Abstract
Alpha glucosidase inhibitors (AGIs) are a unique class of anti-diabetic drugs. Derived from bacteria, these oral drugs are enzyme inhibitors which do not have a pancreato-centred mechanism of action. Working to delay carbohydrate absorption in the gastrointestinal tract, they control postprandial hyperglycaemia and provide unquestioned cardiovascular benefit. Specially suited for a traditional Pakistani carbohydrate-rich diet, AGIs have been termed the ‘untapped diamonds’ of diabetology. The use of these oral antidiabetic drugs (OADs) that target pathophysiology in the early stages of type 2 diabetes, notably to reduce postprandial hyperglycaemia and hyperinsulinaemia will inevitably increase with time. This review describes the history of their development, mechanism of action, basic and clinical pharmacology, and suggests practical, evidence-based guidance for their optimal use.

Keywords: Alpha glucosidase inhibitors, Bacteria, Pakistani.

History
The alpha glucosidase inhibitors (AGIs) were initially isolated from bacterial cultures or their derivatives: acarbose from Actinoplanes, miglitol, a semisynthetic derivative of 1-deoxynojirimycin, from Bacillus and Streptomyces sp., and voglibose, from validamycin A, a product of Streptomyces hygroscopicus var. limoneus.1 While acarbose was first developed in Germany, and later approved the world over, including USA, voglibose is a Japanese invention, while miglitol is an American discovery.

Mechanism of Action
To understand the action of AGIs, we first need to revisit the physiology of digestion. Carbohydrates contribute to over 60% of the usual Pakistani or South Asian diet. Most of these carbohydrates are present as oligo — or poly — saccharides, and have to be broken down to monosaccharides (glucose, galactose, fructose) for digestion. Starch is digested through a two step procedure, with alpha amylase breaking it down to disaccharides, before sucrose, isomaltase, maltase, glyco-amylase and lactase break them into digestable mono-saccharides.1

Acarbose inhibits both alpha amylase and the other alpha-glucosidases, thus preventing absorption of starch and other carbohydrates from the brush border of the intestine.2 Voglibose3 and miglitol4 inhibit the disaccharide-digesting enzymes well, but have no effect on the starch digesting enzyme alpha amylase.

This class of compounds delays intestinal carbohydrate absorption, reduces postprandial glycaemia, and helps manage diabetes. It also has an insulin-sparing effect,5 leads to increase in incretin hormones, glucagon like peptide-1 and inhibits the postprandial release of gastric inhibitory polypeptide (GIP), and helps reduce body weight.6

Basic Pharmacology
Acarbose and voglibose are not absorbed from the intestine, and have poor bioavailability. Miglitol, on the contrary, is almost completely absorbed from the upper part of the intestine. All three AGIs are distributed in extracellular space, with low tissue affinity and variable protein binding. Acarbose and voglibose are excreted through the faecal route, while miglitol is excreted by the kidneys.1

Use in Diabetes
AGIs are recommended as first line therapy by the international Diabetes Federation (IDF)7 and American Association of Clinical Endocrinologists (AACE).8 Their efficacy, safety, tolerability cardiovascular benefits, and lack of hypoglycaemia make them suitable for use in diabetes. AGIs can be used as monotherapy, part of combination therapy with other oral drugs and insulin, and as fixed dose combinations.9

Studies have been performed on acarbose in type 1 diabetes. Acarbose, in combination with dietary intervention and insulin therapy, can be a useful management approach leading to a reduction in postprandial glucose fluctuations and the number of nocturnal hypoglycaemic excursions in type 1 diabetes.10,11

Though not recommended on-label, the use of acarbose...
may justify in gestational diabetes who do not accept injectable therapy and also ADA's multidisciplinary Professional Practice Committee classified acarbose as category B (no evidence of risk in humans). AGIs preferentially control postprandial glucose, but also have a domino effect on fasting glycaemia, and are able to reduce HbA1c levels effectively. While there is a general perception that AGIs are less potent drugs, this is not true. Results of Cochrane review and meta-analysis clearly highlight the efficacy of these drugs. Their mechanism of action, in fact, makes them preferred drugs for diabetes control in carbohydrate consuming populations.

**Use in Prediabetes**

Acarbose is able to reduce body weight, improve blood pressure, lower glucose levels, decrease in the incidence of newly diagnosed cardiovascular events and attenuate both fasting and post prandial hypertriglyceridaemia. These actions make it a useful option for management of metabolic syndrome and pre-diabetes. Acarbose and metformin are suggested as first line drug of choice for pre-diabetes, by AACE. It is also approved for this purpose in many countries including USA and India. Voglibose is approved in Japan for the management of pre-diabetes.

