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Intestinal Absorption Inhibitors in the Prevention and Treatment of Type 2 Diabetes Mellitus

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Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder resulting from peripheral insulin resistance and relative insulin deficiency secondary to dysfunctional pancreatic beta cell secretion of insulin. It remains a leading cause of end-stage renal disease,¹ blindness,² and non-traumatic limb amputations, and portends a significant increase in the risk for cardiovascular morbidity and mortality.³ Given the serious impact of this chronic disease, prevention of the development of T2DM would result in significant public health benefits. Thus, interest in this topic is increasing, especially with the encouraging results of recent trials. Lifestyle modification remains critical for both the prevention and management of T2DM. Of the pharmacological agents, absorption inhibitors, metformin, and an early thiazolidinedione (TZD) that is no longer available, troglitazone, have been studied in the context of diabetes prevention.⁴⁻⁷ This issue of *Endocrinology Rounds* will focus on the role of the intestinal absorption inhibitors, namely alpha-glucosidase inhibitors (eg, acarbose) and the lipase inhibitor (orlistat). The mechanism of action and efficacy of both drug classes will be discussed, with particular emphasis on their use in the prevention of T2DM.

Alpha-glucosidase inhibitors (AGIs)

Mechanism of action

Complex carbohydrates from the diet are cleaved into oligosaccharides and disaccharides by pancreatic amylases in the duodenum. Oligosaccharides and disaccharides then require further breakdown into monosaccharides by brush border enzymes, the alpha-glucosidases, for absorption by the enterocytes of the jejunum. Most of the digestion and absorption of carbohydrate occurs in the upper segment of the jejunum, with little carbohydrate reaching the distal jejunum or ileum. Since slowing the absorption of carbohydrate is associated with improved glycemic control, alpha-glucosidase inhibitors (AGIs) were developed to delay intestinal absorption of carbohydrates.⁸ Acarbose is the most widely used AGI. AGIs bind competitively to the carbohydrate-binding region of alpha-glucosidase enzymes, thereby competing with oligosaccharides and preventing their cleavage to absorbable monosaccharides. As expected, co-administration of AGIs with carbohydrate slows the digestion and absorption of carbohydrate such that it is redistributed distally from the proximal jejunum to the distal segment of the small bowel. Any remaining undigested carbohydrate may move into the large bowel where bacteria can metabolize the carbohydrates into short chain fatty acids and other byproducts, including methane and hydrogen. The delayed absorption of carbohydrates from the proximal jejunum mitigates the postprandial rise in blood glucose.



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Efficacy in the treatment of T2DM

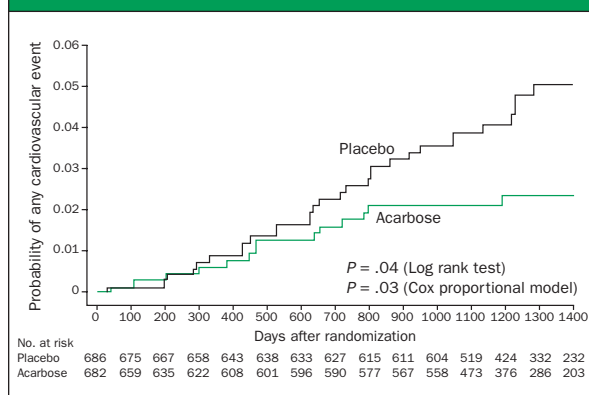
The glucose-lowering effect of the AGIs is generally less than that of the other oral antihyperglycemic agents, with an average glycated hemoglobin (A1c) reduction of 0.5% to 1.0% compared with placebo.⁹ The greatest effect is on postprandial glucose levels. The 2003 Canadian Clinical Practice Guidelines do not recommend AGIs as initial therapy for severe hyperglycemia (A1c \geq 9.0%) because of its relatively mild glucose-lowering effect.² They are usually used in combination with other glucose-lowering therapies. Although AGIs are safe agents that do not cause hypoglycemia when used as monotherapy, associated adverse effects (eg, flatulence, abdominal discomfort, and diarrhea) can affect the tolerability of the medication for some patients.^{8,9} However, treatment with acarbose does not cause significant malabsorption or weight loss.

