Review

Beyond glucose lowering: Glucagon-like peptide-1 receptor agonists, body weight and the cardiovascular system

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Abstract

Aim. – Glucagon-like peptide-1 (GLP-1) belongs to the incretin hormone family: in the presence of elevated blood glucose, it stimulates insulin secretion and inhibits glucagon production. In addition, GLP-1 slows gastric emptying. GLP-1 secretion has also been reported to potentially affect patients with type 2 diabetes (T2DM) compared with non-diabetics and, as enzymatic inactivation by dipeptidyl peptidase-4 (DPP-4) shortens the GLP-1 half-life to a few minutes, GLP-1 receptor agonists such as exenatide twice daily (BID) and liraglutide have been developed, and have become part of the management of patients with T2DM. This review focuses on the potential beneficial effects of these compounds beyond those associated with improvements in blood glucose control and weight loss, including changes in the cardiovascular and central nervous systems.

Methods. – This was a state-of-the-art review of the literature to evaluate the relationships between GLP-1, GLP-1 receptor agonists, weight and the cardiovascular system.

Results. – GLP-1 receptor agonists improve glucose control and do not significantly increase the risk of hypoglycaemia. Also, this new class of antidiabetic drugs was shown to favour weight loss. Mechanisms may involve central action, direct action by reduction of food intake and probably indirect action through slowing of gastric emptying. The relative importance of each activity remains unclear. Weight loss may improve cardiovascular outcomes in patients with T2DM, although GLP-1 receptor agonists may have other direct and indirect effects on the cardiovascular system. Reductions in myocardial infarct size and improvements in cardiac function have been seen in animal models. Beneficial changes in cardiac function were also demonstrated in patients with myocardial infarcts or heart failure. Indirect effects could involve a reduction in blood pressure and potential effects on oxidation. However, the mechanisms involved in the pleiotropic effects of GLP-1 receptor agonists have yet to be completely elucidated and require further study.

Conclusion. – These compounds may play an important role in the treatment of patients with T2DM as their potential effects go beyond glucose-lowering (weight loss, potential improvement of cardiovascular risk factors). However, to better understand their place in the management of T2DM, further experimental and clinical prospective studies are required.

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Keywords: GLP-1; Exenatide twice daily (BID); Liraglutide; Weight; Cardioprotection; Review

Résumé

Au-delà du contrôle glycéémique : GLP-1, agonistes du récepteur du GLP-1, poids et appareil cardiovasculaire.

Introduction. – Le «glucagon-like peptide-1» (GLP-1) est une hormone de la famille des incrétines: en présence de glucose il stimule la sécrétion d’insuline et inhibe la production de glucagon. En outre, le GLP-1 ralentit la vidange gastrique. Dans la mesure où la sécrétion de GLP-1 en réponse à l’alimentation a été rapportée comme potentiellement diminuée au cours du diabète de type 2 (DT2) et où l’inactivation enzymatique par la dipeptidylpeptidase-4 (DPP-4) réduit la demi-vie du GLP-1 à quelques minutes, des analogues du GLP-1 tels que l’exénatide et le liraglutide ont été développés et font maintenant partie de la stratégie thérapeutique pour les patients présentant un DT2. Cette revue s’intéresse aux potentiels effets bénéfiques de ces composés, au-delà de ceux associés à l’amélioration du contrôle de la glycémie et à la perte de poids (effets potentiels sur les facteurs de risque cardiovasculaire).

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Méthodes. – Revue de la littérature concernant les relations existantes entre GLP-1, agonistes du récepteur du GLP-1, poids et appareil cardiovasculaire.

Résultats. – Les agonistes du récepteur du GLP-1 améliorent l’équilibre glycémique sans induire de prise de poids ou d’hypoglycémie. Au contraire, cette nouvelle classe de médicaments anti-diabétiques favorise la perte de poids. Les mécanismes impliqués sont multiples: une action centrale directe par la réduction des prises alimentaires, et indirecte par le ralentissement de la vidange gastrique. Mais l’importance relative de chacun de ces phénomènes n’est pas encore bien définie. La perte de poids pourra améliorer le pronostic cardiovasculaire des patients ayant un DT2 mais les agonistes du récepteur du GLP-1 peuvent avoir également des effets directs et indirects sur l’appareil cardiovasculaire. Une action de réduction de la taille des infarctus du myocarde et une amélioration de la fonction cardiaque a été montrée dans des modèles animaux. Chez l’homme, de potentiels effets bénéfiques sur la fonction cardiaque ont été retrouvés chez des patients avec infarctus ou insuffisance cardiaque. Les effets indirects pourraient impliquer une baisse de la pression artérielle et des effets éventuels sur l’oxydation. Les mécanismes impliqués dans les effets pléiotropes des agonistes du récepteur du GLP-1 ne sont pas totalement connus et restent encore à éclaircir.

