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REVIEW ARTICLE

History of the Development of Oral Antidiabetic Agents

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Keywords: ***History of Diabetes,Oral Antidiabetic Agents, Evolution of Oral Anti diabetics***

Introduction

The history of antidiabetic medications maintain a great importance due to the so-called 'epidemic disease of the century', i.e. diabetes mellitus.[1] The so-called Coca-Colanization or industrialization of the civilization has a negative impact on diet and lifestyle, and as a result, the incidence of type 2 diabetes mellitus has become a serious public health issue.

The classic symptoms of diabetes were described long back in the ancient Egypt. At that time the first attempts to treat the symptoms involved the mixtures of many natural products of animal or veterinary origin. Till the beginning of the 20th century there were still no therapeutic options sufficiently successful to treat diabetes. The discovery of insulin was undoubtedly a breakthrough in the history of diabetes, saving thousands of patients and also improving their life quality, particularly of those with type 1 diabetes.

With the increasing wealth and the associated growing food supply in the industrialised countries, the incidence of type 2 diabetes has augmented. Consequently, the development of drugs targeting the underlying causes of type 2 diabetes, such as insulin resistance and beta-cell failure, became a topic of interest for pharmacological intervention. The management of diabetes has changed dramatically during the past several thousand years. The option preferred by "experts" of the pharaoh of Egypt 3,500 years ago was a mixture of "water from the bird pond," elderberry, fibres from the as it plant, milk, beer, cucumber flower,and green dates.[1]

Although our therapeutic options today are significantly more effective, they will likely be considered arcane by our successors 100 years from now if the current trajectory in treatment development continues. The current pharmacological armamentarium used to manage diabetes has gifted us a dramatic reduction in morbidity and mortality. This article provides a brief overview of the development history and effectiveness of various agents used in the pharmacological management of diabetes in a satisfactory way. Now we have many oral agents for treating diabetes other than injectables as described below.

Biguanides

The first drugs to be available for treatment of type 2 diabetes were the biguanides with its origins in nature.

It was observed during medieval times that the plant goat's rue, scientifically known as *Galegaofficinalis*, had a beneficial effect on blood sugar.[2] It was used as folk remedy for diabetes in Southern and Eastern Europe during medieval times.[3] Two synthetic biguanides were tried between 1920 and 1930 but were discontinued from clinical use because of their toxic nature.[4] Further research with biguanides was done in the early 20th century, before the discovery of insulin in 1921.

Frank et al. isolated a guanidine compound called Synthalin in Germany and used it to treat diabetes during the 1920s.[5] Homologs of guanidine (e.g., Synthalin) were used for a short period of time,but were seen to be hepatotoxic. As a result, the use of these compounds were stuck up with the discovery and proliferation of insulin. Due to this fact the discovery of biguanides got a set back and biguanides were not targeted until the late 1950s, when they experienced a hope with metformin and later with phenformin and buformin. Initially, Jean Sterne investigated about Metformin and published encouraging results in 1957 about its toxicity and hypoglycaemic effect.[6]

In the 1960s and 1970s, phenformin was widely studied in the United States, whereas metformin was studied in France and buformin was studied in Germany.[7] Phenformin and buformin were later on withdrawn due to the high risk of lactic acidosis, a potential risk that is still debatable for metformin. Currently, metformin, is the only biguanide in the market and the most widely used anti hyperglycemic agent in the world . It is also the first antidiabetic agent to demonstrate a beneficial effect on cardiovascular morbidity and mortality in the UKPD-study.[8]

In the year of 1950s, three biguanides, metformin, phenformin, and buformin, were introduced. Metformin and phenformin were introduced in the United States but were later withdrawn in 1978 due to the phenformin related increase in incidences of lactic acidosis.[9] In 1995, metformin was again approved in the United States after being in use in Europe for 20 years.[10] Its primary mechanism of action is its ability to reduce hepatic glucose production,but it also reduces glucose via mild increase in insulin-stimulated glucose uptake.[3]

