Brief Report

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Luminal Inhibition of A-Glucosidase Activity Improves Insulinogenic Actions on Glycemic and Lipid Parameters in Obese T2dm Rats

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Abstract: Inhibitors of luminal α-glucosidase activity are well established agents to improve glycemic parameters in glucose intolerant states, but their secondary insulinogenic effects on plasma lipid profiles are less well established. Atherogenic elevations in plasma lipid profiles are a common observation in overweight, obese, hyperinsulinemic, and adult-onset diabetes (T2DM). The effects of luminal inhibition of starch digestion on parameters of weight gain and plasma lipid profiles were determined in groups of adult male obese T2DM SHR/Ntul//-*cp* rats. Animals were fed a USDA-formulated, nutritionally complete diet containing 54% sucrose as the carbohydrate component (Control) or the same diet containing a pharmacologic α-glucosidase inhibitor (1,5 dideoxy-1,5-[(2-hydroxyethyl) imino]-D glucitol; generic miglitol), 150 mg/kg diet as an admixture, *ad libitum* for up to 8 weeks. Miglitol resulted in modest decreases in food intake, net weight gain, adiposity and while the net efficiency of weight gain was similar in both groups. At the end of the study bloods were collected for determination of plasma glucose, Insulin, triglycerides, cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions. The miglitol-associated luminal inhibition of α-glucosidase activity resulted in 20% reduction in glucose area under the curve (AUC) and glycosylated hemoglobin, 15% reduction in triglycerides, 20% reduction in total cholesterol, and in both α- (LDL) and β-lipoprotein (HDL) fractions, a 14% decrease in net fat pad mass, and a 10% decrease in net weight gain at the end of the study. These results indicate that simple inhibition of luminal α-glucosidase activity via miglitol may be a useful adjunct in the long-term clinical management of hypercholesterolemia and hypertriglyceridemia in states of obesity, T2DM and other glucose intolerant states, in addition to therapeutic applications in enhancing and improving glycemic control in man and animals.

Keywords: Obesity; Diabetes; T2DM; Miglitol; α-glucosidase Activity; Glycemic parameters; Lipid profiles; SHR/Ntul//-*cp* Rat

Introduction

Recent reports indicate that the prevalence of obesity and type 2 diabetes (T2DM) now impacts up to one sixth of the populations of some Westernized countries, where the common pathophysiologic sequalae of obesity and T2DM are now approaching epidemic proportions with no clear preventative or therapeutic solutions on the horizon. [1-3] Dietary and lifestyle changes are projected to improvement in glycemic markers and remain a hallmark of conventional therapeutic approaches to treat the diabetes element of the obesity syndrome. Sadly, current approaches to reduce the burden of obesity and T2DM although well intentioned, are often less than successful. Satisfactory dietary and lifestyle modifications are often difficult to change, and the pathophysiologic progression of the typical sequelae may be well established and incompletely reversible by the time the therapeutic measures are initiated. While the glycemic improvement may commence soon after implementation of a dietary or luminal therapeutic intervention, restoration of plasma lipid profiles may resolve more gradually, and typically require longer term intervention to restore and become normalized. In addition, once systemic inflammation and advanced states of atheroma and vascular

 doi:10.20944/preprints202411.1127.v1

plaque have become established full recovery including atheromatous reversal may be difficult to achieve. [4,5]

Chronic elevations in plasma lipid profiles are common observations in Obesity+T2DM and represent a major contributor to a progression of cardiovascular disorders that often accompany the condition. [1-4] In addition, chronic hyperinsulinemia contributes to systemic inflammation in the CNS and other tissues, adding to the pathophysiologic burden of the disorder.4,5 Thus, implementation of therapeutic measures that can bring about reduction in the magnitude of inflammation, along with measures to decrease the magnitude of elevated triglycerides, total cholesterol (TC) and LDL Cholesterol (LDL-C) are deemed essential and desirable long term treatment goals and often require a prolonged duration to achieve.2 The industrialization of the food supply chain has also introduced dietary changes in industrialized populations, including the abundance of commercially processed foods that while retaining generally nutritious qualities, may be less healthful than traditional wholesome home prepared meals of past generations. [1,6] The influx of high fructose corn syrup (HFCS) sweeteners for example, have resulted in a 5-fold increase in fructose intake, and resulting in further pathophysiologic divergences in optimal metabolic pathways. [7] Healthful dietary changes are often a challenge to implement in a population accustomed to the convenience and prevalence of industrialized food choices readily available in the marketplace, where the inclusion of lipids and sweeteners and ease of meal preparation adds to their palatability and popularity. [3-7] In addition, the modernization and macronutrient and micronutrient composition of the food supply may not be adequate to address chronic Insulin resistance and associated pathophysiologic systemic inflammation common in obese, T2DM states. [6]

