Journal of Medical, Clinical and Surgical Case Reports

Editorial

WRJMCSCR-25-003

Can Inhibitors of Luminal Carbohydrate Digestion Decrease Insulin Resistance in Obesity and T2DM?

Orien L Tulp*

Department of Medicine, University of Science Arts and Technology, Olveston, Montserrat

Correspondence: Orien L Tulp, Department of Medicine, University of Science Arts and Technology, Olveston, Montserrat, E-mail: o.tulp@usat.edu; DOI: https://doi.org/10.56147/jmcscr.1.1.3

Citation: Tulp OL (2024) Can Inhibitors of Luminal Carbohydrate Digestion Decrease Insulin Resistance in Obesity and T2DM?. J Med Clin Surg Case Reports 1: 3.

Abstract

Premature dysregulation of gastric emptying in concert with hyperinsulinemia are a common observation in early stages of Type 2 Diabetes (T2DM) and contributes to the magnitude of the typical glycemic excursions and insulinogenic responses following carbohydrate-laden meals. In contrast, in later stages of the disorder gastroparesis may occur secondary to diabetic neuropathy. While dietary measures are often a first line approach, inhibitors of luminal starch digestion have been demonstrated to slow the rate of α-glucosidase and sucrase activity following a carbohydrate meal in man and animals, thereby attenuating the immediate glycemic and insulinogenic responses. The improved glycemic and insulinogenic responses if maintained over the course of weeks or months result in improvements in glycated hemoglobin, insulin sensitivity and glucose disposal in peripheral tissues, with secondary improvements in lipogenesis, plasma lipid profiles including plasma triglycerides and LDL cholesterol fractions. Thus, incorporation of inhibitors of α-glucosidase and sucrase activity posit to become useful adjuncts as monotherapy or in combination with other therapeutic agents including GLP-1 incretin mimetics, phototherapeutics, phyto therapeutics and other obesity and diabetic therapeutic agents in the clinical management of hyperinsulinemia, obesity, prediabetes, T2DM and insulin resistant states as they occur in man and animals.

Keywords: Glucosidase; Sucrase; Miglitol; Acarbose; Obesity; Diabetes; T2DM; Glycemic parameters

Received date: March 29, 2025; **Accepted date:** April 02, 2025; **Published date:** April 21, 2025

Introduction

The prevalence of obesity and overweight conditions now impacts over one third of the adults of some westernized nations. In addition, the excess adiposity that accompanies the condition is a major contributor to the progression of a myriad of comorbidities including pre-diabetes and Type 2 diabetes that often accompany overweight states [1-3]. Type 2 Diabetes (T2DM) and atherogenic progression of cardiovascular disease are among the most serious of the comorbidities and impact both longevity and the quality of life of patients inflicted with the disorder. Moreover, once diagnosed, the comorbidities typically require prolonged therapeutic measures to manage the progress and outcome of the often-adverse clinical sequelae [4-6]. The insulin response to meals is typically proportional to and dependent upon the magnitude of the glycemic response to dietary carbohydrate and becomes progressively greater in the presence of insulin resistance, a key hallmark of both obesity and T2DM [7-9]. The chronic elevations in plasma glucose concentrations also result in increases in the glycation of Hemoglobin A1c (HbA1c), which impedes oxygen delivery to peripheral tissues, thereby impinging on oxygen-dependent cellular processes, while also serving as a useful clinical diagnostic marker of recent glycemic control [10,11]. Inhibitors of luminal carbohydrate digestion slow the rate of intestinal hydrolysis of starchy polymers *via* competitive inhibition of glucosidase and sucrase enzymes in the brush border domains of the uppermost regions of the small intestine and where the primary carbohydrate hydrolytic processes typically exhibit the greatest activity [12,13]. Once generated *via* α-glucosidase activity, the monosaccharide