In 1998, the first prospective outcome trial for type 2 diabetes, UK Prospective Diabetes Study (UKPDS)-34 evaluated the effect of intensive glucose control in overweight (mean BMI, 31), treated with metformin. UKPDS documented that metformin decreased the risk of diabetes related-end points and was associated with less weight gain and hypoglycaemic events compared with sulfonylureas and insulin.[11]

The important contraindication for patients treated with biguanides is renal impairment, with GFR level 60ml. Lactic acidosis considered as an important side effect, is rarely observed when metformin is administered properly.[12] But gastrointestinal side effects, such as nausea,diarrhoea and abdominal discomfort, may occur which is genetically determined.

Sulfonylureas

In 1937 the hypoglycaemic activity of synthetic sulfur compounds was observed by chance when they were being used to treat typhoid.[2] Five years later, Marcel Janbon and his colleagues were treating patients with the antibiotic para-amino-sulfonamide isopropyl-thio diazole for typhoid and observed hypoglycaemia.[13] In 1946, Auguste Loubatieres confirmed that arylSulphonyl ()compounds stimulated release of insulin and therefore required some pancreatic β-cell function to elicit an effect.[14,15]

In 1956, the first sulfonylurea, tolbutamide, was introduced commercially in Germany followed by chlorpropamide, acetohexamide, tolazamide and tolbutamide, the first-generation sulfonylureas.[16,17] The next advancement in SU therapy in the United States did not occur until the release of the more potent second-generation agents glipizide and glyburide in 1984. These agents had been in use in Europe for several years before the United States.[13] The next SU agent, glimepiride, which is sometimes referred to as a third-generation agent, was released in 1995.

Sulfnoylureas are linked to hypoglycaemia and

weight gain, and numerous population-based surveys indicate that they are linked to an increase in overall and cardiovascular mortality.[18–20]

In contrast, controversial results regarding safety have been obtained from randomized controlled clinical trials.[21–23] Furthermore, increasing evidence suggests that the treatment with sulfonylureas might cause faster exhaustion of beta cells.[24,25]

SUs are widely used, generally safe,inexpensive, and relatively predictable. Generally, an A1C reduction of 1–2%can be expected in a responsive patient with type 2 diabetes.[3] Sulfonylureas stimulate pancreatic b-cells to secrete insulin by binding to receptors that block the potassium ATP-dependent channels, leading to cell depolarization and subsequently insulin exocytosis.

Thiazolidinediones

Biguanides and sulfonylureas were the only two oral drug options available for oral treatment for a long time, with little being achieved in the field of new pharmacological targets. Patients with diabetes had to wait till the 1990s for a new generation of innovative drugs with different mechanisms of actions to appear. The decade of the 1990s was marked by the arrival of new drug classes with innovative mechanisms.

The thiazolidinediones (briefly known as 'glitazones') were introduced for the treatment of type 2 diabetes mellitus in 1996, when troglitazone as first drug of the class was approved by the FDA.[26] These drugs had a different molecular effect but the benefits for the patients were noteworthy. But, shortly after its release, cases of idiosyncratic hepatic failure were reported. The drug was removed from the market when 63 fatal cases were reported.[2] With on-going research in the field, rosiglitazone was introduced almost simultaneously with pioglitazone in 1999. Both these compounds were commercially successful, and in fact, pioglitazone was one of best-selling drugs in 2008 in the United States. Pioglitazone has been shown to have a beneficial impact on cardiovascular disease and to reduce the risk of stroke, although it has also been associated with a possible increase in the incidence of bladder cancer. Nevertheless, the evidence in this regard is rather inconsistent and new evidence contradicts this notion.[27] Rosiglitazone was withdrawn from the market due to an alleged increase in cardiovascular mortality .[28]

