectiveness of glucagon receptor antagonists relative to approved immunotherapies and the potential for synergistic combination strategies require rigorous evaluation in adequately powered randomized controlled trials with extended follow-up. While current evidence supports continued investigation of glucagon receptor antagonism as a disease-modifying approach, substantial gaps in knowledge regarding long term safety, optimal treatment protocols, and patient selection criteria must be addressed before these agents can be routinely recommended for beta cell preservation in clinical practice. Future research should prioritize multicenter randomized controlled trials comparing glucagon receptor antagonists, alone and in combination with immunomodulatory agents, against standard care with long-term follow-up to definitively establish efficacy, safety, and optimal patient selection strategies for beta cell preservation in early type 1 diabetes.

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CITE AS: Mercy Latricia (2026). Glucagon Receptor Antagonists versus Standard Care: Beta-Cell Preservation in Early Type 1 Diabetes. IAA Journal of Biological Sciences 14(1):60-64. https://doi.org/10.59298/IAAJB/2026/1416064