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Short Communication

# Incretin-Like Glycemic and Metabolic Effects of Luminal Starch Blockers

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## Abstract

Luminal glucosidase inhibitors and GLP-1 agents (incretins) bring about similar, dose-related improvements in post-prandial glycemic and insulinogenic responses to ingested carbohydrates in man and animals. The metabolic improvements are likely due to the combined physiological effects of both decreasing the rate of gastric emptying and subsequent delays in carbohydrate digestion and luminal glucose uptake, combined with modest decreases in caloric intake with both therapeutic regimens. The combined impact of the above ultimately results in decreases in insulinogenic responses and improved insulin sensitivity in peripheral tissues. Both therapeutic approaches result in an approximate 15% decrease in daily caloric intake and decreases in plasma insulin and improved plasma lipid profiles, in a manner that is somewhat analogous to the consumption of a higher fiber, low glycemic index, and complex carbohydrate diet. While the duration of the GLP-1 approach may prove to be therapeutically effective for only a limited duration often of one year or less, dietary approaches to control caloric intake including glucosidase inhibitors typically may be continued indefinitely and with minimal risk of long-term adverse or rebound effects. Thus, the combination of GLP-1 (incretin) agonists, α-glucosidase inhibitors, and dietary and lifestyle interventions as monotherapy or combined therapy may prove to be useful adjuncts in addressing the global burgeoning problems linked to obesity, T2DM and insulin-resistant states in man and animals.

**Keywords:** Obesity; Diabetes; GLP-1; Glucosidase Inhibitors; Glycemic Responses

## Introduction

The prevalence of obesity and overweight conditions and their common comorbidities are now approaching epidemic proportions, affecting one third or more of the adult population of industrialized nations [1-3]. The investigation of incretin hormone agents for the potential treatment of obesity and adult onset (Type 2; T2DM) diabetes over the past several decades has resulted in the development of several GLP-1 agents now known to be therapeutically effective in curbing the glycemic responses to meals and decreasing the magnitude of adiposity in obese and obese+T2DM states [4-7]. The beneficial glycemic effects have been deemed to result from delaying the rate of gastric emptying, thereby modulating the entry of carbohydrates into the upper regions of the small intestine, where the majority of starch digestion typically occurs [5-8]. In addition, the rate-limiting stage of luminal glucose absorption into the peripheral circulation closely parallels the Km of the digestive process, with the anticipated result of decreasing the rate and magnitude of the glycemic response, with corresponding amelioration in the post prandial insulinogenic responses. The physiological mechanism of gastric emptying is a complex process, involving hormonal, digestive, osmotic, and physicochemical components [9-12]. Dietary factors including gums, complex fibers, minerals, simple vs complex carbohydrates, and a large spectrum of phytochemical constituents commonly found in fruits and vegetables may impede the efficiency of the brush border enzymatic processes, resulting in variations in the postprandial glycemic responses observed. As the digestive residual transits down the gastrointestinal tract, numerous gut peptides and incretin hormones are released from the duodenal epithelium that contribute to both satiety and the continuation of the digestive process [9,10]. The elevations in glycemic responses also result in elevations in the percent of glycated hemoglobin in circulation, Glycated hemoglobin contributes to pathophysiologic actions in vascular tissues and their supporting structures [2,7,8]. Because Glycation results in movement of the

hemoglobin saturation curve to the left, it impedes the release of oxygen from the hemoglobin moiety, and contributes to a state of relative hypoxia in erythrocytes and their supported tissues [11]. Hypoxia is a contributor to formation of inflammatory highly reactive oxygen species (iROS) and generation of pathophysiologically damaging free radicals and membrane damage within the affected erythrocytes and other tissues [12]. The membrane damage contributes to an increased propensity for erythrocyte aggregation, an increase in the blood viscosity and in impaired peripheral blood flow, thereby impeding efficient oxygen delivery.

The peptide hormone amylin is co-secreted with insulin and normally impacts receptor domains located on the antrum of the stomach, to bring about a gated, dose related response in the rate of gastric emptying, [13,14] while the incretin hormones GLP (Glucagon-like peptide, i.e., the satiety hormone) and the gastric inhibitory peptide GIP) are released from the intestinal tissues after food ingestion [5]. Both amylin and incretin hormones ultimately exert satiating effects on appetite and food intake, which contribute to the culmination of their metabolic actions in peripheral tissues [4-8]. Both GLP and GIP release from the intestine following ingestion of glucose other nutrients facilitate the stimulation of insulin secretion from pancreatic β cells. Incretins GIP and GLP-1 initiate their hormonal effects by binding to specific receptors (the GIP receptor, GIPR, and the GLP-1 receptor (GLP-1R) [15]. Both hormones are members of the coupled guanosine linked G-protein family, which activate intracellular processes attributed to the incretin mediated functions [15]. GLP-1 agonists alone or in combination with GIP agonists result in a sustained decrease in appetite, and an approximate 15% decrease in *ad libitum* energy intake [4]. The decreases in daily energy intake contributes to a gradual weight loss and accompanying improvements in plasma lipid profiles and other insulinogenic actions. Because of the gradual nature of weight loss, the improvements in the BMI and the associated comorbidities are often more lasting than other dietary approaches to weight management, possibly do to secondary neurologic actions on the hypothalamic ventromedial nucleus, the primary controller of appetite [4-6,9]. Upon stimulation by incretins, the satiety center transcends a sensation of fullness and gastric/gastrointestinal satiation thus the combined gastric and CNS effects limit further voluntary food ingestion for several hours, independent of macronutrient composition of the dietary selections [9,10,12].

