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REVIEW ARTICLE

Glucagon Like Peptide 1 Receptor Agonists: Glycaemic Control and Beyond

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Abstract:

Glycemic targets are not met with in the best of setups which manage type 2 diabetes mellitus (T2DM) patients. The way forward to improve outcomes is to adopt a personalized approach to diabetes management, taking into account the characteristics of the individual patient and linking those characteristics to the appropriate management regimen. Incretinmimetics are a new class of pharmacological agents with multiple mechanisms of antihyperglycemic actions that mimic several of the actions of incretin hormones which originate in the gut, such as glucagon-like peptide (GLP)-1.Glucagon-like peptide (GLP)-1 receptor agonist (GLP-1 RA)-based therapies represent an emerging class of therapeutics for the treatment of T2DM.Although nausea and vomiting are well-established and significant side effects of this group of agents, these effects diminish over time in the majority of treated subjects. The newer molecule of this group, liraglutide has a wider scope and clinical application probably beyond glycaemic control. Of late, the cardiovascular safety of medicines of this group has been established and also many trials are coming out comparing molecules of this group amongst each other and also with molecules from other groups. Addition of molecules which may be given once a week is probably a way forward to solve the issues of clinical inertia and noncompliance.

Keywords: *GLP-1 receptor agonists, Type 2 diabetes mellitus, Hypoglycaemia, cardiovascular safety*

Introduction

The prevalence and incidence of diabetes in India is increasing drastically since the first epidemiological study carried out in 1977.[1] T2DM is a progressive disease warranting intensification of treatment, as beta-cell function declines over time. Current treatment algorithms recommend metformin as the first-line agent, while advocating the addition of either basal-bolus or

premixed insulin as the final level of intervention. The cardiovascular morbidity and mortality associated with diabetes are well established, so much so that T2DM has been described as a cardiovascular disease presenting as a metabolic disorder. Patients with T2DM are particularly at risk for atherosclerosis; consequently glycaemic therapies with ancillary vascular benefits are particularly useful, and the pleiotropic effects of glucose-lowering medications are of interest with regards to their effects on markers of cardiovascular health. It has been said that the major challenges to good glycemic control are encompassed by what has been called the "deadly triad": (1) the progressive nature of the disease; (2) clinical inertia; and, perhaps the most important of these, (3) poor adherence to management regimens. Of course, all of these factors are very much interlinked. It has been proposed that the way to overcome both clinical inertia and poor adherence to therapy is to personalize or individualize treatment for diabetes. Patient-centered or personalized care has been defined as a process providing care that is respectful of, and responsive to, individual patient preferences, needs, and values; and that ensures that patient values guide all clinical decisions.[2, 3, 4]

Glucagon-like peptide-1 (GLP-1) receptors are widely expressed in a number of tissues including the myocardium and cardiovasculature, and GLP-1 appears to have a range of neurotrophic, neuroprotective and cardioprotective effects[2] (Fig.1). As a consequence there may be potential therapeutic benefit from these drugs. Glucagon-like peptide-1 (GLP-1) has been the focus of considerable research activity in the treatment of type 2 diabetes mellitus (T2DM) because the incretin effect is significantly reduced or absent in individuals with T2DM.

General Characteristics of Molecules

Glucagon-like peptide-1 (GLP-1) agonists bind to GLP-1 receptors that are present in various tissues. Improved glycaemic control is achieved through its effect on receptors in the pancreas (increased insulin release, decreased glucagon release), in the brain (decreased appetite) and in the stomach with delayed gastric emptying (decreased appetite).[2,5,13,16] Four GLP-1 agonists are currently available: exenatide, which has a half-life of four hours and requires twice-daily injection,[2] and liraglutide, which has a half-life of 11–13 hours and requires once-daily injections.[11] Third one is a long-acting, once-weekly formulation of exenatide which has recently been granted marketing authorisation by the licensing authority in Europe.[4,7] Latest in the line is Delaglutide, a once a week GLP-1 RA which has been recently introduced to our armamentarium in India.