glucose moieties undergo rapid uptake into the peripheral circulation in transit to muscle, adipose tissue, liver, neural and other tissues, where in most tissues their direct cellular uptake is dependent upon the availability of insulin-dependent GLUT4 glucose transporters [14]. Adrenal glucocorticoids, sirtuins and other epigenetic factors contribute to silent roles in the endoplasmic generation and intracellular availability of GLUT4 glucose transporters, thereby contributing to parameters of insulin sensitivity and insulin resistance. As the process for cellular glucose uptake becomes progressively deranged, it can thus further impede insulin-mediated actions including those reflective of insulin resistance on the plasma membranes in skeletal muscle and adipose tissue, where the majority of insulin resistance is manifested [15]. The luminal, brush border hydrolytic step is essentially the most rate limiting step in the glucose uptake process; Once free luminal glucose is generated, glucose subsequently undergoes rapid uptake and transit to the circulation while en route to multiple peripheral tissues where it may undergo oxidation *via* biochemical processes or contribute to the biosynthesis and selective storage of glycogen or fatty acids in those tissues [16,17].

The dietary monosaccharide fructose represents a special case in the carbohydrate digestion process however, because insulin and other hormones do not play a direct role in its tissue uptake or metabolism [12]. The luminal hydrolysis of sucrose undergoes a somewhat analogous fate to starch polymers, generating equimolar amounts of fructose and glucose moieties. The characteristics of luminal uptake of fructose however, is similar to a rate limiting process, characteristically similar to a facilitated diffusion process, as the luminal Michaelis-Menton Kinetics (KM) for fructose occurs more slowly than for glucose. In addition, once fructose enters the circulation, most fructose is destined for the liver, where specialized insulin-independent GLUT transporters (*i.e.,* GLUT1, GLUT2 and GLUT5) facilitate hepatocellular uptake and metabolism into two trioses that can enter into multiple metabolic or oxidative pathways. In present day Western civilization, most fructose is now derived from High Fructose Corn Syrup (HFCS), an industry preferred sweetener for manufactured foods and beverages and which typically now contains over 70% free fructose. While the minimal amounts of naturally occurring fructose in many fruits and vegetables have always been part of the human food supply of most populations, normal dietary intakes seldom exceeded 20 grams per day with a typical diet [16]. The development of HFCS and its wide commercial use in commercially manufactured foods as a sweetener over the past three decades has inadvertently resulted in marked and sometimes extraordinary (<5-fold) increases in daily fructose consumption that now often approach the upper limits of safe ingestion and net capacity for luminal absorption. When consumed in large amounts, fructose may contribute to 20% or more of normal daily caloric intake and can independently contribute to the development of obesity, gout and other metabolic disorders and where excess fructose consumption is contraindicated including symptoms of gastrointestinal distress when absorptive capacity has been exceeded [16,17].

In laboratory studies, glucosidase inhibitors are often derived from a class of naturally occurring phytochemicals, that exert varying degrees of luminal enzymatic inhibition when ingested [12]. Qualitatively, they somewhat mimic dietary gums, fibers and other nutritionally based agents commonly found in wholesome foods that help to moderate the digestive processes of macronutrient energy sources in the small intestine. In animal studies conducted in obese and obese T2DM rats, glucosidase inhibitor compounds including commercially available acarbose and miglitol, resulted in decreases in the energy intake and in the AUC for both glucose and insulin, in addition to decreases in the percent of glycated hemoglobin after several weeks or months of α-glucosidase inhibitor treatment [13,18,19]. More recently, hepatic insulin-dependent enzyme activities of both glycemic and lipogenic enzymes glucokinase, malic enzyme and glucose-6-phosphate dehydrogenase were found to become decreased after 8 weeks of treatment of obese-T2DM rats with a modest daily dose of miglitol, administered as an admixture in the diet. Of interest, the elevated plasma lipid profiles typical of those commonly observed in most strains of obese rats and mice were also improved, in both the triglycerides and LDL-cholesterol lipoprotein fractions, consistent with improved insulin-to-glucose ratios and indicative of improved insulin sensitivity (*i.e.,* a decrease in insulin resistance). In clinical trials conducted in subjects with established mild to moderate T2DM, the metabolic responses were similar to those observed in the animal studies, whether administered as mono- or combination therapy. In all reports in both human trials and animal studies, the α-glucosidase inhibitors were found to be effective in improving the pathophysiological magnitude of the common stigmata of T2DM and limited improvements in obesity as well. Thus, oral administration of these agents facilitates patient compliance and can contribute to progressive metabolic improvements in appetite regulation, hyperinsulinemia and glycemic control over time, in addition to secondary benefits generated by delaying the progression of common pathophysiologic comorbidities of the disorder [5,11,12,18,19].