Thiazolidinediones (TZDs), areperoxisome pro lifer at or-activated receptor-γ activators whose mechanisms of action are enhancement of skeletal muscle insulin sensitivity and reduction in hepatic glucose production.[12] These agents do not increase the risk of hypoglycaemia and have a more durable effect than metformin or SUs.[29]

Two other TZDs, pioglitazone and rosiglitazone, which are currently on the market, have each been linked tonon-hypoglycaemic issues. Both agents have been linked to fluid retention and must be used with caution inpatients with congestive heart failure (CHF). Until recently, rosiglitazone was not widely available because of concerns that it was associated with an increased risk of myocardial infarction(MI). The FDA, which had previously placed restrictions on rosiglitazone, began to ease those restrictions in November 2013. Their change in position was based on the findings of the large Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) study, which concluded that people treated with rosiglitazone did not have an elevated risk of MIcompared to patients taking other anti hyperglycaemic medications.[30]

Thiazolidinediones improve insulin sensitivity by binding to the peroxisome proliferator activator receptors in the target cell nucleus. This causes conformational changes with the retinoic X receptor. The discovery of thiazolidinediones was the result of the observation that patients with type 2 diabetes on clofibrate had lower fasting glucose levels.[31] In the quest for formulating more potent fibrates in the early 1980s, Takeda Pharmaceuticals,Japan, made analogs of clofibrates that had positive effects on hyperglycaemia, hyperinsulinaemia and hypertriglyceridemiain animals with type 2 diabetes. This led to the discovery of the first thiazolidinedione, ciglitazone,which had a modest effect on glucose and significant effects on lipids but caused oedema and lenticular opacities in rodents.[31] Ciglitazone was never marketed.

In 1997, troglitazone became the first thiazolidinedione to be approved for clinical use. Though effective, it was withdrawn in 2000 after it was found to cause liver damage. Two other thiazolidinediones, rosiglitazone andpioglitazone, were approved in 1999 for treatment of type 2 diabetes. In September 2010, the US Food and Drug Administration (US FDA) restricted the use ofrosiglitazone because of its potential to cause cardiovascular ischaemia,[32] and a recent study found that longterm use of pioglitazone slightly increases the risk of bladder cancer.[33,34] The use of pioglitazone, alone or in combination with other diabetes agents, is permitted in the United States.

A1C is decreased by 1–1.5% and there are no significant differences in A1C lowering between pioglitazone and rosiglitazone. The most common side effect is oedema, which is dose related. Pioglitazone should be used with caution in patients with CHF stage I and II, and it is contraindicated in CHF stage III and IV. Anaemia and osteoporosis may alsooccur.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors (AGIs) exert a local effect on the brush border of the small intestine, inhibitingα-glucosidase enzymes, which are responsible for the breakdown of oligosaccharides, trisaccharides and disaccharides. These enzymes include maltase, isomaltase, gluocoamylase and sucrase. Inhibition of these enzyme systems effectively reduces the rate of absorption of carbohydrates but does not alter the absolute absorption. The result is reduced postprandial glucose levels, with a modest effect on fasting glucose.[3] The reduction of A1C observed with AGIs is typically 0.5–1.0%.

The first drug in this category to reach the market was acarbose, which was approved by the FDA in 1995. A second AGI, miglitol, was approved in 1996. In the twenty-first century another molecule voglibose was introduced. Voglibose was discovered in Japan in 1981, after its isolation from validamyan on culture media and the producing organism was *Streptomyces hygroscopicus*var. limonons. It became a commercially available treatment of diabetes in Japan since 1994.

These drugs are available but not widely used in western countries, probably because of their modest impact on A1C, their need for multiple daily doses and their-gastrointestinal (GI) side effects. Voglibose is now the top most amongst the AGIs and very useful in India as people in India consume more carbohydrates in diet.

The idea behind these drugs was to slow down the rate of absorption of carbohydrates. These drugs have been increasingly popular in Asia, but are less commonly used in other parts of the world due to the necessity of multiple doses and the presence of bothering gastrointestinal effects.