Conclusion. – Cette classe thérapeutique pourrait jouer un rôle important dans le traitement des patients ayant un DT2, en raison de leurs effets allant au-delà du contrôle glycémique (perte de poids, amélioration potentielle des facteurs de risque cardiovasculaire). Cependant, afin de mieux comprendre la place de ces composés dans la prise en charge du diabète de type 2, de plus amples analyses expérimentales et essais cliniques sont nécessaires.

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Mots clés : GLP-1 ; Exénatide ; Liraglutide ; Poids ; Cardioprotection ; Revue générale

1. Introduction

Glucagon-like peptide-1 (GLP-1) is derived from proglucagon, and mainly synthesized by intestinal L cells in response to meals [1]; it is a peptide hormone belonging to the incretin hormone family together with glucose-dependent insulinotropic peptide (GIP). The incretin effect describes the higher insulin secretion resulting from oral absorption of glucose compared with intravenous (IV) glucose-induced secretion for a similar blood glucose rise [1]. In healthy individuals, GLP-1 and GIP account for 20 to 60% of postprandial insulin release, depending on the size of the glucose load [2].

In addition to the effect on insulin secretion, incretins also modify glucagon secretion and gastric emptying [1,2]. Blocking the action of endogenous GLP-1 in non-diabetic healthy subjects causes an approximately 80% increase in postprandial glucagon secretion [3], indicating a major action on glucagon inhibition. GLP-1 also slows gastric emptying, which affects postprandial glucose concentrations [4]. The effect of GLP-1 receptor agonists on insulin sensitivity has been shown to be limited [5–7]. However, in experiments, exendin-4 (a GLP-1 receptor agonist) has been found to reverse hepatic steatosis in mice [8], and there is anecdotal evidence of similar changes in humans [9]. GLP-1 and GLP-1 receptor agonists increase β-cell mass and pancreatic islet size in rodents [10,11], and inhibit apoptosis of β cells [12–14].

There is growing evidence that GLP-1 secretion is not much affected in patients with type 2 diabetes (T2DM) compared with healthy non-diabetics [15,16], and some studies have even shown no differences at all [17–19]. However, administration of GLP-1 receptor agonists at pharmacological doses has been identified as an interesting therapeutic option in T2DM. As GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) and has a relatively short half-life (less than 10 min) [20], two different strategies have been developed to increase the incretin effect: inhibition of GLP-1 degradation by DPP-4 using DPP-4 inhibitors; and using GLP-1 receptor agonists that are resistant to DPP-4-mediated degradation [21]. Exenatide twice daily (BID) was launched in the US in June 2005 and in European markets in November 2006, while liraglutide was launched in January 2010 in the US and in July 2009 in Europe.

When added to oral antidiabetic therapy, GLP-1 receptor agonists provide better glucose control than do DPP-4 inhibitors, particularly the long-acting formulations (HbA_{1c} range change vs baseline: with GLP-1 receptor agonists, −0.4% to −1.9%; with DPP-4 inhibitors, −0.2% to −1.0%) [22–41]. Thus, GLP-1 receptor agonists are superior to DPP-4 inhibitors in terms of blood glucose reduction [42,43]. While GLP-1 receptor agonists are associated with significant weight loss (weight-lowering range from baseline: −0.9 to −3.7 kg), DPP-4 inhibitors are relatively weight neutral (+2.7 to −1.5 kg from baseline) [22–41]. With both agents, the risk of mild-to-moderate hypoglycaemic events is similar compared with placebo in combination with metformin with or without thiazolidinedione (percentage of patients experiencing mild-to-moderate hypoglycaemic events: with GLP-1 receptor agonists, 3 to 10.7%; with DPP-4 inhibitors, 1.1 to 7.0%) [22–41]. However, when each is used together with sulphonylurea, the risk of hypoglycaemia is increased (percentage of patients experiencing mild-to-moderate hypoglycaemic events: with GLP-1 receptor agonists, 14 to 36%; with DPP-4 inhibitors, 7.5 to 14.6%) [22–41].

