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The incretin system in the management of type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) is a progressive disease characterised by a variable degree of β-cell dysfunction, insulin resistance and hyperglycaemia. Recently there has been enormous interest in developing pharmacological agents which modulate the incretin system. These therapeutic agents improve glycaemic control through multiple mechanisms similar to the endogenous incretin hormone glucagon-like peptide-1 (GLP-1).[1–3]

The incretin effect

The incretin effect is a phenomenon by which oral glucose ingestion elicits a much higher insulin secretory response than intravenous glucose.[1,4] Following an oral glucose load, GLP-1 is secreted from the intestinal mucosa and augments the insulin response to hyperglycaemia. Plasma levels of GLP-1 increase six- to eightfold after a carbohydrate meal.[5] The action of GLP-1 is therefore dependent on residual insulin secretory capacity. GLP-1 is released in response to nutrient ingestion from L-cells distributed throughout the intestine, but preferentially located in the distal gut.[6] It is of interest that plasma levels of GLP-1 increase within minutes of food consumption, suggesting that a combination of endocrine and neural signals promotes early GLP-1 secretion before digested food passes through the gut to directly engage the L-cells.[1]

In addition to its insulinotropic effect, GLP-1 inhibits glucagon release,[6] prolongs gastric emptying and leads to a decrease in body weight, all of which explain the 'antidiabetic' effect of this incretin hormone.[7] Endogenous GLP-1 undergoes rapid inactivation by the enzyme dipeptidyl peptidase-IV (DPP-IV), resulting in a plasma half-life of 1–2 min. Therefore, the therapeutic potential of endogenous GLP-1 would be limited without attempts to prolong its duration of action.

The therapeutic potential of the incretin system in type 2 diabetes mellitus

There is a moderate degree of GLP-1 hyposecretion in subjects with T2DM. The typical phenotype of T2DM consists of a heterogeneous picture of diminished insulin secretion, excess glucagon secretion relative to the plasma glucose, and increased body weight with associated insulin resistance. Rodent and *in vitro* studies have shown an increase in β-cell mass following long-term administration of GLP-1. An improvement in β-cell function has been observed in humans, with increased insulin secretory capacity in response to GLP-1.[8] Infusion of GLP-1 results in the suppression of glucagon secretion and normalisation of fasting plasma glucose.[8] Importantly, GLP-1 administration does not impair the glucagon counter-regulatory response to hypoglycaemia since glucagon secretion is glucose-dependent.[9] GLP-1 has a direct action on the hypothalamus to induce satiety[10] and also delays gastric emptying.[11] Both these factors induce a feeling of postprandial 'fullness'.

The physiological effects of GLP-1 in improving β-cell function, reducing glucagon secretion and gastric emptying, inducing satiety and facilitating weight loss would be ideal in the therapy of a typical subject with T2DM.

Therapeutic strategies based on the incretin system

The main challenge in using GLP-1 to treat T2DM relates to its rapid metabolism by plasma DPP-IV. Initial interest in the use of GLP-1 based therapies for T2DM focused on DPP-IV resistant

Key points

- Glucagon-like peptide-1 (GLP-1) levels are low in patients with type 2 diabetes mellitus (T2DM)
- GLP-1 administration improves insulin secretion, reduces glucagon secretion, promotes satiety and delays gastric emptying
- GLP-1 mimetics are efficacious in the treatment of T2DM; currently available agents include exenatide and liraglutide
- Inhibitors of enzyme dipeptidyl peptidase-IV are available as oral agents for the treatment of T2DM

KEY WORDS: dipeptidyl peptidase-IV (DPP-IV), exenatide, glucagon-like peptide-1 (GLP-1) analogues, glycaemic control, liraglutide, obesity, type 2 diabetes mellitus

peptides that bound to the GLP-1 receptor (GLP-1 agonists) or substances inhibiting DPP-IV which would increase endogenous levels of GLP-1.[12] This led first to the development of incretin mimetics and subsequently of DPP-IV inhibitors.