Meglitinides

The meglitinides,which are also known as glinides, have a mechanism of action same as of the SUs but are structurally different from SUs. The meglitinides lowers blood glucose levels by stimulating insulin release from the pancreas.[3] This glinide-induced insulin stimulation is dependent on functioning pancreatic β-cells like the SUs. But, the effect is glucose dependent and diminishes at low glucose concentrations.

The glinides bind to receptors in the pancreas, but the configuration of their binding is different from that observed with SUs. These medications bind to the SUR1 binding site in the pancreas unlike the SUs. They should be given 15–30 min before the meal to manage the postprandial rise in glucose and they can decrease the A1C by 1–1.5%.[3,13]

The limitations of their use are the need for multiple meal-timed doses and the incidence of hypoglycaemia. They have a more rapid onset and a shorter duration of action than the second generation SUs. The rate of hypoglycaemia with the glinides are of lower rate than that observed with the SUs. The first drug of this class is repaglinide and was approved by the FDA in 1997, and the second agent nateglinide, was approved in 2000.[13] But these drugs could not be very popular because of multiple times doses a day and limited efficacy.

DPP-4 Inhibitors

Glucagon-like peptide-1 (GLP-1) is a hormone secreted by the L cells of the small intestines within minutes following a carbohydrate- or fat-containing meal. GLP-1 stimulates insulin synthesis and glucose dependent insulin secretion. Moreover, GLP-1 suppresses glucagon release and delays gastric emptying. It has a short half-life of 1–2 min because of rapid degradation by dipeptidyl peptidase-4 (DPP-4).These physiologic benefits led to the development of GLP-1 receptor agonists and DPP-4 inhibitors for the treatment of type 2 diabetes.

As noted above, with the elucidation of the incretin-insulin pathway,researchers became interested in the development of DPP-4 inhibitors,agents that could be taken orally and would prolong the circulating half-life of endogenous in cretins. The first of these agents to become available in the United States was sitagliptin, which was approved in 2006.[1,35] This was followed by the release of saxagliptin and linagliptin. Alogliptin was approved by the FDA in 2013. Vildagliptin has been approved for use in Europe butis not available in the United States.

At present moment, there are six approved DPP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, and linagliptin,gemigliptin and teneligliptin. They effect a modest A1C reduction of up to 0.8%. They are available alone or in combination with metformin. The near absence of hypoglycaemia makes their use desirable. It should be noted that pancreatitis has been reported among patients using DPP-4 inhibitors.[36]

Dipeptidyl peptidase-4 (DPP-4) inhibitors, which became available shortly after exenatide, also use GLP-1 as the underlying mechanism of action by blocking the enzymatic degradation of incretins. In India, the first drug of this class, sitagliptin, gained approval in 2006 and was followed by saxagliptin, vildagliptin and linagliptin. Although the blood-glucose-lowering effects of DPP-4 inhibitors are weaker than those of GLP-1 RAs, this drug class has become increasingly popular as they are well tolerated and available for oral administration.

These compounds are associated with an A1C reduction of~0.8%.[15] They are weight neutral and do not tend to cause hypoglycemia.[7] The near absence of hypoglycaemia makes their use desirable. However, pancreatitis has been reported in patients treated withDPP-4 inhibitors.[13] They are available alone or in combination with metformin.