Table 1 | Different Incretin Mimetics[2]

GLP-1 and GLP have extremely short half lives due to DPPIV degradation		
Degradation resistant GLP-1 receptor agonists		**DPP IV Inhibitors**
Injectables	**Oral**	
Exendin-4-based	GLP-1 analogue	Sitagliptin
Exenatide BID	Liraglutide Sexagliptin	
Exenatide LAR	Albiglutide Vildagliptin	
Lixisenatide Dulaglutide Alogliptin and Linagliptin		

Comparative Features of Different Molecules

On the basis of molecular structure, exendin-4 analogues have 50% homology to human GLP-1 while GLP-1 RA have about 90% homology to native GLP-1, Liraglutide being closest by 98% homology. On the basis of molecular weight, these molecules may be classified as follows:

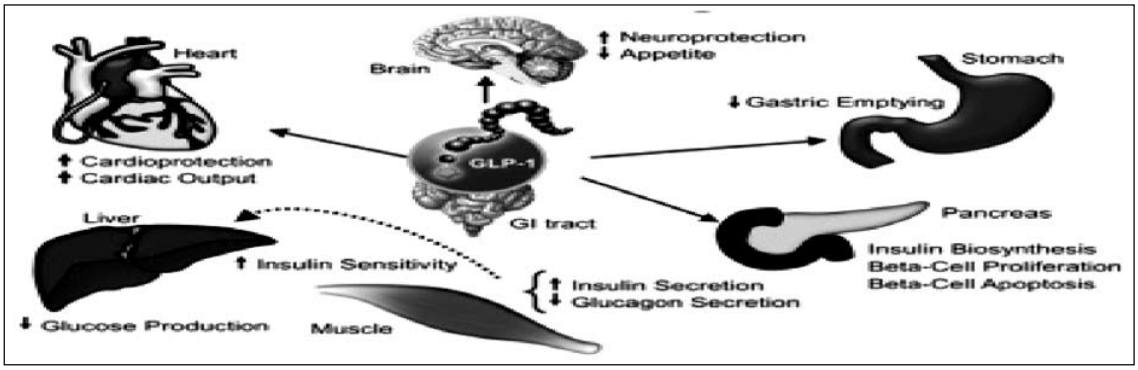

Figure 1 | Showing Pharmacologic Incretin Effect on Different Target Tissues

Table 2 | Classification of GLP-1 RA molecules as per molecular weight[21,22]	
G L P I Receptor Agonists	
Small molecules	**Large molecules (Do not cross blood brain barrier)**
Liraglutide 3.75 kDa	Albiglutide 72.97 kDa
Exenatide 4.19 kDa	Dulaglutide 59.67 kDa
Lixisenatide 4.86 kDa	
Semaglutide 4.11 kDa	

GLP-1 RA with larger molecular weight do not cross blood brain barrier and therefore, have much less effect on stimulating satiety center and therefore, weight loss is less as compared with GLP-1 RA with less molecular weight. Pharmacokinetic property can also be used to classify these molecules as follows:

Table 3 | Showing Pharmacokinetic Properties of Different GLP-1 RA Molecules [21,22]			
Category	**Molecule**	**Half-life**	**Tmax**
Short acting < 24 hours	Exenatide BID	2-4 hours	2 hours
	Lixisenatide OD	2.7-4.3 hours	1.25-2.25 hours
Intermediate acting	Liraglutide	13 hours	5-12 hours
Long acting	Dulaglutide OW	90 hours	24-48 hours
	Albiglutide OW	6-7 days	3-5 days
	Semaglutide OW	6.5-7 days	36 hours
	Exenatide OW	7-14 days	6-7 weeks

A greater reduction in haemoglobin A1c (HbA1c) and fasting plasma glucose was found with the once-weekly GLP-1 receptor agonists compared with exenatide BID, while the effect on postprandial hyperglycaemia was modest with the once-weekly GLP-1 receptor agonist. The reduction in HbA1c was in most studies greater compared to oral antidiabetic drugs and insulin glargine. The reduction in weight did not differ between the short- and long-acting agonists. The gastrointestinal side effects were less with the once-weekly agonists compared with exenatide BID, except for taspoglutide. Antibodies seem to be most frequent with exenatide once weekly, while hypersensitivity has been described in few patients treated with taspoglutide. Injection site reactions differ among the long-acting GLP-1 receptor agonists and are observed more frequently than with exenatide BID and liraglutide. In humans, no signal has been found indicating an association between the once-weekly agonists and C-cell cancer. Next table gives a comparative features of available GLP-1 RA.