The magnitude and duration of the insulin response to a meal is generally proportional to the type and quantity of the carbohydrate consumed in the meal. The compound 1,5 dideoxy-1,5-[(2-hydroxyethyl) imino]-D glucitol; generic = miglitol) is an established competitive inhibitor of luminal starch digestion and acts within the brush border glucosidase receptor domains of the small intestine.[8-10] Once the compound is competitively bound to the glucosidase receptor domains, it effectively delays the rate-limiting process of starch of digestion into absorbable monosaccharide moieties and their subsequent luminal glucose uptake from the gastrointestinal tract.[8-11] Since the usual digestive process occurs rapidly, and the generation of monosaccharide moieties also represent the rate-limiting step in glucose uptake, and is proportional to the approximate rate of dietary post-ingestive α-glucosidase activity. Numerous physicochemical factors including diet composition influence the interactions with the brush border enzymes and consequently the efficiency of digestive activity. Specifically, the presence of dietary fibers, gums and pectins in addition to plant-derived phytochemicals can effectively decrease the efficiency of luminal brush border digestion, with corresponding attenuation of the glycemic and secondary insulinogenic responses. [8] The addition of inhibitors of $\alpha-$glucoidase activity can further attenuate the insulinogenic and glycemic responses, while not compromising the net digestion and luminal monosaccharide absorption.[8-10] Glucosidase activity is greatest in the proximal regions of the upper intestinal track and decreases progressively as the digestive contents continue their distal movement.[9-12] As the rates of luminal CHO digestion become decreased, the generation of absorbable monosaccharide moieties also occurs more slowly, resulting in less extreme excursions in plasma glucose and insulin following carbohydrate ingestion. As the glycemic excursions become attenuated, plasma insulin requirements may also plateau at a lower magnitude because less insulin would then likely be required to facilitate peripheral monosaccharide uptake, oxidation and disposal. [8] Thus, the insulin-lowering phenomenon of α-glucosidase activity as mono- or combined therapy may be enhanced in the presence of inhibitors of luminal starch digestive activity. [12-16] In addition, because the physiologic haff-life of insulin receptor activity typically extends considerably longer than that of starch digestion and subsequent monosaccharide oxidation, downstream improvements in biochemical pathways of intermediary metabolism and lipogenesis would likely follow. [15-17] Thus, dietary supplements or additives that might extend the process of luminal digestion of starches and luminal absorption of simple carbohydrates pose an interesting prospect in

 doi:10.20944/preprints202411.1127.v1

modulating downstream physiological events including appetite, satiety factors, plasma insulin activation, and including the metabolic effects of insulin on lipogenic and cholesterol generating parameters. [8]

The Insulinogenic actions exert numerous downstream effects on several key parameters of intermediary metabolism, in peripheral tissues including modulation of the rates of protein synthesis and degradation (protein turnover), monosaccharide oxidation and storage, and lipogenesis to cite just a few responses that are pertinent to this study. Thus, the purpose of the present investigation was to determine the effects of partial luminal α-glucosidase inhibition via miglitol on plasma glycemic and lipid profiles, and were conducted in an animal model where early onset obesity, hyperinsulinemia, insulin resistance and T2DM occurs during early stages of adolescence and the pathophysiologic stigmata remain present thereafter.[17-21] The epigenetic expression of obesity and further progression to T2DM occurs via expression of an autosomal recessive trait, and becomes accompanied soon afterward with the commonly observed progression of chronic pathophysiologic sequelae including derangements in plasma cholesterol and lipid profiles.[19-21]

The SHR/Ntul//-*cp* rat model was developed in the small animal genetics unit by Hansen at the NIH by incorporating the -*cp* trait from the Koletsky rat into a longevity-prone NIH (N) strain of unknown origin.21 This was followed by crossing the N-*cp* strain with the spontaneously hypertensive and diabetes prone SHR rat and completing 12 or more cycles of backcrossing sufficient to establish a congenic status while preserving the SHR and -*cp* traits. The hypertensive trait was preserved only in the lean phenotype while the T2DM developed soon after weaning in the obese phenotype, and the newly developed SHR/N-*cp* strain preserved the albino coat characteristic of the donor SHR strain. Both phenotypes exhibit a significantly decreased lifespan due to complications of T2DM compared to their longevity-prone NIH (N) heritage. [19] The independent contributions of the obesity and T2DM traits may be assessed in the nondiabetic LA/Ntul-*cp* vs the SHR/Ntul//-*cp* strains. [17-21]