Bromocriptine

Bromocriptine is a sympatholytic D2-receptor agonist approved in 2009 for the treatment of type 2 diabetes as an anti hyperglycaemic medication, as an adjunct to diet and in the United States.[37] Its mechanism is probably due toits dopaminergic activity in the brain and the subsequent inhibition of sympathetictone.[13] Orally administered Bromocriptine once daily within 2 hours of awakening reduces postprandial glucose levels with A1C reductions of up to 0.7%.[38]

Colesevelam

Colesevelam was initially developed for its ability to bind bile acids, effectively removing them from circulation and resulting in reductions in LDL cholesterol. But it has a dual effect of lowering LDL cholesterol and reducing blood glucose levels also. The exact mechanism of its action on the glucose lowering with this compound is not known. In the United States, FDA approved Colesevelam for use in patients with type 2 diabetes in 2008.[13]

Colesevelam shows an A1C reduction of ~0.5% and LDL cholesterol reduction of 13% and slight increase in triglycerides.[7] It is given twice daily. Its side effects are primarily gastrointestinal similar to those encountered with AGIs.

Sodium Glucose Co-Transporter 2 Inhibitors

A revolutionary situation in the history of OADs is the introduction of sodium glucose co-transporter 2 (SGLT-2) inhibitors, an interesting group of drugs presenting with a completely novel mechanism of action. The glucose lowering effect of this drug class is mediated by an increase in renal glucose excretion. They actually interfere with the glucose reabsorption (which is enhanced in presence of type 2 diabetes) from the renal tubules. Interestingly, two recent studies known as EMPAREG[39,40] with empagliflozin and CANVAS with canagliflozin showed a reduction

in overall and cardiovascular mortality and a marked reduction in hospitalisation due to heart failure , a fact that might further promote its use in the future.

The sodium glucose co-transporters 2 (SGLT-2) inhibitors antagonizea high-capacity, low-affinity glucose transporter responsible for ~90% of glucose reabsorption found primarily in the kidney.[41] With inhibition of this transporter, excess glucose in the renal tubules is not reabsorbed, and glucose is excreted in the urine. This results in a net loss of glucose and a lowering of hyperglycaemia.

A recent meta-analysis evaluating SGLT-2inhibitors showed A1C reductions of 0.5–0.6% in patients treated with these agents.[42] In addition, SGLT-2 inhibitors show slight reductions in weight and BMI. The primary side effect of these drugs is an increase in urinary or genital infections, but are usually mild.[42]

Canagliflozin was the first SGLT-2 inhibitor to be approved by the FDA,in March 2013.[43] Subsequently,Dapagliflozin was approved in the United States in early 2014 and Empagliflozin in late 2014. SGLT 2 inhibitors are the first group of drugs to show improvement in both cardiovascular and renal outcome.

Oral Insulin

Before the 1920s, there were no effective pharmacological agents for the management of diabetes. Because of this, type 1 diabetes had a fatal malady. This changed dramatically with Frederick Banting's work. Dr. Banting served as a surgeon in World War I. Captain Banting initially spent some time in hospitals in England, but later was sent to the front as a battalion medical officer, where he was wounded by shrapnel. He received a Military Cross for his courage in action.[44] After returning from the war, Dr. Banting opened an office outside of Toronto, Canada. After seeing only one patient in the first month of his practice (a patient seeking a prescription for ethanol), Banting embarked upon a career in academics. One of his first teaching assignments involved carbohydrate metabolism. This led to his interest in diabetes and his erroneous assumption that one needed to surgically ligate the pancreatic duct and then wait 6–8 weeks before extracting anything that might be useful from the endocrine portion of the gland.

Over time, and without the ligation step, he was able to extract a substance from canine pancreas glands that had an impact on hyperglycaemia in other diabetic animals. Banting and his student, Charles Best, continued working on various extraction processes.

Leonard Thompson,the first patient to receive insulin was a 14-year-old boy who weighed 65 lb with uncontrolled diabetes. On 11 January 1922, a young house officer, Ed Jeffery, injected 7.5 cc of Banting and Best's extract into each buttock of the patient. Though a sterile abscess developed at the site of one of the injections, the patient's blood glucose dropped.