AGIs in the prevention of T2DM

In 2002, the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) was published, establishing a potential role for the use of acarbose in the prevention of T2DM.⁴ In this multicentre, placebo-controlled trial, 1492 patients with impaired glucose tolerance (IGT) based on a 75-gram oral glucose tolerance test (OGTT), were randomized to receive either acarbose (up to 100 mg 3 times daily), or placebo. Patients in *both* groups met with a dietician on a yearly basis, were instructed on an appropriate diet, and encouraged to exercise regularly. They also underwent yearly 75-gram OGTTs to assess for the development of diabetes mellitus – the primary outcome. Of the 1429 randomized participants, 61 were excluded because they did not meet criteria for IGT or they discontinued the trial immediately after randomization without taking any study medication. Among the remaining 682 participants in the acarbose group and 686 participants in the placebo group, an additional 211 (31%) and 130 (19%) participants, respectively, discontinued their treatment early.

The most common cause of early discontinuation was gastrointestinal side effects. Based on a modified intention-to-treat analysis (not including the 61 participants excluded immediately after randomization because of absence of post-randomization data), the relative risk of developing DM was reduced by 25% (95% CI, 10%-37%; $p=0.0015$) based on 1 positive OGTT result or by 36.4% (95% CI, 19%-50%; $p=0.0003$) based on 2 consecutive positive OGTTs. The number needed to treat (NNT) was only 11

Figure 1: Effect of acarbose on the probability of remaining free of cardiovascular disease in the STOP-NIDDM trial⁵



subjects with IGT for 3.3 years to prevent 1 case of T2DM. This benefit persisted irrespective of age, sex, or body mass index. An increase in the conversion of IGT back to normal glucose tolerance was also observed in the acarbose group compared with the placebo group. This study demonstrated that acarbose is an effective pharmacological strategy for reducing the progression from IGT to DM. However, it is important to note that early discontinuation rates were high, suggesting that the practical application of this treatment strategy in the general population with IGT may be challenging.

In addition to reducing the risk of conversion from IGT to DM, acarbose also significantly reduced the risk of cardiovascular disease and hypertension.⁵ The development of major cardiovascular events (coronary heart disease, congestive heart failure, cerebrovascular event, and peripheral vascular disease) and hypertension (\geq 140/90 mm Hg) were *a priori* secondary endpoints when the study was designed. Although not powered to detect a difference in cardiovascular events, analysis of the data demonstrated statistically significant differences. The adjusted relative risk of developing a cardiovascular event over the course of the study was reduced by 53% (95% CI, 10%-76%; $p=0.02$) in the acarbose group (Figure 1). Among cardiovascular events, the largest reduction was in the risk of myocardial infarction (MI) (hazard ratio 0.09; 95% CI, 0.01-0.72; $p=0.02$). The NNT to prevent 1 cardiovascular event was 40 subjects with IGT over 3.3 years. The incidence of new cases of hypertension was also reduced in the acarbose group. The adjusted relative risk reduction was 38% (95% CI, 14%-55%; $p=0.004$).

Although the cardiovascular results of STOP-NIDDM are positive and encouraging, there are some

limitations to the study. There was a high rate of premature discontinuation in both groups. The intention-to-treat analysis was modified by excluding the 61 patients who had no post-randomization data. Adjustments were not made for multiple testing, potentially increasing the possibility that the current findings could be a result of chance. Finally, the study was powered for incidence of diabetes, not cardiovascular disease.⁵ Despite these limitations, the cardiovascular findings from this trial are impressive and generate interesting hypotheses that warrant further study.

The lipase inhibitor – orlistat

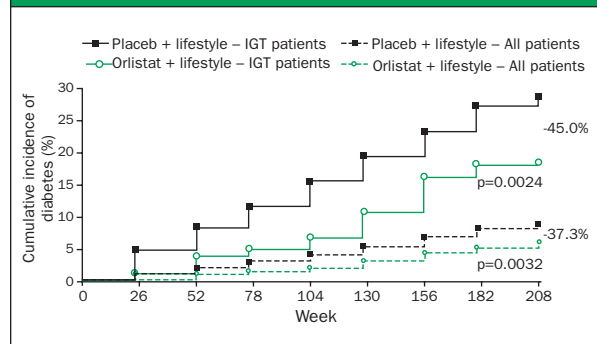
Mechanism of action

The primary indication for the lipase inhibitor, orlistat, is weight loss. Orlistat binds to gastric and pancreatic lipases and acts as a selective inhibitor of these enzymes. The enzymes are rendered unavailable to hydrolyze dietary fat into absorbable free fatty acids and monoglycerides. The reduction in fat absorption and the associated calorie deficit accounts for the weight loss seen with the use of orlistat.¹⁰ Given the mechanism of action, patients who consume high fat meals while taking orlistat will develop fat malabsorption and the associated adverse effects, including flatulence with discharge, oily spotting, fecal urgency, and steatorrhea.