Materials and Methods

Groups of congenic obese male SHR/Ntul//-*cp* rats (n= 8 rats/group) housed under standard laboratory conditions of temperature (21-22 degrees C/ 50% RH) on a reverse light cycle (dark 0800-2000 daily) in adjacent hanging steel cages with individual occupancy. Animals were fed Purina Chow and house water *ad libitum* from weaning to 8 weeks of age, at which time early stages of obesity and T2DM were clearly established and glycosuria and T2DM confirmed. When 8 weeks of age, rats were switched to a semi-purified control diet developed at the Carbohydrate Nutrition Laboratories of the USDA that contained 54% carbohydrate as sucrose, 20% protein as equal parts casein and lactalbumin, 5.9 % cellulose, 16% fats as equal parts beef tallow, lard, corn oil, and hydrogenated coconut oil, 3.1% AIN vitamin salt mix, and 1% Teklad vitamin fortification mix (Control diet).[20] The energy content of the diet was computed to provide 48.2 % of calories from CHO, 33.3 % of calories from fats, and 18.5% of calories from protein respectively, and provided 4.4 kcal/gram as described elsewhere.[20] The semi-purified diet was fed *ad libitum* for up to 8 weeks. In addition, additional quantities of the control diet were fortified with 150 mg of the α-glucosidase inhibitor (1,5 dideoxy-1,5-[(2-hydroxyethyl)-imino]-D glucitol; generic = miglitol) per kg. diet (equal to ~ 2.5 mg of miglitol/rat/day) and was fed to the α-glucosidase inhibitor treatment group for up to 8 weeks duration. Body weights were monitored periodically throughout as an indicator of wellness. At the end of the study, rats were fasted overnight and blood obtained via tail bleeding in heparinized tubes for plasma glucose area under the glucose tolerance curve (AUC)[9,10], Glycated hemoglobin (HbA1c, GHb), and lipid analysis. Plasma triglycerides, cholesterol and the α-lipoprotein (LDL) and β-lipoprotein (HDL) fractions were determined spectrophotometrically following affinity chromatographic separation via the procedure of Bentzen et al and triglycerides by the enzymatic method of Bucolo and David.[22,23] Data were analyzed via standard statistical procedures including application of Pages 'L' test for trend analysis where statistical significance via the 't' test was suggestive but not confirmatory.[24,25] The study was approved by the Institutional Animal care and Use Committee.

 doi:10.20944/preprints202411.1127.v1

Results

Initial and final Body weights and net weight gain of rats over <8 weeks of observations are depicted in Figure 1 and indicate that initial weights were similar in both treatment groups (263±11 g. vs. 263±12 g). The a-glucosidase inhibitor miglitol resulted in modestly (~13%) lower rates of weight gain and in similarly lower final body weights during the 8 weeks of observation of the study. (Control vs. Drug FBW: p. = < 0.05 via trend analysis; Control vs Net Gain: p=<0.05 via trend analysis.) The energy intake of rats is depicted in Figure 2 and shows that energy intake of control rats over the entire course of the study was 13% greater than in the miglitol treated animals (p=< 0.05, Students t test). Thus, the net efficiency of weight gain over the duration of the study was similar in both phenotypes.

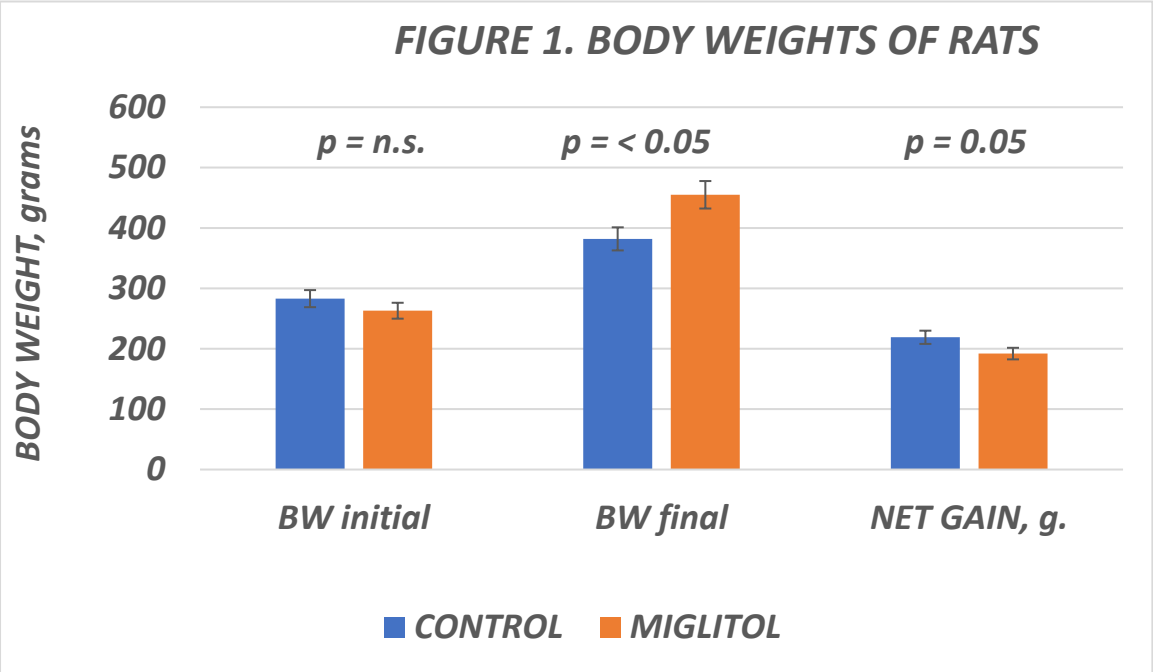

Figure 1. Body weights of rats. Data are mean ± 1 SEM, n = 8 rats/group. P = < 0.05 as indicated by students t test. .