Discussion

Accelerated gastric emptying, also sometimes referred to as dumping syndrome, is a common observation in diabetes, where the acid chyme including partially digested carbohydrate residues transits to the duodenum prematurely, resulting in premature enzymatic hydrolysis of any excess carbohydrate contained in the digestive bolus [21]. A premature surge of duodenal carbohydrate content normally undergoes rapid digestion and exaggerates the hyperglycemic and insulinogenic

excursions following the carbohydrate meal. Typical therapeutic measures including dietary modifications to increase the relative proportions of dietary fat and protein and while decreasing the proportion of simple or complex carbohydrate sources are often applied as an initial dietary remedy. Dietary modifications, in combination with pharmacologic agents that may decrease stomach motility are also often attempted as an initial approach to ameliorate the digestive symptoms [22,23]. Early dumping syndrome is characterized by a group of symptoms, such as diarrhea, nausea and light-headedness in addition to undue fatigue following a meal that may be caused by secondary effects of diabetic-induced dysregulation of gastric emptying. In contrast, late dumping syndrome is characteristic of gastroparesis, linked to diminished neurologic or hormonal actions. While not life threatening, the dumping syndromes directly impact the quality of life and overall productivity of the individuals so inflicted. The complex physiological process of gastric emptying is neuronally and hormonally regulated. The normal physiologic control of gastric emptying results from contributions of the incretins (particularly the effects of Gastric Inhibitory Peptide (GIP), Glucagon-Like Peptide-1 (GLP-1) and Peptide Tyrosine-Tyrosine (PYY), glucagon, the gastric orexigenic hormones ghrelin and motilin, the hormonal effects of amylin, neurologic control and gastric tone and which may become individually or collectively impaired in obesity and T2DM. Thus, the glucosidase inhibitors with or without incretins or other agents may prove effective in restoring most glycemic and insulinogenic parameters in obesity and T2DM, as both classes of agents result in improvements in favorable postprandial glycemic excursions. In combination therapy, potential side effects of the participating agents may be decreased as smaller dosages of each agent may be required where the agents exert complimentary mechanisms of action. In addition, because adverse effects tend to be virtually nil with glucosidase agents, monitoring patient safety issues is typically uneventful. Early studies with amylin, a peptide hormone co-secreted with insulin, also exhibited favorable effects on delaying gastric emptying with corresponding improvements in glycemic and insulinogenic excursions, although discovering a suitable injectable or oral formula proved problematic [7-9,24,25].

Primary objectives in treating obesity and T2DM diabetes therapy are also to decrease the magnitude of insulin resistance, improve the efficiency of glucose utilization, improve dietary compliance and slow or impede the continued progression of pathophysiologic sequelae of those disorders. Decreases in the magnitude of obesity, when present, are also key objectives of effective therapy, further emphasizing the importance of attention to dietary preferences and eating habits. Thus, the life style, nutritional and clinical strategies that improve the efficiency of post-prandial glucose disposal in peripheral tissues, without incurring adverse effects of the therapeutic measures undertaken contribute a key role in the therapeutics of diabetes management. Therapeutic strategies that improve or normalize the dynamics of gastric emptying often contribute to a first approach in modulating the glycemic responses to a carbohydrate meal [16]. Note that complex carbohydrate, consumed in moderation or in combination with fresh, wholesome fiber rich foods, are important energy components of most dietary strategies. In contrast, consumption of simple carbohydrates including common table sugar (sucrose) or HFCS, often as added sweeteners, are typically considered neither nutritionally essential nor desirable in diabetic diet planning. When minimal quantities of sweeteners are deemed necessary to improve client acceptance or dietary compliance, however, minimal amounts of naturally occurring sugar alcohols such as the polyols Xylitol, Sorbitol, Erythritol, Mannitol and others may be included in limited quantities to increase the sweetness of selected beverages and foodstuffs without adding to the absorbable caloric content [16,20,21]. Consumed in moderation, polyols enhance the sweetness, while in abundant quantities, residual colonic digestion of polyol residuals may result in unpleasant gastrointestinal symptoms that can be managed by dialing back the net quantities consumed.