From 1921, many advances have taken place in the history of Insulin, but till date it can be only given by injections. The first attempt to develop a short-acting oral insulin formulation was done in 1930s. Early attempts were made to assess if insulin could be absorbed via the portal vein by directly injecting insulin in the intestinal loop .[45]

In another study, a hexylresorcinol solution containing insulin was administered to 10 healthy volunteers. There was a successful a reduction in blood glucose levels, but that oral delivery of insulin showed great variability and poor bioavailability.[46] Recently, short-acting oral insulins with varying times of onset are being developed by Emisphere Technologies (Tarrytown, NJ, USA) and Biocon (Bangalore, India).

Biocon from India is developing a new analogue called IN-105 (insulin modified with a small polyethylene glycol) which is an advanced next generation molecule to HIM2 .In the early clinical development,IN-105 was tried in 20 patients with T2DM poorly controlled on metformin. The doses tried were 10, 15, 20 and 30 mg of IN-105 and were compared with a placebo control arm. The insulin levels peaked at approximately 20 min post administration and the returned to baseline by about 80 min. Correspondingly, glucose levels reached a

nadir at around 40 min and showed a statistically lower glucose values across all the data points measured. It was found that IN-105 reduced 2 h postprandial glucose excursion in dose-dependent manner and the response was found to be linear all the way up to the highest dose studied. IN-105 was well tolerated by all the patients and caused symptomatic, biochemically confirmed hypoglycaemia in only one patient at 20 mg dose.[47] Long-term data demonstrating reduction in HbA1c from such a treatment are not yet available.

Biocon has initiated a long-term study (Trial ID: CTRI/2009/091/000479) with IN-105 in Indian patients with T2DM where the primary endpoint will be HbA1c drop and secondary endpoints are 2-h PPG and fasting plasma glucose (FPG) reduction.

There are several reports on the encapsulation of insulin using nanoparticles, and it has been successfully shown to reduce the glucose levels in animalmodels.[48]

Intesulin (Coremed, Lake Bluff, IL, USA), long-acting insulin, involves encapsulation of insulin in nanoparticles made of bioadhesive polymers. A study conducted in streptozotocin induced diabetic rats showed a statistically significant reduction in glucose levels from 15 min from the time of administration all the way up to 300 min.[49]

No data in humans are available in literature as of now. Another company Oramed (Jerusalem, Israel) has developed an oral insulin capsule, which has been tried in early phase clinical trials. The technology involves an enteric coated capsule where the insulin is released in the intestine; absorption is promoted by use of a permeation enhancers (PE). A study in eight normal healthy volunteers, to identify a lead formulation, showed administration of an oral form of insulin in the fasted state demonstrated a reduction in blood glucose (7–37%) and a significant decrease in C-peptide levels in all formulations (13–87%). All the formulations were well tolerated by the volunteers, and no serious adverse events have been reported. The onset of action for this insulin was delayed beyond 2 h and lasted up to 5 h from the time of administration.[50]

Another oral insulin formulation (Capsulin™) is being developed by Diabetology (Jersey,UK), demonstrates a peak plasma insulin concentration at ~80–90 min post-dosing and duration of action lasting up to 4–6 h.[51]

Successful discovery of oral insulin will definitely improve the quality of life of diabetes patients who routinely receive insulin by the subcutaneous route. The oral delivery of insulin will offer many advantages like higher patient compliance, rapid hepatic insulinization, and avoidance of peripheral hyperinsulinaemia and other adverse effects such as possible hypoglycaemia and weight gain. But, the oral delivery of insulin remains a challenge because of its problem in oral absorption due to the gastrointestinal tract degradation by proteolytic enzymes and lack of transport across the intestinal epithelium.

During past years, different drug delivery strategies have been introduced to overcome these problems of low oral bioavailability of insulin. Several insulin delivery systems, like tablets, capsules, intestinal patches, hydrogels, micro-particles, and nanoparticles, have been tried to release insulin by para cellular and/or trans cellular transport throughout the ileum and colon. The delivery methods uses excipients, which protect insulin from aggregation and enzymatic degradation, prolong its residence time in the gastrointestinal tract, and enhance its intestinal uptake.