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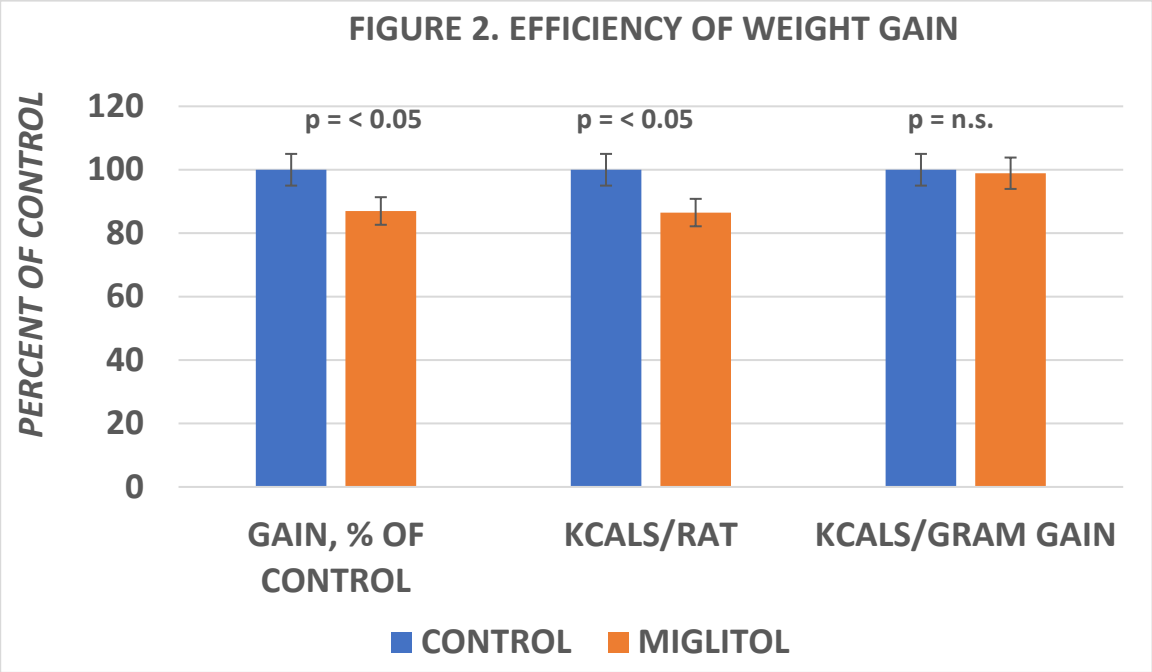

Figure 2. Energy intake and caloric efficiency of rats. Data are mean ± 1 SEM, n = 8 rats/group. P = < 0.05.

The effects of α-glucosidase inhibition on glycemic parameters is depicted in Figure 3 and indicates that the AUCglucose was decreased by an average of 20% and glycated hemoglobin by 25% following the 8 weeks of the miglitol admixture in the diet. It is likely that a longer duration of miglitol treatment may have resulted in further improvement toward normalization of the percent HbA1c. This is an important consideration, as glycated hemoglobin moves the oxygen saturation curve of hemoglobin to the left and therefore impedes the release of oxygen from the glycated moieties, thereby decreasing the net efficiency of oxygen delivery to myoglobin where it can contribute to oxidative metabolism.

The effects of miglitol on adipose tissue depots is depicted in Figure 4 and indicated that miglitol depicted in the right panel was associated with a 15% decrease in the sum of the epididymal, retroperitoneal and dorsal adipose tissue depots, but not all individual adipose tissue depots were decreased proportionately. The most significant decrease in depot mass was observed in the retroperitoneal depot, while epididymal and depots were similar in both groups, and the dorsal depot reflected only a downward trend following the miglitol regimen. When the sum of the WAT depots was computed as a percentage of body weight, the net WAT decrease in the miglitol treated rats depicted in bars to far right of each panel Figure 4 averaged 10% of final body weights, and 18.5% of weight gain. This the decreases in WAT mass were of similar magnitude to the decreases in net energy intake and weight gain.

The effects of luminal α-glucoside inhibition on plasma triglycerides and total cholesterol are depicted in Figure 5 and indicate that α-glucosidase inhibition resulted in an approximate 20% decrease in total concentrations of plasma triglycerides, cholesterol and lipoprotein cholesterol fractions s after <8 weeks of the dietary and pharmacologic treatment. In addition, the final concentrations of both the LDL and the HDL lipoprotein fractions were both decreased by an average of ~18-20% following the α-glucosidase treatment, and the effects were nearly evenly distributed across both LDL and HDL fractions. In addition, the lipoprotein ratios are depicted in Figure 3 and further indicate evidence that the pharmacologic treatment of luminal α-glucosidase activity with miglitol was without significant effect on lipoprotein ratios, thereby indicating that the effects of the α-glucosidase inhibitor agent were equally distributed across all triglyceride and lipoprotein fractions, consistent with a predicted global effect of improvements in insulin actions on lipid and cholesterol biosynthesis and metabolism.