GLP-1 mimetics

Two GLP-1 mimetics (also known as GLP-1 receptor agonists) are currently available in clinical practice: exenatide and liraglutide. They are DPP-IV resistant analogues of human GLP-1 that improve glycaemic control through multiple mechanisms similar to the endogenous incretin hormone GLP-1.[1,2] The efficacy of both these agents has been established in phase III clinical trials.

Exenatide

The first product licensed was exenatide, a synthetic analogue of a 39-amino acid peptide (exendin-4) originally found in the saliva of the lizard *Heloderma suspectum*. It is a functional, partly DPP-IV-resistant analogue of human GLP-1.[13] Studies have examined the efficacy of adding exenatide to concurrent oral therapy (metformin,[14] sulphonylureas,[15] a combination of both[16] or thiazolidinediones[17]) in patients with suboptimal glycaemic control. The starting dose of exenatide is 5 μg twice daily for four weeks followed by 10 μg twice daily thereafter.

Exenatide was associated with a mean reduction in HbA_{1c} of 0.8–1.0% during 30 weeks of treatment, with a weight loss of 1.5–3.0 kg.[14–16] Patients continuing in an open-label extension lost as much as 4–5 kg after 80 weeks.[18,19] Furthermore, in a 26-week comparator study against insulin-glargine[20] there was a similar overall improvement in glycaemic control (−1.1% reduction in HbA_{1c}) with the additional benefit of sustained weight reduction (−2.3 kg

Table 1. Summary of changes in HbA_{1c}, body weight and systolic blood pressure (BP) in the Liraglutide Effects and Action in Diabetes (LEAD) studies.

		Changes		
Study	No.	HbA_{1c} (%)	Body weight (kg)	Systolic BP (%)
LEAD-1: Liraglutide added to glimepiride (26 weeks' duration)				
Liraglutide 1.2 mg	228	−1.08	+0.32	−2.56
Liraglutide 1.8 mg	228	−1.13	−0.23	−2.81
Rosiglitazone 4 mg	228	−0.44	+2.11	−0.93
Placebo	114	+0.23	−0.10	−2.32
LEAD-2: Liraglutide added to metformin (26 weeks' duration)				
Liraglutide 1.2 mg	228	−0.97	−2.58	−2.81
Liraglutide 1.8 mg	228	−1.00	−2.79	−2.29
Glimepiride 4 mg	228	−0.98	+0.95	+0.41
Placebo	114	+0.09	−1.51	−1.76
LEAD-3: Liraglutide as monotherapy (52 weeks' duration)				
Liraglutide 1.2 mg	234	−0.84	−2.05	−2.12
Liraglutide 1.8 mg	234	−1.14	−2.45	−3.64
Glimepiride 8 mg	234	−.0.51	+1.12	−0.69
LEAD-4: Liraglutide added to metformin + rosiglitazone (26 weeks' duration)				
Liraglutide 1.2 mg	178	−1.48	−1.02	−6.71
Liraglutide 1.8 mg	178	−1.48	−2.02	−5.65
Placebo	177	−0.54	+0.60	−1.11
LEAD-5: Liraglutide added to metformin + glimepiride (26 weeks' duration)				
Liraglutide 1.8 mg	207	−1.33	−1.81	−3.97
Glargine	219	−1.09	+1.62	+0.54
Placebo	96	−0.24	−0.42	−1.44
LEAD-6: Liraglutide added to metformin and/or sulphonylurea (26 weeks' duration)				
Liraglutide 1.8 mg	233	−1.12	−3.24	−2.51
Exenatide 10 μg	231	−0.79	−2.87	−2.00

with exenatide, +1.8 kg with insulin glargine).

A more recent study[21] compared exenatide with biphasic insulin aspart as additional therapy in patients already receiving metformin and a sulphonylurea over a 52-week period. The HbA_{1c} reduction was similar (−1% reduction) but weight loss was observed in the exenatide treated participants (−2.5 kg with exenatide, +2.9 kg with biphasic insulin). Favourable reports have also been obtained with exenatide in the routine clinical setting.[22]

Liraglutide

Liraglutide is a long-acting GLP-1 analogue with 97% sequence homology to human GLP-1 but with structural modifications that result in reversible albumin binding, resistance to GLP-1 inactivation by DPP-IV, and prolonged duration of action.[23] The starting dose of liraglutide is 0.6 mg once a day increased weekly to a maximum of 1.8 mg daily.