Two of the GLP-1 receptor agonists, liraglutide and exenatide QW, do not require dose timing with meals. Liraglutide and exenatide BID are delivered with pen devices with 31- or 32-gauge needles, whereas exenatide QW has a delivery kit that simplifies the mixing of diluent and powdered medication but requires a syringe with an 8-mm, 23-gauge needle. With exenatide BID and liraglutide, it is not uncommon to see glucose-lowering within the first few days. However, exenatide QW requires a few weeks to begin showing effects; maximal benefit may not be seen for up to 10 weeks. The loss in weight usually plateaus in about 8 weeks with exenatide BID and 8–12 weeks with liraglutide.

Liraglutide has become the "gold" standard GLP-1 RA, producing significantly greater glycemic control in head-to-head trials than the other GLP-1 RAs. Liraglutide has 97% homology with native GLP-1; it has amino acid substitutions to prevent degradation by DPP-4 and a fatty acid side chain to enable albumin binding. Liraglutide has a half-life of approximately 12 hours and is administered once daily, producing continuous stimulation of the GLP-1 receptor.

Albiglutide is a "double" copy of a GLP-1 analogue bound to human albumin with a half-life of approximately 5-8 days; it is dosed once weekly. Delaglutide, which is the recent entrant to Indian markets, bear most of the characteristics and efficacy of Liraglutide. In head to head, study, it was non inferior in efficacy. However, weight reduction was less than that seen with Liraglutide. It is long acting molecule and need to be administered once a week.

Comparison with DPP IV Inhibitors: Liraglutide provides higher pharmacological, steady-state levels of GLP-1RA in the range of 60-90 pmol/l of free active liraglutide as compared to GLP-1 levels of 10-20 pmol/l when treated with vildagliptin.[5,13,16] It can also provide more stable steady-state levels of GLP-1RA than the respective levels for exenatide. This could also be the cause of less glucose reduction and absence of weight loss when therapy with DPP-4 is being utilised. (Table 2)

Some studies have compared starting with a DPP-4 inhibitor and then changing to a GLP-1 RA, and it can have some extra effect. Even when the patient was doing

Table 4 | Showing Comparative Characteristics of Different GLP-1 RA[2, 3, 11, 16]

Parameter	Exenatide	Liraglutide	Exenatide once weekly	Delaglutide OAW
Description	Synthetic exendin-4	Human GLP-1 analog	Extended release	GLP-1 Analogue
Half-life	2-4 hours	12-14 hours	➢ 1 week	>10 days
Administration	Twice daily	Once daily	Once a week	Once a week
Effect on fasting sugar	++	+++	+++	+++
Effect on prandial sugar	+++	++	++	+
HbA1c reduction	0.9 approx.	1.1 to 1.6 approx	1.7 approx	1.1
Weight reduction	0-5kgs	0-5 kgs	0-5 kgs	0-3 kgs
Side effect	Nausea	Nausea	Nausea	Nausea

Table 5 | Comparison of GLP-1 RA v/s DPP-4 iInhibitors[5,13,16].

	GLP-1 agonists	DPP IV Inhibitors
Route of administration	Subcutaneous injection	Oral
Pharmacology	Promotes pharmacologic levels of GLP-1 activity	Increases the half-life of endogenous GLP-1
Effect on body weight	Weight loss	Weight neutral
HbA1c reduction	0.5-1.0%	0.8-1.9%
Side effect Common/Rare	Gastrointestinal/ Pancreatitis	Nasopharyngitis/ Hypersensitivity reaction
AACE/ADA/ EASD ?	Yes	Yes

good, he can do better in terms of HbA1c and blood glucose if you just change it to a GLP-1 RA. It is not possible to absolutely predict who will respond to GLP-1 RA therapy; however, it is reasonable to try a course of therapy in most patients. In general, patients who initiate therapy earlier in the course of disease and with a lower HbA1c will respond better. In those patients who do not respond to therapy, it is important to stop the agent.