Summary and Conclusion

Inhibitors of luminal α-glucosidase and sucrase activity are effective natural or pharmacologic agents in controlling postprandial glycemic and insulinemic excursions following carbohydrate meals in man and animals in mild to moderate glucose intolerance in man and animals. Beneficial effects have been demonstrated on postprandial glycemic and insulinemia, glycated hemoglobin, plasma lipid profiles, energy intake and a modest attenuation of adiposity. Animal studies and human trials have demonstrated minimal side effects, which typically may be easily treated without incident by adjustment in the dosage, timing and meal schedule. Glucosidase inhibitors in concert with prudent dietary planning may also prove beneficial in minimizing the side effects of GLP-1 and other therapeutic agents, due to their complementary mechanism of physiological action on fundamental gastric and peripheral functions. In the animal studies from the authors laboratory, the effects of a modest dosage of miglitol resulted in favorable responses in the activity of key hepatic glycemic and lipogenic enzymes, AUC for glucose and insulin and glycated hemoglobin, in association with modest decreases in energy intake and body fat accretion in some but not all adipose tissue depots. In other studies, acarbose and miglitol were both observed to decrease daily food and energy intake similarly, which may have been a contributing factor to the favorable responses in the insulin-linked enzymes and lipid profiles in those studies [22]. The uncontrolled variables in human trials *vs.* non-human studies are typically greater than those observed in animal studies, due to greater subject variability in the human studies, often precluding determination of the

biological mechanisms implicated in the experimental studies. Regardless of the experimental designs and protocols reviewed, the beneficial impact of α-glucosidase inhibitors on important metabolic parameters clearly indicate that this class of natural and pharmacologic agents can facilitate favorable contributions in the treatment of obesity, T2DM and insulin resistance conditions in man and animals. Thus, measured incorporation of inhibitors of α-glucosidase and sucrase activity posit to become useful adjuncts as monotherapy or in combination with other therapeutic agents including incretin mimetics, phytotherapeutics and other obesity and diabetic therapeutic agents in the clinical management of mild to moderate hyperinsulinemia, obesity, prediabetes, T2DM and insulin resistant states as they occur in man and animals.

Acknowledgment

The author is grateful to the University of Science Arts and Technology, Montserrat for the resources to develop this editorial.

Conflicts of Interest

Author has declared that no competing interests exist.

Applications of Artificial Intelligence (AI) Disclaimer

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

Consent

It is not applicable.

Ethical Approval

It is not applicable.