Efficacy

The efficacy of orlistat for weight loss has been demonstrated in a number of trials and recently reviewed systematically.¹¹ An absolute weight reduction of approximately 5 -10 kg was observed in most placebo-controlled studies of orlistat in conjunction with a calorie-reduced diet for up to 1 year.¹¹ In general, weight loss in patients with T2DM is more difficult to achieve and this was demonstrated in studies of orlistat in obese patients with T2DM.¹¹ It is well established, however, that even mild to moderate weight loss in an obese patient with T2DM can result in improvements in glycemic control.¹² Therefore, orlistat has been studied in patients with T2DM on various antihyperglycemic agents. One such study of insulin-treated overweight or obese patients with T2DM compared the efficacy of orlistat to a placebo and demonstrated greater weight loss (-3.89% vs -1.27%; $p < 0.0001$), greater hemoglobin A1c reduction (-0.62% vs -0.27%; $p = 0.002$), and greater reduction in fasting serum glucose (-1.63 vs -1.08 mmol/L; $p = 0.02$).¹³ Thus, orlistat has recently been added to the list of antihyperglycemic agents available to treat T2DM.² Although the glycemic effect is mild and

Figure 2: Cumulative incidence of development of T2DM over 4 years among subjects with impaired glucose tolerance (IGT) or all subjects, treated with orlistat or placebo (XENDOS trial).¹⁶



believed to be predominantly secondary to the associated weight loss, several statistical analyses have suggested that some metabolic benefits are independent of weight loss.¹³ Therefore, at this time, orlistat is only considered as adjunctive therapy for the treatment of T2DM in an obese patient.

Orlistat in the prevention of T2DM

Although orlistat is not strongly recommended for the treatment of T2DM, it may play a role in prevention. Modest weight loss of 5%-10% is known to reduce the risk of developing T2DM.¹⁴ Given the weight loss properties of orlistat, its ability to prevent the development of T2DM in obese patients was initially tested with an analysis of pooled data from 3 trials of 675 obese subjects randomized to orlistat or placebo for 104 weeks.¹⁵ Among participants with IGT at baseline, fewer participants in the orlistat-treated group converted to T2DM compared with the placebo group (3.0% vs. 7.6%; $p = 0.04$) at study end. The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study provided further evidence to support these initial findings.¹⁶ In this 4-year, double-blind, prospective study, 3305 obese participants with normal or IGT were randomized to lifestyle changes plus orlistat or placebo. All participants received dietary counseling every 2 weeks for the first 6 months and monthly thereafter. Of the 1650 participants randomized to orlistat, only 850 completed the study (52%), which was significantly higher than the placebo group, in which only 564 of 1655 participants completed the study (34%). The intention to treat analysis of the data demonstrated a 37% (95% CI, 24%-55%) relative risk reduction in the cumulative incidence of T2DM after 4 years (Figure 2). Among the participants with baseline IGT, the relative risk reduction was 45% ($p = 0.00024$) with

Table 1: Comparison of alpha-glucosidase inhibitors and lipase inhibitors

	Alpha-glucosidase inhibitors	Lipase inhibitor (orlistat)
Mechanism of action	<ul style="list-style-type: none"> Competitive binding of alpha-glucosidase enzymes preventing cleavage of oligosaccharides to absorbable monosaccharides Delays carbohydrate absorption 	<ul style="list-style-type: none"> Selective inhibitor of gastric and pancreatic lipases Prevents hydrolysis of dietary fat thereby preventing absorption
Properties	<ul style="list-style-type: none"> Mild glucose-lowering effect (A1c) Reduction in postprandial glucose rise No risk of hypoglycemia 	<ul style="list-style-type: none"> Modest weight loss (5-10 kg) Mild glucose-lowering effect (A1c) No risk of hypoglycemia
Side effects	<ul style="list-style-type: none"> Gastrointestinal side effects (flatulence, abdominal discomfort, diarrhea) 	<ul style="list-style-type: none"> Gastrointestinal side effects (steatorrhea, oily spotting, fecal urgency, flatulence) High cost
Prevention of type 2 diabetes evidence	STOP-NIDDM trial: ⁴ <ul style="list-style-type: none"> 25%-36% RRR in the progression of IGT to DM over 3 years 53% RRR in CV events and 38% RRR in new hypertension in subjects with IGT over 3 years 	XENDOS trial: ¹⁶ <ul style="list-style-type: none"> 37%-45% RRR in the development of type 2 DM among obese subjects over 4 years

