New treatments for type 2 diabetes

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Abstract

Type 2 diabetes (T2D) has become a burden for society, and the incidence of the disease continues to increase. A range of therapies is available to control glycaemia in T2D patients; however, these drugs have undesired side-effects and there is a need to develop improved treatments. Extensive research in diabetes has led to a better understanding of the disease and therefore to the design of new therapies. Incretin-based therapies are of special interest because they have numerous advantages over traditional treatments, for example, they do not produce hypoglycaemia and they induce weight loss, reduce appetite, provide β -cell protection, and reduce the risk of cardiovascular disease. There are two different incretin therapy approaches: glucagon-like peptide-1 agonists and dipeptidyl peptidase-4 inhibitors. In this article, the incretinbased therapies available on the market are described and compared with the traditional therapies to control diabetes. Finally, preventive steps are pointed out as an option to control diabetes, which has become a pandemic of the twenty-first century.

Keywords: Diabetes, Diabetes treatments, Incretin, GLP-1, DPP-4, Obesity

Introduction

Diabetes is a chronic disease in which either insulin production is impaired or insulin is used inefficiently by the body. Insulin is a hormone that is released by pancreatic β -cells in response to an increase in plasma glucose levels after food intake. In patients with type 1 diabetes (T1D) the body cannot produce insulin and the patients are insulin-dependent, meaning that they need to inject insulin to survive. In patients with type 2 diabetes (T2D) the body does not release enough insulin or it becomes insensitive to insulin, also known as insulin resistance. T2D accounts for 90%

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of the cases of diabetes and will be the focus of this article. 1

Currently, 346 million people have diabetes in the world, a number that continues to increase.² This increase has been attributed to changes in diet and lifestyle. Generally, a sedentary lifestyle and the consumption of more fats and sugars are the causes of T2D. The complications associated with diabetes are numerous, including cardiovascular disease, stroke, and microvascular complications that can lead to blindness and renal failure. Therefore, diabetic patients have a reduced quality-of-life and life expectancy, not to mention enormous health costs. In the United States alone, diabetes costs were 174 billion US dollars in 2007.³ Therefore, there is an urgent need to prevent and control this disease, which has become a burden for society.

Conventional treatments for diabetes: the long history of insulin and more

Insulin has been used to control glycaemia in diabetic patients since 1922.⁴ Long-lasting formulations of insulin and many other treatments have been developed. Conventional treatments to control hyperglycaemia in diabetes include insulin, insulin analogues, insulin secretagogues, and insulin sensitisers.

- *Insulin analogues* with improved properties compared with basal insulin have been developed.⁵ The long-acting *insulin glargine* is injected only once daily. It is marketed as Luntus[®] by Sanofi-Aventis. Likewise, Novo Nordisk has the long-acting *insulin degludec* in clinical trials, and so far, it appears to have similar properties as *insulin glargine*.
- *Insulin secretagogues* are drugs that stimulate pancreatic β-cells to secrete insulin. They include sulfonylureas and meglitinides.⁶

• *Insulin sensitisers* decrease insulin resistance by improving insulin sensitivity. Biguanides (*metformin*) and thiazolidinediones fall into this classification.⁷ Nowadays, *metformin* is the first choice of medication to treat T2D, together with changes in diet and increased physical activity.

These conventional medicines have been useful in controlling diabetes, but many problems remain. In particular, conventional medicines have associated side-effects, such as hypoglycaemia, which is particularly an issue with sulfonylureas and insulin therapy. The conventional medicines, especially sulfonylureas, can also cause β -cell destruction. In addition, with the exception of *metformin*, most antidiabetic drugs cause weight gain, which is an added problem for the many diabetic patients that are obese. Thus, drugs with fewer side-effects and that do not cause weight gain – or even better, produce weight loss – are desired.

Research in the last decade has provided a better understanding of diabetes and led to the development of new treatments. Drugs based on incretin hormones are especially interesting and are discussed below.

Incretin hormones: a gut feeling

Incretin hormones are released from the gut within minutes of eating a meal, causing what is known as the 'incretin effect.' Incretin hormones stimulate the secretion of insulin by pancreatic β -cells and are therefore insulinotropic hormones. In healthy individuals, the incretin effect is responsible for 50–70% of the insulin secreted after a meal.⁸

Two incretin hormones have been identified: glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1). GIP and GLP-1 are released from the K-cells and L-cells of the intestine, respectively. Studies with exogenous incretins have shown that GIP does not stimulate insulin secretion in T2D patients.⁹ Conversely, GLP-1 stimulated insulin secretion in diabetic patients and is therefore the focus of drug development efforts.