The actions of the so-called orally administered 'starch blockers' exert complementary effects on food intake to those discussed above, albeit via a different physiological mechanism. Rather than slowing the transit of nutriments from the antrum to the duodenum as above, α-glucosidase inhibitors delay the rate of carbohydrate digestion of starches and sucrose at the level of the brush border enzymes via competitive inhibition, thereby slowing the rate of post-digestion luminal glucose uptake [8,16]. Since the digestive actions resulting in monosaccharide generation represent the de facto rate-limiting step in luminal glucose uptake, the end result on glycemic excursions and their insulinotropic sequela are similar to those following GLP-1 or GIP incretin agonist agents [15,16]. The physicochemical effects of the delayed digestive activity following α-glucosidase inhibition transiently increases the osmotic pressure and luminal distention, which collectively contribute to a curbing in appetite that is qualitatively similar to that which occurs with the incretin agents [15,16]. In animal studies, administration of α-glucosidase inhibitors was also found to decrease the hepatic activities of glucokinase, malic enzyme, and glucose-6-phosphate dehydrogenase, key mediators of glycogenic and lipogenic actions. Adiposity and weight gain were modestly decreased, and plasma glucose, insulin, triglyceride and cholesterol fractions were also improved after 8 weeks of treatment [15-18]. Regardless of the mechanism of action that results in decreases in the glycemic response to carbohydrate feeding, the improved insulin sensitivity results in improvements in glucose uptake in peripheral tissues as a result of improved efficiency of glucose transporter (GLUT4) actions, with beneficial impacts on cellular energy and substrate metabolism [19,20].

Disregarding differential factors, the ease of oral administration of the α-glucosidase inhibitors vs. the subcutaneous administration of the incretin agonists may contribute to improved compliance, in addition to potentially pathophysiologic adverse effects of prolonged incretin therapy [6,7]. The α-glucosidase inhibitors exert their actions via luminal brush border competitive inhibition, thus the most common adverse effects of glucosidase inhibitors consist of mild gastrointestinal distress symptoms due to actions of the colonic microbiota on undigested carbohydrate residues and are easily remedied by adjustments to the dosages or formulae of the α-glucosidase agent being administered [16,18,19]. Of the two most common agents, acarbose does not undergo significant intestinal absorption, thereby potentially prolonging the duration of luminal transit, and simple overdosing may give rise to gastrointestinal distress as the undigested starches generate acid and gas via intestinal microbiota actions [11,12,21-25]. In contrast, miglitol undergoes complete luminal absorption in the small intestine soon after ingestion typically within two hours of ingestion and undergoes renal excretion without further metabolism in the liver or other tissues.

The rapid metabolic clearance thereby limits the duration of action, and minimizing the potential for adverse complications while facilitating a similar magnitude of antiglycemic and antilipogenic actions [21-23]. The effects of α-glucosidase inhibitors on intestinal release of incretins in clinical settings are variable, as are the are the effects on the VMH satiety centers [10]. The luminal agents are associated with a similar magnitude of appetite suppression to those of the incretin agents, equivalent to an approximate 15 percent reduction in caloric intake that is sustained throughout the duration of pharmacologic administration [5,14,17,25,26]. While most clinical trials of inhibitors of α-glucosidase inhibitors have reported their effects in T2DM, Nagai., *et al*. (2011) also reported increases in GLP-1 and decreases in GIP following miglitol administration in Type 1 DM, in addition to decreases in Hemoglobin A1c and improved glycemic responses to an oral glucose tolerance, thus broadening the clinical applications for this class of antidiabetic agents [25]. Modest improvements on plasma lipid profiles and body mass index have also been reported in clinical studies with α-glucosidase inhibitors [26]. In animal studies with obese-T2DM rats, Tulp and Rizvi (2025) reported that following 8 weeks of dietary treatment with miglitol, *in vitro* activities of hepatic lipogenic and glycemic enzymes were decreased in liver homogenates, in association with decreases in the magnitude of adiposity and weight gain, compared to similarly fed untreated littermate controls [17,18]. The glycemic response to an oral glucose tolerance, and the AUC for both glucose and insulin were significantly decreased, toward those of non-obese littermates. While assessment of VMH nucleus have not been obtained in those studies, the 15% decrease in energy intake was of similar magnitude to clinical studies with incretin agonists reported elsewhere, suggestive of GLP-modulating both luminal and central effects with the luminal miglitol therapy in that study. In contrast, the effects of miglitol in similarly fed obese, non-diabetic animals were associated with significant improvements in glycemic parameters, while only modest improvements in hepatic enzymes and adiposity were observed [8,9,17,18]. In all studies, as glycemic control improves, glycated hemoglobin concentrations also decrease, thereby improving oxygen delivery to peripheral tissues [33].