RRR = relative risk reduction; IGT = impaired glucose tolerance; DM = diabetes mellitus; A1c = glycated hemoglobin; CV = cardiovascular

an NNT of only 10. This differs from the group with normal baseline glucose tolerance in which very few participants developed T2DM over 4 years (2.6% orlistat group vs. 2.7% placebo group). The orlistat group experienced a greater weight loss compared with placebo at 1 year (-10.6 vs -6.2 kg; $p < 0.001$) and at 4 years (-5.8 vs -3.0 kg; $p < 0.001$). Orlistat was well tolerated during the study, although there was a higher incidence of gastrointestinal adverse events in the orlistat group compared with placebo.

The results of the XENDOS trial are promising; however, the rates of early discontinuation in both the treatment and placebo groups are extremely high (48% and 66%, respectively), calling into question the feasibility of this strategy in the general obese population. Despite this limitation, XENDOS demonstrated the potential role of orlistat combined with lifestyle changes for the prevention of diabetes in obese subjects with IGT.

Discussion

A comparison of AGIs and lipase inhibitors is summarized in Table 1. Both classes possess relatively weak glucose-lowering effects when compared with other antihyperglycemic agents, although the AGIs are somewhat more effective than the lipase inhibitors.² AGIs may be considered in combination with other agent(s) and

orlistat may be considered in the context of weight loss. Although their role in treatment may be limited to an adjunctive status, these agents may be more beneficial for the prevention of T2DM.

The STOP-NIDDM trial and the XENDOS trial demonstrated the potential benefits of acarbose and orlistat, respectively. All participants in both studies received dietary counseling and advice on physical activity. Thus, these agents provided additional benefits above lifestyle modifications. The results are promising; however, one's interpretation must take into account the significant rates of premature discontinuation in both studies. The occurrence of gastrointestinal adverse events with both drugs accounted for a proportion of the premature discontinuations and calls into question the long-term feasibility of such measures. In addition, the results should be interpreted in the context of results from other diabetes prevention studies consistently demonstrating that intensive lifestyle modification with increased physical activity, improved dietary habits, and weight loss, result in impressive relative reductions of 58% in the rate of progression to T2DM compared with controls.^{6,17}

Some physicians have argued, however, that the intensity of lifestyle modifications in these studies may not be readily achievable in routine clinical practice. The pharmacologic arm of the

Diabetes Prevention Program (DPP) using metformin was able to reduce the incidence of DM by 31%.⁶ This is similar to the relative reductions seen in STOP-NIDDM and XENDOS; however, it remains much lower than the benefits of intensive lifestyle intervention. Therefore, clinical practice guidelines in North America recommend lifestyle interventions for all patients with abnormal glucose tolerance as first line prevention of T2DM.^{2,18} However, the guidelines differ in the recommendations for pharmacologic therapy in prevention of T2DM, with the Canadian guidelines suggesting that pharmacologic therapy may be *considered* in patients with IGT;² while the American guidelines do not recommend the use of drug therapy for prevention until more information is available about cost-effectiveness.¹⁸ Although pharmacologic therapies are not commonly used for prevention at this time, STOP-NIDDM and XENDOS have shown that absorption inhibitors could be effective and safe options for the prevention of T2DM.