If in future, oral insulin become a reality for patients there are many challenges that need to be solved. First, long-term efficacy and safety should be established through adequately powered studies in different types of patient populations all over the world in terms of reproducible absorption of the drug after meal. Second, long-term clinical studies should show superiority over injectable insulins and OHAs including improved hypoglycaemic profile, reduced weight gain and better disease progression outcome . Third, the important unknown apprehension of long-term insulin delivery through oral route is its potential for inducing mitogenic changes in the gut mucosa as insulin is a growth promoter .Finally, the success of oral insulin will be determined by its ability to

manufacture insulin both in sufficient quantities for oral delivery as well as efficiently in a cost-balanced production. If all these four issues are successfully satisfied, a magical treatment paradigm-changing oral insulin therapy may be the result.

Oral Glucagon-Like Peptide-1 (GLP1) Receptor Agonists

For a long time, the idea of an "incretin effect" was known, being based on experimental data demonstrating a greater insulin response with oral glucose administration versus intravenous glucose administration. The generalities of the incretin-insulin pathway were evaluated by the 1980s. Two studies evaluated the impact of native glucagon-like peptide-1 (GLP-1) in normal subjects and in patients with type 2 diabetes.[52,53] The studies showed a significant increase in insulin response and in the reversal of hyperglycaemia in type 2 diabetes who were hyperglycaemic and received native GLP-1. GLP-1 and its analogs reduce glucose levels via a glucose dependent insulin secretion.

One analog, exendin-4, was isolated from the salivary gland venom of the Gila monster (Helodermasuspectum).[3] Exenatide, a synthetic form of exendin-4, was the first GLP-1 receptor agonist available for clinical use in 2005.[54] A second GLP-1 receptor agonist, liraglutide, was approved in 2010.

Currently, GLP-1 receptor agonists are only available as injectables. Semaglutide is a long-acting GLP-1 receptor agonist that is also being developed as a once-weekly injectable preparation. An oral semaglutide version leading to higher solubility and protection from enzymatic degradation is also under development. If the drug gets approval for marketing, this version of semaglutide would be the first-ever GLP-1 receptor agonist available as oral daily pill.

In the phase 2 dose-finding study, HbA1C and weight reduction were of similar magnitude to that seen with the injectable GLP-1 receptor agonist formulations, and there were no major concern in terms of safety. However, there may be issues relating to how food and other medications might affect the drug's absorption and activity, and whether people with delayed gastric emptying or achlorhydria might respond differently to the drug. Also, that the higher doses required for efficacy compared with the injectable form might be costlier to produce.[55]

Conclusion

Several new agents have been introduced in the last decades and have extended the armamentarium for the treatment of type 2 diabetes. Although good blood glucose control is achievable in many patients with type 2 diabetes, only few drugs have shown beneficial effects on hard clinical endpoints so far. More research is, therefore, urgently needed to control the excess of cardiovascular morbidity and mortality in patients with type 2 diabetes.

There are now different categories of medications for the management of hyperglycaemia in patients with diabetes. These compounds have been developed during the past 90 years), and among these categories, myriad subtypes exist.

Moreover, the potential permutations and combinations of these agents is staggering and can be bewildering to the clinicians trying to design the optimum therapy regimen for a particular patient. We have in our mind both the questions of efficacy and the potential detrimental effects of anti hyperglycaemic medications. At the same time, we should acknowledge the fact that the outlook for patients with diabetes today is much better than what they would have encountered in the 1920s or even in the 1970s.

Clearly, we are marching in the right direction, with the goal of having no gap between the two populations in terms of life expectancy or even the outright prevention of all types of diabetes. Advances in research, that is, diabetesgene therapy and human insulin-producing cell therapy,may personalize treatment and make cure possible. The future advances will continue to make a positive difference in the lives of our patients.

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