When secreted, GLP-1 lowers plasma glucose to normal levels, inhibits glucagon secretion, delays gastric emptying, decreases appetite, and increases pancreatic β -cells proliferation.¹⁰ GLP-1 is only secreted when food is ingested and not when glucose is injected intravenously (the so-called incretin effect). The intracellular effect of GLP-1 is mediated by the GLP-1 receptor (GLP-1R), a member of the G-coupled protein receptor (GPCR) family that is expressed in many tissues. GLP-1 has a very short half-life (approximately 1.5 minutes). The active form of GLP-1₇₋₃₆, which is referred to as native GLP-1, is cleaved by the enzyme dipeptidyl peptidase-4 (DPP-4), generating the inactive peptide GLP-1₉₋₃₆.⁸ Therefore, the administration of exogenous GLP-1 as a therapy is not feasible because it is rapidly inactivated. Two approaches based on incretin hormones are being developed for the treatment of diabetes: (1) GLP-1 analogues that activate GLP-1R and are resistant to DPP-4 and (2) inhibitors of DPP-4, which act by increasing the half-life of endogenous GLP-1.

GLP-1R agonists: emulating GLP-1

The rapid degradation of GLP-1 by DPP-4 has encouraged scientists to develop GLP-1 analogues that are resistant to degradation. Two GLP-1R agonists are already on the market.¹¹ *Exenatide* was approved in the USA in 2005 and is marketed under the name Byetta[®] (Amylin Pharmaceuticals). *Liraglutide* was approved in Europe in 2009 and is distributed by Novo Nordisk as Victoza[®].

Exenatide is a synthetic version of exendin-4, a naturally occurring 39-amino acid peptide originally isolated from the saliva of the Gila monster lizard (*Heloderma suspectum*), and it shares 53% amino acid sequence identity with native GLP-1.¹² By contrast, *liraglutide* shares 97% amino acid sequence identity with GLP-1; it has one amino acid substitution and an added glutamate-linked fatty acid side chain that promotes albumin binding.¹³

Exenatide is administered intravenously twice daily. A once-weekly formulation has recently been approved and is marketed under the name Bydureon[®]. *Liraglutide* is administered once daily intravenously, a disadvantage compared with metformin, which can be taken orally. However, exenatide and liraglutide have many advantages over metformin. Since they are glucose-dependent, they do not induce hypoglycaemia, a common problem with the conventional diabetes drugs. In addition, they promote weight loss, may improve pancreatic β-cell function, and may reduce the risk of cardiovascular diseases.¹⁴ This last point is of paramount importance since cardiovascular complications are the most common cause of morbidity and mortality amongst T2D patients.¹⁵

Altogether, GLP-1R agonists appear to be promising molecules for the control of T2D. Clinical trials to date have reported few side-effects, mostly nausea and stomach discomfort that tends to resolve after a few weeks of treatment. However, the long-term safety of GLP-1R agonists remains to be determined. Tumours have been observed in the thyroid tissue of rodents treated with *liraglutide*,¹⁶ although whether *liraglutide* causes thyroid tumours in humans is not yet known. Thus, the long-term consequences of sustained GLP-1R activation in the human thyroid require further investigation. For this reason, GLP-1R agonists are currently only recommended as second- or thirdline therapies in T2D, only when *metformin* and other traditional therapies are not effective in controlling the disease.

Apart from *exenatide* and *liraglutide*, there is a long list of new molecules in the development pipeline.^{11,17} Among others, *lixisenatide* (Sanofi-Aventis), *albiglutide* (GlaxoSmithKline), *semaglutide* (Novo Nordisk), *LY2189265* (Eli Lilly & Co.), and *CJC-1134-PC* (ConjuChem) are currently in clinical development. Clinical trials of *taspoglutide* (Roche) have been suspended due to safety concerns.

DPP-4 inhibitors: another pro-incretin alternative

A second approach based on incretins to control glycaemia in diabetic patients is to block DPP-4 with inhibitors. DPP-4 is the enzyme that degrades endogenous GLP-1 and is widely distributed throughout the body.¹⁸ Molecules that inhibit DPP-4 increase endogenous GLP-1 concentrations two- to three-fold, depending on the inhibitor.

The DPP-4 inhibitor *sitagliptin* (Januvia[®] by Merck & Co.) was approved by the FDA in 2006, followed by *saxagliptin* (Onglyza[®], Bristol-Myers Squibb), *vil-dagliptin* (Galvus[®], Novartis), *linagliptin* (Tradjenta[®], Boehringer Ingelheim and Eli Lilly & Co.), and *alogliptin* (Nesina[®], Takeda, currently only approved in Japan).