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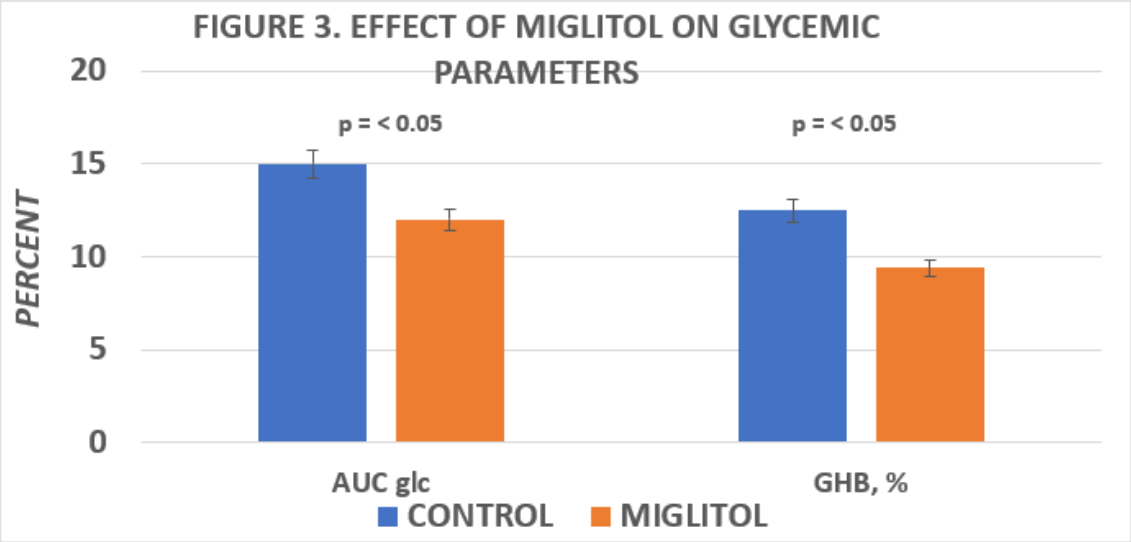

Figure 3. Effect of miglitol on glycemic parameters. Data are mean ± 1 SEM, n= 8 rats/group. p = < 0.05 as determined by Students t test.