GLP-1 receptor agonists and DPP-4 inhibitors may have beneficial effects beyond those associated with improvements in blood glucose control and weight loss. Indeed, GLP-1 receptor agonists have also been reported to have actions on the cardiovascular (CV) and central nervous systems [44].

The present review focuses on the effects of GLP-1 and GLP-1 receptor agonists beyond blood glucose control, including body-weight changes and the CV system.

2. Methods

A literature search was conducted using the key words ‘incretin hormones’, ‘GLP-1’ and ‘GLP-1 receptor agonists’. Abstracts captured by this search of MEDLINE (1966 up to
the present) were then screened against their relevance to the topics ‘body weight’ and ‘cardiac function’ (including ‘blood pressure’, ‘lipids’, ‘endothelial function’ and ‘myocardium’). Articles were included in the searches if they met the following criteria:

1) reports published in the English language;
2) studies in vitro or in vivo (animals and human subjects);
3) clinical studies with only adult samples (age 18 years or older).

As for class of GLP-1 receptor agonists, the focus was on treatments approved in Europe by regulatory agencies: exenatide twice daily (BID); liraglutide once daily; and exenatide once weekly (QW).

2.1. GLP-1 and GLP-1 receptor agonist effects on body weight

GLP-1 secretion appears to be lower in obese patients [19], but the mechanism by which obesity reduces GLP-1 secretion is not known, although it is likely to be associated with insulin resistance [45]. However, it should be noted that some studies have not confirmed the lower GLP-1 secretion in obese patients, but these were carried out in a very small sample population [46].

In obese patients with normal or impaired glucose tolerance, or impaired fasting glucose, following a lifestyle-modification programme, exenatide BID induced a placebo-subtracted 3.3 ± 0.5% decrease in weight (P < 0.001), and normalization of glucose tolerance in 77% of cases (vs 56% in the placebo group) [47]. In non-diabetic obese patients [body mass index (BMI) 30–40 kg/m²], liraglutide 1.2 to 3.0 mg once a day for 20 weeks induced significantly greater weight loss than either placebo or orlistat 120 mg (three times a day orally) [48], with more subjects (76%) losing more than 5% body weight with liraglutide 3.0 mg than with either placebo (30%) or orlistat (44%).

Until now, one disadvantage of anti-diabetic treatments such as sulphfonylurea, thiazolidinedione and insulin was the weight gain they caused in T2DM patients. For the first time, with GLP-1 receptor agonists, this weight gain can be reduced in addition to the improvement in blood glucose control. Exenatide BID, exenatide QW and liraglutide have all demonstrated, in addition to their effects on blood glucose control, beneficial effects on body weight. However, the link between the weight loss following the administration of GLP-1 receptor agonists and the improvement in blood glucose control requires further evaluation. So far, it is not clear what aspects of the two effects are relevant.