DPP-4 inhibitors are administered orally, an advantage over GLP-1R agonists that have to be injected intravenously. Like GLP-1R agonists, DPP-4 inhibitors do not produce hypoglycaemia and might preserve β-cell function. However, DPP-4 inhibitors do not affect gastric emptying or decrease appetite and therefore do not promote weight loss. Nevertheless, they are considered weight neutral, which is an improvement over other treatments. Clinical trials suggest that DPP-4 inhibitors reduce cardiovascular risk, although more studies are needed to clarify the relationship between the use of DPP-4 inhibitors and cardiovascular protection.¹⁹ Overall, DPP-4 inhibitors appear to be less efficient than GLP-1R agonists in lowering plasma glucose levels.²⁰

The various DPP-4 inhibitors available on the market differ in their potency, metabolism, and excretion route.^{21,22} Understanding the pharmacological properties of the different drugs is necessary for choosing the appropriate therapy for each patient. The most common side-effects of DPP-4 inhibitors are an increased risk of infections (nasopharyngitis, upper respiratory tract infections, and urinary tract infections) and headaches. However, the consequences of long-term DPP-4 inhibition in T2D patients are unknown. Therefore, like GLP-1R agonists, they are a second- or thirdline option used when conventional therapies fail to control hyperglycaemia.

Prevention of diabetes: the clue to stopping the disease?

Although genetic factors influence the risk of developing diabetes, obesity is well established as the main cause of T2D.²³ In 2008, 1.4 billion people were overweight (body mass index \geq 25), of which 500 million were obese (body mass index \geq 30).²⁴ Worldwide, obesity has more than doubled since 1980, which explains the outbreak of diabetes in the last decades. The increase in obesity is attributed to the modern sedentary lifestyle, with diets rich in fats and sugars. Obesity can be easily prevented by introducing changes in diet and lifestyle. Targeting obesity in order to control diabetes is therefore a logical strategy.

Obesity is a key risk factor for T2D since it is the main cause of insulin resistance.²⁵ An individual can be obese and be insulin resistant but will not necessarily develop diabetes. Pancreatic β-cells compensate for insulin resistance by producing more insulin. T2D occurs when β -cells are damaged and are unable to compensate for insulin resistance, which leads to hyperglycaemia. The release of increased amounts of free fatty acids from adipose tissue in obese individuals is a crucial factor linking obesity, insulin resistance, and impaired Furthermore, β-cell function. obesity-induced tissue inflammation leads to the release of proinflammatory cytokines and the activation of protein kinases known to participate in the development of insulin resistance.²⁶

The Finnish Diabetes Prevention Study suggested that the incidence of diabetes can be reduced by lifestyle intervention. The study found that relative risk of contracting T2D was reduced by 43% by controlling body weight, increasing physical activity, and reducing the amount of fat consumed. Another study conducted by the Diabetes Prevention Program Research Group found that in individuals at high risk for diabetes, lifestyle changes and treatment with *metformin* reduced the incidence of diabetes, although lifestyle changes were far more effective than *metformin* alone (58 and 31% reduction in incidence, respectively).²⁷ Interestingly, dietary changes produce spectacular improvements in the insulin sensitivity of T2D patients, challenging the paradigm that T2D is a chronic disease.²⁸

Conclusion

T2D has become a global disease of pandemic proportions. New treatments to treat diabetes have emerged and many more are in the pipeline. The increasing number of therapies has led various clinical bodies such as the American Diabetes Association, the European Association for the Study of Diabetes and the National Institute for Health and Clinical Excellence in the UK, to develop guidelines to help physicians choose the best treatment for patients. Currently, *metformin* is the first option to control the disease due to its glucose-lowering effects, absence of weight gain, relatively few side-effects, and relatively low cost. However, additional treatments are needed when *metformin* fails to control glycaemia.

Incretin-based therapies offer an exciting new approach and have valuable advantages over conventional therapies. GLP-1R agonists and DPP-4 inhibitors control glycaemia in a glucose-dependent manner and therefore do not cause hypoglycaemia. In addition, they seem to increase pancreatic β -cells proliferation and to reduce cardiovascular risk. The ability of GLP-1R agonists to promote weight loss is especially interesting since most T2D patients suffer from obesity. Incretin-based therapies are currently second- or third-line therapies in T2D, mainly because long-term safety studies of these drugs have not yet been completed. However, the promising results obtained so far in clinical trials suggest that they will largely replace conventional therapies.

Diabetes is a serious disease that in many cases can be prevented. Obesity appears to be the main cause of T2D, and often simple changes to lifestyle can prevent this condition from ever developing. Educational campaigns to inform the public about the associated risks of obesity are extremely important. Motivating people to make changes in lifestyle by modifying eating habits and increasing physical activity would save health care systems and society in general a great deal of money and would increase the quality of life of people suffering from obesity and diabetes.

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