Evidence Based Medicine: Safety and Efficacy

Evidence for Improved Glycaemic Control

Exenatide has by now more than 6 years data while Liraglutide has more than 4 years data for efficacy and safety. The newer molecule, Exenatide once a week (ExQW) has more than 1 year of data for clinical use. In placebo-controlled, randomised trials, both exenatide and liraglutide reduce glycosylated haemoglobin (HbA1c) by about 1% when used in combination with metformin and/or sulphonylureas (and in combination with metformin and a thiazoledinedione for liraglutide). In a head-to-head study, liraglutide was more effective than exenatide twice daily in reducing HbA1c.[16] After 26 weeks, once-daily liraglutide reduced HbA1c from 8.2% to 7.1%, with twice-daily exenatide reducing HbA1c from 8.2% to 7.4%. Weight reduction was similar with the two treatments at around 3 kg, but there was less persisting nausea with liraglutide. In a recent study, liraglutide once daily was also more effective than the once-weekly formulation of exenatide.[11,13,16] ExQW therapy for 52 weeks increased patients' prospect of achieving clinically relevant composite outcomes, and therefore offers a distinct advantage over many other currently available treatment options.[3,9,10] Once-weekly monotherapy with the GLP-1 analog, dulaglutide, in patients with T2DM resulted in dose-dependent improvements in glycemic control, evidenced by decreased A1C and fasting plasma glucose levels, and an increase in the number of patients achieving goal A1C levels.[6, 16, 19]

Evidence for Effects beyond Glycemic Control:

Weight: A large body of data regarding the effects of GLP-1 RAs beyond glycemic control is developing.[12] We know that GLP-1 receptors are widely spread throughout the human body and that the phenotype of T2DM is much more than high plasma glucose. When GLP-1 receptors are stimulated in the central nervous system, people have feeling of fullness of stomach and appetite is decreased. Therefore, in addition to providing glycemic control, patients receiving GLP-1 RAs can also reduce body weight. (Fig.2).

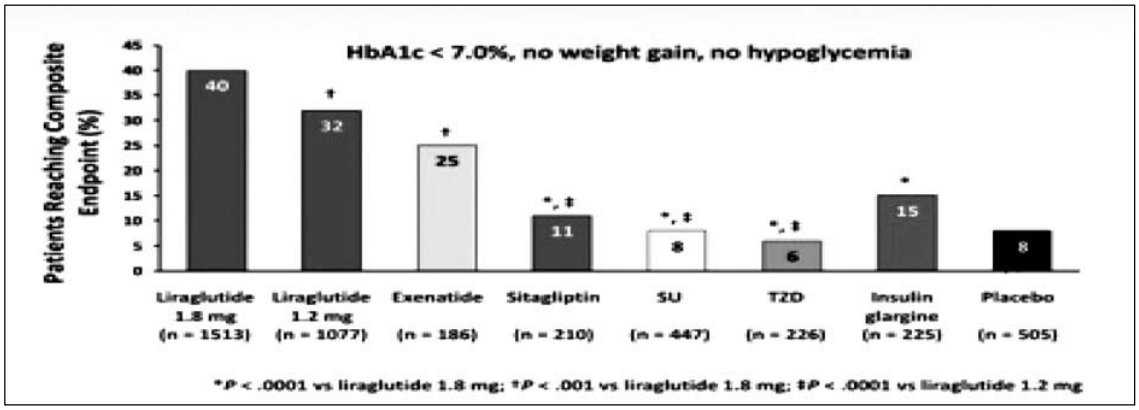

Figure 2 | Efficacy and Safety Of GLP-1 RA Compared with Other Agents [5,13,16]

Markers of cardiovascular (CV) disease: Beneficial effects on markers of CV disease, including B-type natriuretic peptide, plasminogen activator inhibitor-1, and hS C-reactive protein, have been observed following GLP-1 RA treatment. These results suggest that the effects do go in the right direction.[12] Both liraglutide and exenatide have been shown to have a beneficial effect on both fasting and post-prandial lipid profiles in T2DM.[16,17,18,19,20] In humans, GLP-1 and GLP-1 receptor agonists tend to cause a small reduction in blood pressure, although it remains to be seen whether this will be of clinical significance. The Liraglutide Effect and Action in Diabetes (LEAD) trial reported reductions of 3.6 mmHg to 6.7 mmHg in systolic blood pressure in the liraglutide-treated group compared with those treated with other agents or placebo.[11] Interestingly, these blood pressure reductions were observed prior to weight loss, suggesting that the effects on blood pressure are independent of weight reduction.[12,17,18,19] Small but significant increases in heart rate (HR) have also been observed. Meta-analyses suggest that GLP-1 RAs cause an increase in HR of approximately 2 beats/min. These were more evident for liraglutide than exenatide and for exenatide LAR than exenatide twice daily.[40] Whether the reduction in SBP, increase in HR, or other cardioprotective properties have any impact on overall cardiovascular mortality and are clinically relevant will only be established after long-term use.[18,19,20]