Conclusions

Alpha-glucosidase inhibitors delay the absorption of dietary carbohydrates (reducing postprandial hyperglycemia) and lipase inhibitors decrease the absorption of dietary fat. Both classes of medications have proven, albeit mild, glucose-lowering effects, limiting their role in the treatment of diabetes. STOP-NIDDM for acarbose and XENDOS for orlistat, have shown a potential role for these medications in the prevention of T2DM in high-risk populations (IGT or obesity). However, rates of premature treatment discontinuation were high and other diabetes prevention studies have shown greater reductions in the development of T2DM with intensive lifestyle modification – however, the long-term sustainability of this approach remains to be determined. Of interest, only STOP-NIDDM with acarbose has shown a reduction in cardiovascular events; this is an important observation requiring further confirmation from other studies. Thus, the current recommendations support lifestyle modification as first line for prevention of T2DM in high-risk populations and pharmacologic agents (absorption inhibitors or metformin) can be considered for select populations. In the future, arguments for screening and treating subjects with IGT will be strengthened if cost-effectiveness can be demonstrated or if cardiovascular benefit can be confirmed.

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Abstracts of Interest

Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance.

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BACKGROUND AND PURPOSE: Impaired glucose tolerance (IGT)-a prediabetic state-is an important risk factor for atherosclerosis. Acarbose, an alpha-glucosidase inhibitor, was shown in the placebo-controlled prospective study to prevent noninsulin-dependent diabetes mellitus (STOP-NIDDM) trial to reduce the risk of diabetes by 36% in IGT subjects. This article reports on a placebo-controlled

subgroup analysis of the STOP-NIDDM study to examine the efficacy of acarbose to slow progression of intima-media thickness (IMT) in subjects with IGT.

METHODS: One hundred thirty-two IGT subjects were randomized to placebo (n=66) or acarbose (n=66) 100 mg 3 times daily; the study duration was at least 3 years, mean follow-up time 3.9 (SD 0.6) years. Carotid IMT was determined at study entry and the end of the trial. The intent-to-treat analysis included 56 subjects in the acarbose and 59 in the control group who had a baseline and endpoint measurement.

RESULTS: A significant reduction of the progression of IMT (mean) was observed in the acarbose group versus placebo. After an average time of 3.9 years, IMT(mean) increased by 0.02 (0.07) mm in the acarbose group versus 0.05 (0.06) mm in the placebo group (P=0.027). The annual increase of IMT(mean) was reduced by approximately 50% in the acarbose group versus placebo. Multiple linear regression revealed IMT progression as significantly related to acarbose intake.

CONCLUSIONS: Acarbose slows progression of IMT in IGT subjects, a high-risk population for diabetes and atherosclerosis. This is the first placebo-controlled prospective subgroup analysis, demonstrating that counterbalancing of postprandial hyperglycemia may be vasoprotective.

Stroke 2004;35(5):1073-8.

XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients.

TORGERSON JS, HAUPTMAN J, BOLDRIN MN, SJOSTROM L, GOTEBORG, SWEDEN.

OBJECTIVE: It is well established that the risk of developing type 2 diabetes is closely linked to the presence and duration of overweight and obesity. A reduction in the incidence of type 2 diabetes with lifestyle changes has previously been demonstrated. We hypothesized that adding a weight-reducing agent to lifestyle changes may lead to an even greater decrease in body weight, and thus the incidence of type 2 diabetes, in obese patients.

RESEARCH DESIGN AND METHODS: In a 4-year, double-blind, prospective study, we randomized 3,305 patients to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Participants had a BMI ≥ 30 kg/m² and normal (79%) or impaired (21%) glucose tolerance (IGT). Primary endpoints were time to onset of type 2 diabetes and change in body weight. Analyses were by intention to treat.

RESULTS: Of orlistat-treated patients, 52% completed treatment compared with 34% of placebo recipients (P < 0.0001). After 4 years' treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (P = 0.0032). Exploratory analyses indicated that the preventive effect was explained by the difference in subjects with IGT. Mean weight loss after 4 years was signifi-

cantly greater with orlistat (5.8 vs. 3.0 kg with placebo; P < 0.001) and similar between orlistat recipients with impaired (5.7 kg) or normal glucose tolerance (NGT) (5.8 kg) at baseline. A second analysis in which the baseline weights of subjects who dropped out of the study was carried forward also demonstrated greater weight loss in the orlistat group (3.6 vs. 1.4 kg; P < 0.001).

CONCLUSIONS: Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight loss in a clinically representative obese population. Difference in diabetes incidence was detectable only in the IGT subgroup; weight loss was similar in subjects with IGT and or NGT. *Diabetes Care* 2004;27(1):155-61.

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