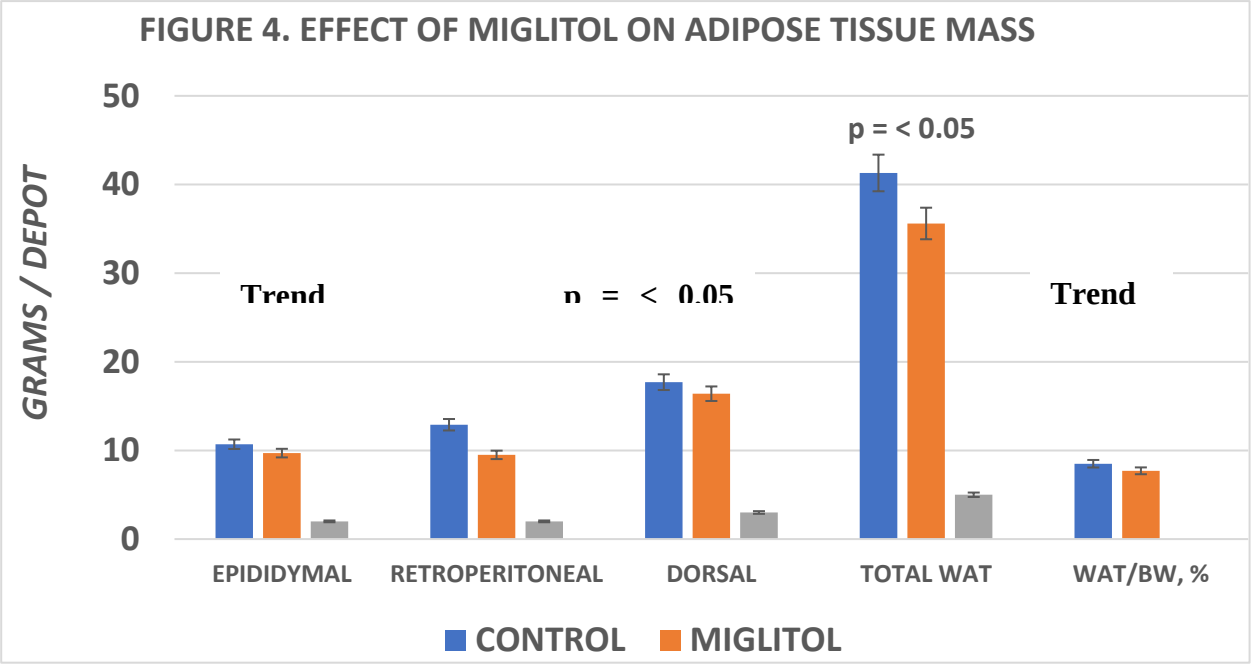

Figure 4. Effect of miglitol on adipose tissue mass. Data are mean ± 1 SEM, n = 8 rats/group. p = < 0.05 for retroperitoneal and total WAT depots. Epididymal, Dorsal, and percent WAT/BW = < 0.05 via Pages L test for trend analysis.

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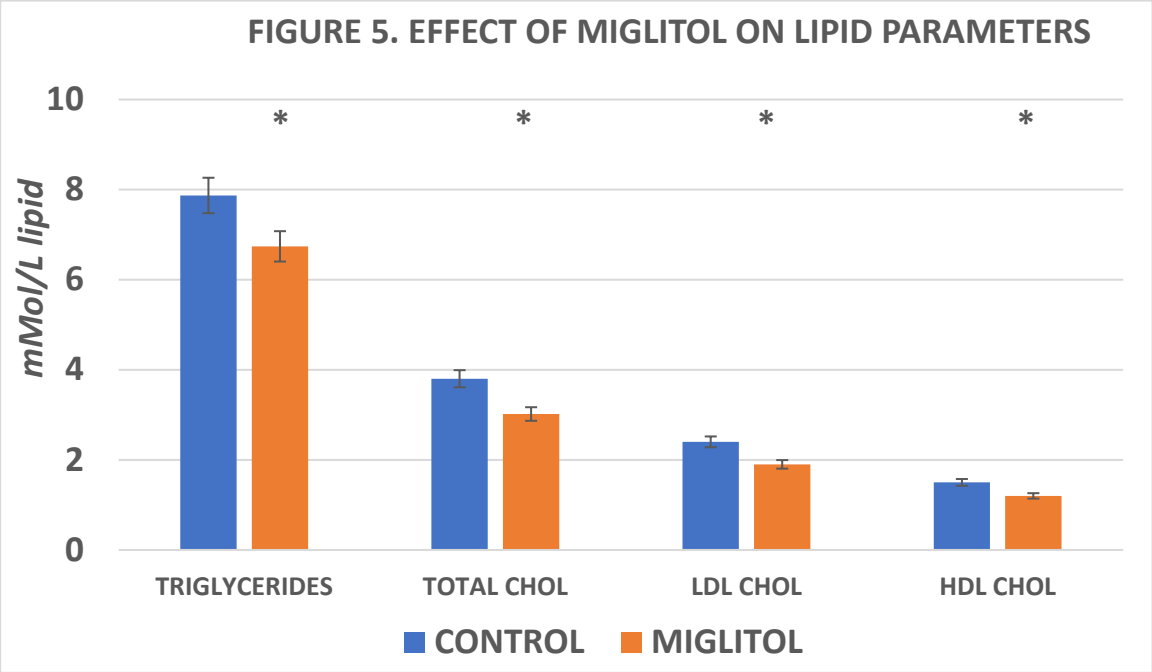

Figure 5. Effect of miglitol on lipid parameters. Data are mean ± 1 SEM, N = 8 rats/group. * = p = < 0.05 by Students t test.

Discussion

In the present study, feeding of an admixture of miglitol in a high carbohydrate, nutritionally complete diet to obese T2DM rats for up to 8 weeks resulted in decreases in energy intake, weight gain, adiposity, key glycemic parameters, and improvement in plasma lipid profiles. The decreases in weight gain and adiposity associated with the α-glucosidase inhibition were generally proportional to the decreases in energy intake and were suggestive of favorable contributions from gastrointestinal satiety factors due to the delayed digestion of the dietary carbohydrate. Luminal digestion of sucrose occurs rapidly in the brush border projections located mostly in the proximal regions of the duodenum where the greatest digestive activity of the glucosidase enzymes are located, and glucosidase activity decreases gradually as the food digestive progresses distally.[8-10] Any residual carbohydrate that may remain undigested in the small intestine for any reason can then likely become energy substrates for the colonic microbiota, but little carbohydrate typically escapes undigested under normal digestive processes. Regardless of where in the small intestine the carbohydrate becomes digested, the luminal uptake of monosaccharide moieties occurs straightforward, thereby accounting for the magnitude and duration of increase in plasma glucose following a carbohydrate meal. Thus, any delay in the luminal carbohydrate digestion would be predicted to decrease the magnitude and intensity of the glycemic excursions including both plasma glucose and insulin following a carbohydrate containing meal.