Renal parameters: The liraglutide outcome trial is looking very carefully into kidney disease. It wants to find out if liraglutide is neutral or even beneficial for renal failure in diabetes. There are some animal data suggesting there could be a beneficial effect mainly because it seems that GLP-1 has an effect on the immune system and is reducing some of the inflammation that goes on in kidney disease, but at present, it is too early to say.[16]

Hypoglycemia: There is an emerging theme from some recent insulin combination studies with GLP-1 RAs that GLP-1 RAs seem to potentially protect patients from hypoglycemia. The rates of hypoglycemia observed with combination of GLP-1 RAs and insulin were actually lower than what we might expect, given the degree of glycemic control. This is a concept that should be studied more in the future.[17]

Alzheimer Disease: There is a link, or at least there has been some association, between GLP-1 RA, Alzheimer disease and diabetes. This has a lot to do with the insulin signalling.[18]

Prevention of diabetes: The best way to control the epidemic of T2DM is to prevent it. Currently, there are no agents that are approved for the prevention of diabetes, but the incretin-based therapies have a great potential. They are very effective in early diabetes, and there are a number of studies planned or currently being conducted to assess whether incretin-based therapies can reduce or prevent the development of diabetes in high-risk populations.[12]

Safety: Acute side effects like nausea, vomiting and diarrhoea (less known but equally prevalent) are dose dependent and reduce in intensity as you titrate up slowly. Most of them are transient. In post marketing studies, case reports of severe and even fatal episodes of acute pancreatitis raised concerns about the GLP-1 agonists.[8,11] Attributing pancreatitis to these drugs, however, it is confounded by the fact that obesity, hypertriglyceridemia, and gallstones, which are all known risk factors for acute pancreatitis, are also very commonly associated with T2DM. Looking to epidemiological studies, the risk does not seem to be increased but the books are not closed yet. However, some patients show an increase in lipase levels without any symptoms. This is not pancreatitis, obviously. It has to do with the slowing of the GI tract

to transient time that might increase some of the lipase levels. No thyroid neoplasms or change in mean calcitonin concentration, a marker of thyroid C-cell hyperplasia and medullary carcinoma, have been observed with liraglutide in clinical trials.[11-14]

Immunogenicity is another factor which may potentially affect the efficacy of intecrin-based therapies, affecting especially GLP-1RA. Most of the data around antibodies is based on the findings of the LEAD-6 and DURATION-1 trials. Overall, liraglutide is less immunogenic than exenatide and antibody titers do not appear to affect glycemic efficacy or safety.[18]

Patients with renal impairment or end-stage renal disease (creatinine clearance < 30 ml/min) should not use exenatide BID or exenatide QW.[18] Liraglutide can be used without dosage reduction but should be used with caution because data are limited regarding its use in patients with various stages of renal impairment. Because exenatide is cleared primarily by the kidneys, blood concentrations of exenatide (BID or QW) are not expected to be altered in patients with hepatic impairment. Liraglutide should be used cautiously, although no dose adjustment is recommended in patients with hepatic impairment

Current Role and Future Prospective of GLP-1RA

GLP-1 receptor agonists should not be prescribed for patients as weight loss drugs. It must be made clear that, although weight loss occurs in ~ 80% of patients, it is not possible to identify which patients will lose weight before initiating the therapy. Unlike microvascular disease, perhaps macrovascular benefit is only demonstrable at normoglycemia, which we have been unable to safely achieve with traditional methods. Newer therapies that limit weight gain and hypoglycemia may play an important role in safely normalizing fasting and postprandial glucose levels. It is incumbent on us as investigators and care providers to methodically evaluate the potential of these therapies to affect morbidity and mortality. Perhaps the question is no longer how low our glycemic targets should be to prove macrovascular and mortality benefit, but whether we can make a difference if we get there safely.[16-20]