The results of phase III clinical studies (Liraglutide Effects and Action in Diabetes (LEAD)) demonstrate the efficacy of liraglutide in reducing HbA_{1c} and also show beneficial effects on body weight. The LEAD programme comprised six randomised controlled, double-blind studies examining the effect of liraglutide directly against commonly used therapies in T2DM. As shown in Table 1, HbA_{1c} reduction is typical and weight loss was observed in all the studies except LEAD-1.[17,24–28]

It is of interest that a recent placebo-controlled study in obese individuals without T2DM demonstrated a significant weight reduction associated with liraglutide at 20 weeks.[29] The mean weight loss observed with liraglutide doses of 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg were −4.8 kg, −5.5 kg, −6.3 kg and −7.2 kg, respectively, compared with −2.8 kg with placebo. At present, liraglutide is not licensed for use as a weight reducing agent.

In the LEAD-6 study[24] the efficacy of liraglutide was compared with exenatide as add-on therapy to metformin and/or sulphonylurea. There was greater improvement in glycaemic control with once daily liraglutide compared with twice a day exenatide (reduction in mean HbA_{1c}, −1.12% with liraglutide, 0.7% with exenatide).

Adverse effects

Table 2 summarises the main adverse effects associated with GLP-1 mimetics. Essentially, these are gastrointestinal (GI) disturbances and risk of hypoglycaemia. The former include nausea, vomiting and diarrhoea. Typically, these adverse events, which are dose-dependent,[17] are often mild and diminish within a few days or weeks on continued therapy. Patients should be counselled with regard to the GI adverse effects to prevent unnecessary discontinuation and improve compliance.

The frequency of hypoglycaemia depends on the oral hypoglycaemic agents co-administered.[22] Importantly, the incidence of minor hypoglycaemia with liraglutide was comparable (3%) with that on placebo and 17% lower than with sulphonylurea.[25,27] Similarly, exenatide is also associated with an increased risk of hypoglycaemia when co-administered with a sulphonylurea.[16,20] Patients should exercise increased vigilance with regard to this potential adverse effect, particularly when using a combination of liraglutide and a sulphonylurea.

Table 2. Summary of common adverse effects associated with incretin-based therapy.

GLP-mimetics	DPP-IV inhibitors
Nausea, vomiting, diarrhoea, jittery, dizziness, headache, dyspepsia	Upper respiratory tract infection, nasopharyngitis, headache
Hypoglycaemia associated with coexisting sulphonylurea therapy	

DPP = dipeptidyl peptidase; GLP = glucagon-like peptide.

DPP-IV inhibitors

An alternative approach to the use of GLP-1 mimetics is to inhibit the breakdown of endogenous GLP-1. DPP-IV inhibitors mimic many actions of the GLP-1 mimetics, including the stimulation of insulin, inhibition of glucagon secretion and preservation of β-cell mass.[30] DPP-IV inhibitors are not typically associated with decreased gastric emptying or clinically significant weight loss.

Several DPP-IV inhibitors are in development and have the advantage of oral administration. Currently licensed available agents include sitagliptin, vildagliptin and saxagliptin. Clinical studies have shown that vildagliptin is associated with a −0.8% change in HbA_{1c} when combined with metformin therapy.[31] As a monotherapy, similar reductions in HbA_{1c} are seen compared with metformin[32] and rosiglitazone.[33] Clinical studies with sitagliptin have shown a −0.65% change in HbA_{1c} when combined with metformin therapy.[34] Monotherapy at a dose of 100 mg/day is associated with a −0.79% change in HbA_{1c}.[35]

Adverse effects

The main adverse effect associated with DPP-IV inhibitors is hypoglycaemia, apparent on combination with sulphonylurea. For this reason, dose reduction and caution are advised when commenced in addition to these agents. The other main adverse effects associated with DPP-IV inhibitors are shown in Table 2.