References

1. World Health Organization (2007) The challenge of obesity in the WHO European region and the strategies for response. Geneva: World Health Organization. [Google Scholar]
2. Kelly T, Yang CS, et al. (2008) Global burden of obesity in 2005 and projections to 2030. Int J Obes 32: 1431-1437. [Crossref][Google Scholar][Indexed]
3. Pantalone KM, Hobbs T, Wells BJ, et al. (2015) Incidence of T2DM clinical characteristics, complications, comorbidities and treatment patterns among patients with type 2 diabetes mellitus in a large integrated health system. BMJ Open Diabetes Res Care 3: e000093. [Crossref][Google Scholar][Indexed]
4. Aggarwal R, Ostromnski JW, Vaduganathan M (2024) Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011–2020. JAMA 331: 1858-1860. [Crossref][Google Scholar][Indexed]
5. Halder F, Imam SM, Tulp OL, Rizvi SAA (2024) A review of incretin mimetics in the management of diabetes and associated comorbidities. [Crossref][Google Scholar]
6. Rahul R, et al. (2024) Prevalence of cardiovascular-kidney-metabolic syndrome stages in US adults, 2011-2020. JAMA. [Crossref][Google Scholar][Indexed]
7. Loscalzo J, Harrison TR (2022) Harrison's Principles of Internal Medicine, (21st Edtn). McGraw Hill Pubs: NY. [Google Scholar]
8. Azpiroz F (1994) Control of gastric emptying by gastric tone. Digest Dis Sci 39: 18S-19S. [Crossref][Google Scholar][Indexed]
9. Camilleri M (2019) Gastrointestinal hormones and regulation of gastric emptying. Curr Opin Endocrinol Diabetes Obes 26: 3-10. [Crossref][Google Scholar][Indexed]
10. Tulp OL, Einstein GP (2024) Can biophotonic therapy ameliorate the metabolic sequelae of NIDDM? Int J Complement Alt Med 17: 97-101. [Google Scholar]
11. Tulp OL, Syed AA, Rizvi SAA, Einstein GP (2024) Effects of biophotonic treatment on hematologic and metabolic parameters. European J Applied Science 12: 185-194. [Google Scholar]
12. Assefa ST, Yang EY, Chae SY, Song M, et al. (2019) Alpha glucosidase inhibitory activities of plants with focus on common vegetables. Plants (Basel) 9: 2-19. [Crossref][Google Scholar][Indexed]
13. Tulp OL, Rizvi SAA (2025) Luminal α-glucosidase inhibition improves insulin sensitivity and modulates glycemic and lipid profiles in obese rats with type 2 diabetes mellitus. Global Transl Med: 13. [Crossref][Google Scholar]
14. Leto D, Saltiel AR (2012) Regulation of glucose transport by insulin: Traffic control of GLUT4. Nat Rev Mol Cell Biol 13: 383-396. [Crossref][Google Scholar][Indexed]
15. Tulp OL (2024) Glucocorticoid ablation restores glycemic and thermogenic parameters in obesity, chapter in: Cortisol between physiology and pathology. Diana Loreta Păun Intech Open press. [Google Scholar]
16. Bray GA (2013) Energy and fructose from beverages sweetened with sugar or high-fructose corn syrup pose a health risk for some people. Adv Nutr 4: 220-225. [Crossref][Google Scholar][Indexed]
17. Anderson ME, Tulp OL (2023) The effects of high dietary fructose consumption on the development of gout. MOJ Public Health 4: 1019. [Google Scholar]
18. Tulp OL (2023) Effects of acarbose on luminal carbohydrate uptake, energy intake and plasma glycemic and lipid profiles in Wistar Fatty Rats. Research developments in medicine and medical science.
19. Tulp OL, Rizvi SAA (2025) Luminal α-glucosidase inhibition improves lipid parameters in obese t2dm rats. The Journal of Pharmacology and Experimental Therapeutics. [Google Scholar]

20. Hubert S, Albert B, Roland V, Eugen S, Markwart K, et al. (2012) Sugar alcohols. Ullmann's Encyclopedia of Industrial Chemistry Weinheim: Wiley-VCH.

21. Milchovich S, Dunn-Long B (2011) Diabetes mellitus: A practical handbook (10th edtn). Bull Publishing Company. [Google Scholar]

22. Tulp OL (2025) Impact of aging and obesity on insulin parameters, T4/T3 ratios, metabolic rates, sirtuins and longevity in congenic LA/Ntul//-cp (corpulent) rats. Ch 2 in: Medical Science: Trends and Innovations 5. [Crossref][Google Scholar]

23. Tulp OL (2024) Effects of miglitol on caloric efficiency and lipid profiles in obese male SHR/Ntul//-cp rats. British Journal of Healthcare & Medical Research 11: 49-58.

24. Huang HJ, Young AA, Koda JE, et al. (1992) Hyperamylinemia, hyperinsulinemia and insulin resistance in genetically obese LA/N-cp rats. Hypertension 19: 101-109. [Crossref][Google Scholar][Indexed]

25. Adeghate E, Kalasz H (2011) Amylin analogues in the treatment of diabetes mellitus: Medicinal chemistry and structural basis of its function. Open Med Chem J 5: 78-81. [Crossref][Google Scholar][Indexed]