Because type-2 diabetes mellitus (T2DM) in association with obesity and overweight conditions including metabolic syndrome are now emerging as one of the most prevalent metabolic disorders in the world, it is imperative that a productive therapeutic strategy be developed and applied if attempts to resolve the phenomena are to be obtained.[1-5] Indeed, currently more than a third of the population throughout Westernized society is now impacted by an overweight or obese condition, with a high prevalence among those with the syndrome of developing T2DM.[1,2] Treatment of T2DM and obesity is often lifelong, thereby imposing a significant burden on healthcare resources due to the large number of patients who may present with comorbidities that may accompany the disorder. [26]

This has placed an enormous economic burden on the available health care resources of many communities.[2,3] The disorder also contributes to economic losses in workplace productivity when

 doi:10.20944/preprints202411.1127.v1

individuals are unable to complete their workplace obligations in a timely manner due to illnesses that are linked to their obesity-T2DM status.1-3 Modernization in the industrialization of food processing and distribution has also brought with it greater safety of the food supply, in addition to emerging changes in diet preferences and nutritional practices from those of past generations. [6]The changes in food availability and practices have also inadvertently contributed to less successful attempts by individuals to maintain energy balance in a more sedentary society. Thus it is important to explore novel approaches to combat the emerging trends in disordered energy balance and their contributions to pathophysiologic sequelae which may result at least in part from the technological advancements. While no single strategy has yet been demonstrated to combat the emerging trends in the obesity+T2DM dilemma, several relevant animal models have been developed, including the SHR/Ntul//-*cp* rat, the LA/Ntul//-*cp* rat, the Wistar Fatty Rat, the Zucker fatty rat and others.[9,17-21,27-31] These models may be applied to provide insight into effective environmental and pharmacologic strategies to address the issues and to further elucidate the pathophysiologic mechanism involved in the epigenetic expression of traits that contribute to obesity and T2DM.

The ingestion of high carbohydrate, overly caloric, and high glycemic index diets common to Western society are typically contraindicated in Obesity+T2DM, where they are commonly associated with unwelcome elevations weight gain, adiposity, and in increases in fasting plasma lipid profiles and other stigmata of obesity+T2DM.[1-3] Current therapeutic strategies often include changes toward a more healthy life style, including diet planning that includes a complex carbohydrate, modest fat diet, with special attention to ensure adequacy in fiber and micronutrient intake. The cumulative effects of dietary and lifestyle changes are projected to bring about in a lower calorie, lower glycemic index diet, while more closely matching nutrient intake to the projected energy requirements of the individual to maintain neutral energy balance. The added incorporation of starch blocker agents such as acarbose, miglitol or other natural inhibitors of starch digestion may be additive to the luminal effects of the lower glycemic index – high fiber complex carbohydrate diet regimen.[1-3] Incorporation of such a regimen may bring about lasting measured weight loss with corresponding improvements in the common pathophysiologic stigmata of obesity+T2DM, which may contribute to improvements in the metabolic profile of the individual. Luminal modulation of CHO digestion and monosaccharide absorption via α-glucosidase inhibitors combined with naturally occurring food components (often from vegetarian sources) may also bring about similar effects on α-glucosidase digestive activity.8 Considering that the primary mechanism of action of most α-glucosidase and sucrase inhibitors is competitive inhibition, and is typically limited to the luminal brush border region, with little if any post-ingestive absorption or systemic distribution, considerations of hepatic or other organ toxicity become minimal. Miglitol, the focus of this study, is a complex oligosaccharide that acts as a competitive, reversible inhibitor of membrane-bound intestinal α-glucoside hydrolase activity.[8-910,27-34] Luminal modulators of starch digestion including acarbose and miglitol have been found to be useful agents in treating mild to moderate severity T2DM.[8,10,32-34] In a previous animal study of <8 weeks duration with the miglitol analog acarbose, the HbA1c and glycemic responses typically demonstrated improvement toward normalization over time.9,33-36 The results of this study are also consistent with previous clinical findings in the Wistar Fatty Rat, and further confirm that the 8-week trial of feeding a highly palatable high carbohydrate sucrose-laden diet to obese adult Wistar Fatty Rats with well-established T2DM is an adequate duration to bring about improvements in glycemic parameters including excess adiposity and weight gain. The metabolic similarity in the development of insulin resistance between the obese phenotypes of the Wistar fatty rat and the SHR/Ntul//-*cp* rats contribute to the development of the obese+T2DM stigmata in both animal models. Both animal models demonstrated significant improvements in glycemic parameters when offered the glucosidase inhibitor regimen including an attenuation of the chronic hyperphagia commonly associated with the obese phenotype. [9,10,37] As reported by Boque' et al [38] when lean male Wistar rats were fed a similar high carbohydrate diet those authors also reported an increase in fasting triglyceride concentrations from the high glycemic index diet. In the present study, the miglitol treatment was associated with improvements in glycemic parameters, plasma triglyceride, total cholesterol, LDL-cholesterol and HDL cholesterol