Conclusions

The use of therapeutic agents that enhance the incretin effect is an important and rapidly developing area of interest within diabetic medicine. Prior to their advent all traditional

available therapies apart from metformin were associated with weight gain. Furthermore, sulphonylureas and insulin are associated with the further risk of hypoglycaemia. Newer GLP-1 mimetics are in development and phase III trials well underway with long-acting preparations such as exenatide LAR which is administered once weekly. This promising agent has shown a reduction in HbA_{1c} of 1.4–1.7% and weight reductions up to 3.8 kg over a 15-week period.[36] Incretin-based therapies offer great potential, but further experience with routine clinical practice is required and long-term evidence on benefit with regard to the micro- and macrovascular complications of T2DM.

Conflict of interest

Dr Stephens has received speaker fees from Lilly and research grant support from Novonordisk.

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Cardiovascular risk and prevention in diabetes mellitus

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Cardiovascular risk in type 2 diabetes

Pathophysiology

Historically, disease of the cardiovascular system accounts for the death of approximately 70% of people with diabetes mellitus (DM).[1] Type 2 DM (T2DM) increases the risk of cardiovascular disease (CVD) 2–4 times.[2] Type 1 DM (T1DM) also markedly increases the risk of premature CVD.[3]

The pathophysiology of CVD in diabetes is complex and not dependent on the effects of hyperglycaemia alone. In T2DM a constellation of risk factors contribute to the development of early CVD, including hypertension and dyslipidaemia. These result in metabolic changes which, coupled with a sedentary lifestyle, obesity and smoking, enhance the deleterious effects of hyperglycaemia and accelerate atherosclerotic disease in the vasculature. People with T1DM are generally diagnosed at a young age and exposure to hyperglycaemia takes place over a prolonged time period compared with T2DM. CVD in T1DM may relate more closely to the burden of hyperglycaemia and its complications.[4]

Over 90% of people with DM have T2DM, and the prevalence is accelerating in the developed and developing world. The current prevalence of diabetes in adults in the UK is estimated to be 7.4%,[5] though rates may be higher in certain ethnic and patient subgroups. This article considers the pathophysiology of CVD in T2DM, the management of cardiovascular risk in this population and the tools available for assessment of cardiovascular risk in T2DM. A brief summary of the pathophysiology, assessment and management of cardiovascular risk in T1DM will also be provided. People with diabetes benefit from secondary prevention strategies at least as much as those without diabetes. This article focuses on primary prevention of cardiovascular events.

The earliest stages in the development of atherosclerosis involve the adhesion and migration of monocytes through the vascular endothelium and into the vascular intima. This may be facilitated by the pro-inflammatory, procoagulant and vasoconstricted state associated with diabetes. Within the intima, monocytes transform into macrophages and take up modified lipoproteins resulting in foam cell formation. Foam cells accumulate within the vascular wall to form a fatty streak. With the recruitment of smooth muscle cells, low-grade chronic inflammation and modulation of the extracellular matrix, the atherosclerotic plaque develops. This comprises a fibrous outer layer in contact with the plasma overlying a procoagulant lipid-rich core. The rupture or erosion of any part of this fibrous cap exposes the procoagulant lipid to the circulating plasma, resulting in platelet activation, thrombosis and an acute vascular event. This atherosclerotic process is accelerated in T2DM (summarised in Fig 1).

Many people with T2DM are also hypertensive[6] which contributes to the premature development of vascular disease. Diabetes is associated with a typical dyslipidaemia comprising mildly elevated levels of small dense low-density lipoprotein (LDL), reduced levels and altered composition of high-density lipoprotein (HDL) and increased triglyceride-rich lipoprotein particles. Glycated, small dense LDL is associated with increased oxidative stress within the vasculature, while reduced concentrations of altered HDL are less able to participate in atheroprotective functions such as reverse cholesterol transport.