## Conclusions

The metabolic effects of the incretin hormones and luminal α-glucosidase inhibitors on glycemic parameters result in improvements of similar magnitude in glycemic responses in man and animals. In addition, the effects of the agents on food and energy intake were also of similar magnitude, while the impact of the agents on adiposity and weight gain or loss were variable in animals and clinical studies. The appetite control center is located in the ventromedical hypothalamus; the VMH nucleus when damaged or dysregulated can result in hyperphagia, aggravation of glycemic parameters, and excess weight gain which may progress to T2DM in genetically susceptible individuals and animals [10,27-31]. In addition, the gastrointestinal hormone ghrelin also contributes to energy balance by stimulating appetite during fasting or food restriction, thereby contributing to energy balance. Ghrelin signals the appetite center in the hypothalamus to initiate food ingestion behaviour, food selection preferences, and other sensory functions that impact on feeding reward activities. Thus it is of interest in anti-obesity and diabetes therapy [31]. Ghrelin also stimulates the release of growth hormone (somatotrophin), with secondary effects on lipid storage and substrate metabolism in adipose tissue and other tissues in addition to its long-known effects on growth and development during early life and in maintaining nitrogen balance via anabolic actions throughout much of the lifespan. Additional studies suggest that ghrelin may also influence learning and memory in the hippocampus, where it enhances hippocampal neuronal interconnections. Additionally, it may have a contributory role in gut motility, gastric acid secretion, and even cardiovascular health [10,31,32]. Thus, in conclusion the combined effects of incretins, α-glucosidase inhibitors, diet and lifestyle factors can contribute to improvements in key glycemic parameters via centrally and tissue mediated actions. As an added benefit, as glycemic status improves, the proportion of glycated hemoglobin also decreases toward euglycemic status, thereby improving the efficiency of oxygen delivery to peripheral tissues [33]. Dysregulation of gastric emptying is a common observation in diabetes, consistent with impaired hormonal actions on gastric emptying, resulting in accelerated transit and luminal digestion of the partially digested meals to the duodenum. Both incretins and α-glucosidase address the disordered digestive processes, albeit by different but complimentary and likely additive mechanisms, resulting in comparable reductions in energy intake, and postprandial glycemic, insulinemic and metabolic responses in man and animals.

## Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

## Consent

It is not applicable.

## Ethical Approval

It is not applicable.

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## Competing Interests

Author has declared that no competing interests exist.

## Addendum

Glycation occurs predominantly to adult (α2β2) hemoglobin, when the hemoglobin is in the taut form and binds oxygen more tightly, thereby impeding oxygen release and essential tissue oxygenation and metabolic processes. Glycation of hemoglobin occurs as the result of a non-enzymatic non-reversible process in proportion to plasma glucose concentrations. The glycation reaction occurs predominantly in adult (α2β2)hemoglobin, and when the hemoglobin is in the taut form.

In the taut form hemoglobin and binds oxygen more tightly, there by impeding oxygen release and essential tissue oxygenation and metabolic processes. Glycated hemoglobin also contributes to inflammation of endothelial cells, and to formation of atherosclerotic plaques. If postprandial hyperglycemia remains left unchecked, the inflammatory responses can also bring alterations in the redox state of Fe2+ in hemoglobin to form Fe3+- and Fe4+ -hemoglobin, both of which are capable of penetrating the subendothelium of veins and arteries, causing greater permeability and further tissue damage. Thus, clinical interventions that can reduce or reverse the formation of glycated hemoglobin in vivo are of considerable potential therapeutic potential in management of T2DM [33]. Thus, mechanisms that can reduce postprandial hyperglycemia toward euglycemic levels are an essential element of T2DM management, where they may bring about decreases in the magnitude of comorbidities associated with T2DM and insulin-resistant states. ....”

Because glycation occurs predominantly to adult (α2β2) hemoglobin, when the hemoglobin is in the taut form and binds oxygen more tightly, thereby impeding oxygen release and essential tissue oxygenation, tissue regeneration, and other essential metabolic processes.

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