**Adverse Events**

AGIs delays complex carbohydrate digestion. This mechanism of action leads to both wanted (lowering of glycaemia) and unwanted (osmotic) effects. Undigested disaccharides which remain in the intestinal lumen may cause flatulence, diarrhoea and abdominal pain.

Counselling patients about the transient nature of these symptoms, and using a ‘start low, go slow’ initiation and up titration strategy help reduce the impact of these events. AGIs are effective when ingested at the onset of a meal and the advice is to take it at the first bite of the meal.

Liver function tests should also be performed prior to, and at regular intervals after initiating acarbose therapy in the first 6-12 months of treatment. Hypoglycaemia rarely occurs with AGI monotherapy. However, concomitant use of AGIs with insulin or sulfonylureas may precipitate hypoglycaemic episodes.

Hypoglycaemia caused by AGIs must be treated by monosaccharides (glucose, fructose) as the drugs block digestion of disaccharides (sucrose, maltose) preventing them from being utilized.

**Data From Pakistan**

AGIs are frequently used in Pakistan, though perhaps not to their full potential. Pakistan has participated in international trials designed to assess the efficacy and tolerability of acarbose. Acarbose has been shown to reduce HbA1c and body weight in Pakistani patients, irrespective of other demographic characteristics. While analyzing ten pooled non interventional and post marketing studies, conducted across the globe, 8738 patients from South Asia region (India and Pakistan) were studied, and compared with the global total. Their mean postprandial glucose (PPG) decreased from 240.0 and 261.1mg/dl at baseline by 70.26±65.10 and 82.96±56.59mg/dl at the last visit in total and South Asian populations, respectively (n= 53,883; n= 7,991, p<0.0001 for both). Mean fasting glucose (FPG) decreased from 171.6 and 176.5mg/dl at baseline by 38.48±47.83 and 49.59±41.41mg/dl at the last visit in total and South Asian populations, respectively (n= 56,672; n= 7,837, p<0.0001 for both). Mean HbA1c decreased from 8.4 and 8.4% at baseline by 1.11±1.31% and 0.91±0.93% at the last visit in total and South Asian populations, respectively (n= 38,843; n= 2,343, p<0.0001 for both). Mean relative reduction of body weight (BW) was 1.40±3.28% and 1.10±3.39% at the last visit for mean baseline BW 73.6 and 74.2kg in total and South Asian populations, respectively (n= 54,760; n= 7,718, p<0.0001 for both). The weight loss noted in Pakistan, however, is less than that seen in Indian cohorts.

**Clinical Use: Pragmatic Recommendations**

AGIs can be used as monotherapy in diabetes if metformin is contraindicated or not tolerated undulated. They are preferentially indicated in persons with relatively less fasting glycaemia, high postprandial glucose values, and high postprandial glucose excursions (PPGEs). They are also preferentially indicated in persons who exhibit a reluctance to avoid high-carbohydrate diet. The potential gastrointestinal effects of taking AGIs in conjunction with high carbohydrate diet must be explained to such patients.

AGIs are indicated as dual or triple therapy in combination with metformin or other drugs as well. Again, the role of AGIs is to reduce postprandial glucose values and thus achieve HbA1c control, in conjunction with drugs that control fasting glycaemia.

Fixed dose combinations of acarbose with metformin, voglibose with metformin, and voglibose with metformin and sulfonylurea are available. Acarbose is approved for use in prediabetes as well. A rational recommendation would be to use it, in low doses, in high risk prediabetes individuals, ie, those with family history of diabetes, past history of gestational diabetes, or concomitant cardiovascular risk factors such as obesity or hypertriglycaemia.
Acarbose has been studied in type 1 diabetes and gestational diabetes mellitus. If prescribed in such situations, the exact reason for doing so, e.g., poor postprandial control or unwillingness to take insulin must be documented clearly. AGIs also have a role to play in management of reactive hypoglycaemia: they prolong release of carbohydrate from the gastrointestinal tract to the circulation, and thus prevent dips in glucose levels.

**Conclusion**

AGIs are an effective, safe and well tolerated treatment for diabetes, which provide cardiovascular benefits as well. Appropriate use of these drugs must be made, as suggested by guidelines and supported by evidence.

**References**

12. ADA Standards of Medical Care in Diabetes-2013. Diabetes Care, Volume 36, Supplement 1, January 2013. [Available at: care.diabetesjournals.org]