Because GLP-1 receptor agonists work in a glucose-dependent manner, they are likely to reduce hyperglycemia safely, without a marked fluctuation toward hypoglycemia. In the process of acutely restoring β-cell function, GLP-1 agonists may allow patients to achieve HbA1c<7% without experiencing weight gain or hypoglycemia. When these drugs first came out, people thought they increase insulin so they are going to work better in people with early diabetes. What people forgot is that these drugs also decrease glucagon, which is increased in people with T2DM. Thus, incretin-based therapies should prove helpful in this respect and more effective than traditional OADs, which do not directly address or effectively curtail PPG. In short, a regimen of incretin-based therapy plus basal insulin could mimic the pharmacological benefits of basal-bolus insulin therapy, but without the attendant calorie counting, and the associated risks of hypoglycemia and weight gain. However, possible advantage of DPP IV inhibitors in this setting also must be weighed. It would also be interesting to study the effects of combination of DPP-4 inhibitors with GLP-1RA, with and without insulin. There is, however, preliminary evidence that the addition of exenatide BID to the combination of sitagliptin plus metformin produces additional (0.3%) A1C reduction beyond the combination of exenatide BID and metformin over 20 weeks. Nonetheless, patients who are taking a DPP-4 inhibitor should discontinue it at the start of GLP-1 therapy.

A patient with T2DM who is overweight or obese, with good liver and kidney function, who has an HbA1c above >7% after using metformin for 3 months and has no phobias with injections, would make an ideal candidate for using a GLP-1 RA. Other situations in which a GLP-1 receptor agonist might be a good choice include in older patients with type 2 diabetes, who are more likely to experience hypoglycemia unawareness. Another group for whom a GLP-1 receptor agonist might be a good choice includes patients who experience excessive hunger or weight gain. It is not uncommon for patients to describe a sensation of "always being hungry." GLP-1 receptor agonists have been noted clinically by some providers to blunt that sensation. Adding liraglutide to multiple daily insulin injections in people with type 2 diabetes improves glycaemic control without an increased risk of hypoglycaemia, reduces body weight, and enables patients to lower their insulin doses.

The ability of GLP-1 receptor agonists to improve blood pressure and postprandial lipidemia in the context of weight neutrality or weight loss may have the potential to ameliorate some of the cardiovascular risks observed in patients with T2DM.

The American Association of Clinical Endocrinologists and the American College of Endocrinology consensus panel recommended the use of GLP-1 agonists and DPP-4 inhibitors earlier in the treatment algorithm in combination with metformin in patients with an HbA1c of 7.5% or

greater and as monotherapy for patients with an HbA1c of 6.5% to 7.5%.[4,7]

When considered about the injectable nature of the molecules, the issue may be a disinclination toward frequent injections rather than a complete rejection of injections per se. The option of offering a once-weekly injection could lead to acceptance of injection-based therapies.

The optimal role of incretin-based therapies is still emerging. However, given their unique pharmacological properties, it is imperative that we explore further their changing roles within our treatment algorithms for T2DM.

In summary, current guidelines recommend a patient-centered approach to hyperglycemia management. This is relevant both in terms of treatment targets and the choice of agents. GLP-1 RAs do not only reduce glycemia but also promote weight loss and are not associated with the risks for hypoglycemia, and also some additional favourable effects on cardiovascular risk factors including a substantial lowering in BP.

Conclusion

HbA1c targets are commonly not being met, and that results in major health consequences. The way forward, to improve outcomes, is to adopt a personalized approach to diabetes management, taking into account the characteristics of the individual patient and linking those characteristics to the appropriate management regimen.

In general, patients who initiate therapy earlier in the course of disease and with a lower HbA1c will respond better with GLP-1 RAs as that is the time when beta cells exhaustion will be minimal. These agents do not prevent hypoglycaemia; they just do not initiate it. They are generally well-tolerated. The relationship of GLP-1 agonists and DPP-4 inhibitors to acute pancreatitis seems to be unclear. Liraglutide does not require self-monitoring of blood glucose for adjusting the dose and it has no clinically relevant drug-drug interactions. Delaglutide has a better side effect profile with fewer gastrointestinal effects than exenatide twice daily or liraglutide daily once a week preparations are of a great help in solving the problems of noncompliance and clinical inertia which pose as great barriers to achieving glycemic goals.

These agents have been with us for a few years, and they bring a really interesting clinical profile—not only excellent lowering of blood glucose values, but the potential for weight changes, protection against hypoglycemia, and maybe even some protection or at least effects on cardiovascular risk profiles.

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"I have never let my schooling interfere with my education."
— Mark Twain