 doi:10.20944/preprints202411.1127.v1

fractions, and an attenuation in the sucrose linked weight gain in addition to a decrease in the glucose AUC and percent HbA1c . Because only animals of the obese phenotype were included in this study, if was not possible to determine if the final weight and metabolic profiles might have equated to those of their lean littermates when fed similar diets in the 8 week duration of the observations. However, since the obese rats were already significantly heavier than their lean littermates at the onset of the study (avg lean = 235±6 g. vs obese = 264±19 g. at 8 weeks of age; p = < 0.05), and the T2DM stigmata were already well established, it is likely that longer treatment have been necessary for full resolution, especially since hyperinsulinemia and atheroma development has been found to commence soon after weaning in this and other strains.[19,20,30-31] In the present study, the decreases in net energy intake and weight gain both averaged 15% following the miglitol feeding regimen, indicative of a favorable correlation between the dietary impact and metabolic sequala, with no apparent rebound effects, metabolic complications, or adverse side effects noted. In an earlier study, Vedula et al noted that the pattern of decreased food intake differed similarly when the glucosidase inhibitor acarbose was fed as an admixture to lean and obese non-diabetic rats, resulting in a comparable improvement in glycemic responses, adiposity and plasma lipid parameters.[37] Indeed, the presumption of evidence from the present study suggests that the dietary regimen linked improvements in glucoseAUC, HbA1c, lipid profiles and weight gain are consistent with improvements in insulinogenic actions in peripheral tissues, including skeletal muscle and adipose tissue, major sources of peripheral insulin resistance in obesity and T2DM. [3]

Summary

In summary, the improvements in plasma lipid and glycemic profiles in the obese+T2DM phenotype of this and other strains following luminal glucosidase inhibition have been clearly established. Left untreated, increases in biochemical markers for free radical development and are clearly consistent with atherogenic lipid profiles, including elevations in serum triglycerides, cholesterol, and including the LDL lipoprotein fraction, which are consistent with senescent, atherogenic alterations in the vascular intima.[4] Although the glycemic and lipid parameters were improved but not completely normalized in the obese+T2DM rats following the miglitol treatment, it is likely that a longer duration of treatment may have resulted in a more complete recovery. As evidence for this conclusion, by the partial recovery of the precent HbA1c in miglitol treated rats is noteworthy, considering that a) the glycation reaction is considered to be non-reversible and non-enzymatic reaction correlated with the average plasma glucose concentrations, and once the glycation reaction has occurred, is dependent on the typical four-month lifespan of the normal erythrocyte, and b) the miglitol treated rats exhibited an approximate 60% recovery after only 8 weeks of study; had the study been extended to months duration, the percent HbA1c decrease would likely have been closer to that obtained from non-diabetic animals, at around 7.5 % or less, since laboratory rats tend to eat more frequently during their feeding cycle than some other mammalian species. Determination of percent HbA1c is considered a reliable marker for monitoring clinical diabetes therapy, and thus was an important consideration for assessing the effectiveness of α-glucosidase actions on luminal monosaccharide generation and insulinogenic actions in peripheral tissues in the present study. Thus, the use of α-glucosidase inhibitors for the treatment of glucose intolerant conditions is deemed a useful clinical approach in attenuating the insulin-dependent, hyperglycemic sequelae of the obese+T2DM phenotype of this strain and supports its usefulness in the treatment of T2DM in humans.[22-31] In conclusion, while the effects of miglitol and other luminal glucosidase inhibitors on lipid parameters have sometimes been inconclusive, those differences are likely due to differences in experimental models, patient populations, duration of pre-existing illness, dosages and agents employed, and duration of the treatment regimens, the improvements noted in the present study are likely attributable to an improved economy of insulin sensitivity, glucose utilization and lipid metabolism in peripheral tissues.

Conclusions

The short-term administration of a modest dosage of the α-glucosidase inhibitor miglitol in the presence of a high glycemic index sucrose-enriched diet was found to be useful in attenuating the excess weight gain and increases in plasma cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations in the adult male obese SHR/Ntul//-*cp* Rats. These observations are consistent with typical dietary recommendations for consumption of complex carbohydrate, fiber rich diets for a variety of glucose-intolerant conditions., and suggest that miglitol when administered as a dietary admixture may be a useful therapeutic adjunct in the treatment of obesity+T2DM, and in an attenuation in the chronic systemic inflammation and pathophysiologic sequelae associated with the obese-diabetic state. Moreover, the clinical effectiveness of luminal glucosidase inhibitors on lipid parameters may be enhanced by the addition of a cholesterol lowering agent or other ttherapeutic adjunct, as has now been demonstrated in multiple clinical trials. The clinical efficacy of miglitol has now been demonstrated in numerous clinical trials and it's demonstrated effectiveness in treating obesity associated T2DM is supported.[30-43]

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Competing Interests: The author reports no competing interests.

USE of Artificial Intelligence: The author reports that no applications of AI were utilized in the generation of this manuscript.

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