In overweight or obese patients with T2DM treated with metformin and/or sulphonylurea, exenatide BID combined with a lifestyle-modification programme has been shown to induce, over a 24-week period, greater changes in weight (−6.16 ± 0.54 kg vs −3.97 ± 0.52 kg; P = 0.003) and in HbA1c (−1.21 ± 0.09% vs −0.73 ± 0.09%; P < 0.0001) than lifestyle modification alone [49]. Exenatide BID 10 μg has also led to significant placebo-adjusted reductions in weight and HbA1c over a 30-week period in patients receiving metformin (−2.8 ± 0.5 kg and −0.78 ± 0.10%; P < 0.001 and P < 0.002, respectively) [22], sulphfonylurea (−1.6 ± 0.3 kg and −0.86 ± 0.11%; P < 0.05 and P < 0.001, respectively) [23] or a metformin–sulphonylurea combination (−1.6 ± 0.2 kg and −0.8 ± 0.1%; P < 0.01 and P < 0.0001, respectively) [24]. These weight losses were dose-dependent, with greater reductions with exenatide BID 10 μg vs 5 μg [22–24]. An open-label extension of these three studies (the AC2993: Diabetes management for improving glucose outcomes or AMIGO studies) showed that the results were sustained over 3 years in the complete population, with a mean reduction in HbA1c from baseline of 1.0 ± 0.1% (P < 0.0001) and weight loss of 5.3 ± 0.4 kg (P < 0.0001); 84% of patients lost weight (68% concomitantly improved their HbA1c) whereas 16% gained weight (6% concomitantly worsened their HbA1c) [50]. There were similar findings in a post-hoc analysis of two large trials [51] (n = 1047) in which exenatide-treated patients had similar blood glucose control compared with insulin-treated patients (glargine or biphasic insulin aspart): 73.3% of the exenatide-treated patients lost weight (averaging 3 kg by the endpoint, with approximately 22% achieving a weight loss greater or equal to 5% and 3.2% achieving greater or equal to 10%) while 75.9% of the insulin-treated patients gained, on average, 3 kg and only 2% achieved a weight loss greater or equal to 5% (and weight loss greater or equal to 10% in 0.2%). In patients with inadequate glucose control with the metformin–sulphonylurea–thiazolidinedione combination, other studies have shown similar glucose control improvements with exenatide and insulin (HbA1c decrease range: with exenatide, −0.8 ± 0.1% to −1.75 ± 1.57%; with insulin, −0.7 ± 0.2% to −2.76 ± 1.79%), whereas weight loss was observed with exenatide vs weight gain with insulin (weight loss with exenatide: −1.9 ± 3.8 kg to −4.1 ± 0.22 kg; weight gain with insulin: 1.0 ± 0.8 kg to 4.1 ± 5.4 kg) [6,52–55].

As for liraglutide, 26-week studies in patients treated with metformin plus thiazolidinedione reported improvements in blood glucose control (reduction of HbA1c vs placebo: liraglutide 1.2 mg, −0.9% to −1.1%; liraglutide 1.8 mg, −1.1%) associated with weight loss in the liraglutide-treated groups in a dose-dependent manner (weight reduction range from baseline: liraglutide 1.2 mg, −1.0 to −2.6 kg; liraglutide 1.8 mg, −2.0 to −2.8 kg) [29,30]. In the Liraglutide Effect and Action in Diabetes (LEAD)-5 study, liraglutide 1.8 mg reduced HbA1c significantly vs insulin glargine (−0.24%, 95% CI: 0.08–0.39%; P = 0.0015) and placebo (−1.09%, 95% CI: 0.90–1.28%; P < 0.0001), and induced greater weight loss vs insulin (−3.43 kg, 95% CI: 4.00–2.86 kg; P < 0.0001) and placebo (−1.39 kg, 95% CI: 2.10–0.69 kg; P = 0.0001) [28].

Comparison of exenatide BID 10 μg and liraglutide 1.8 mg in the LEAD-6 study showed similar weight losses (liraglutide: −3.24 ± 0.33 kg; exenatide BID: −2.87 ± 0.33; P = 0.2235) and similar proportions of participants who lost weight (liraglutide: 78%; exenatide BID: 76%), but there was significantly better glucose control with liraglutide 1.8 mg than with exenatide BID 10 μg (estimated treatment difference: −0.33; 95% CI: −0.47 to −0.18; P < 0.0001) [27].

In comparison to exenatide BID after 30 weeks of treatment, exenatide QW induced greater reductions in HbA1c
between weight loss and nausea in GLP-1 receptor agonist-

−sensitivity C-reactive protein (hsCRP) and leptin levels together

ment [62].

−exenatide BID, and was associated with reduced fasting high-

energy balance and weight loss [75]. However, it was also shown

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tor within the brainstem and hypothalamus [79]. These neuronal

GLP-1 projections probably receive signals via vagal afferents,

accounting for the amplification of the rapidly fading peripheral

GLP-1 signal [80]. Thus, peripheral and central GLP-1 actions

appear to cooperate to regulate food intake and loss of body

weight.

Nevertheless, the mechanism remains unclear: central effects of

exenatide are apparently relatively insensitive to GLP-1 receptor

antagonism, suggesting that exenatide acts partly independently of the GLP-1 receptor [81]. Yet, GLP-1 receptor

presence is required for the effect, as central exenatide has no

−1.5 ± 0.1%, 95% CI: −0.54 to −0.12%;

P = 0.0023) and similar weight losses (−3.7 ± 0.5 kg vs

−3.6 ± 0.5 kg, 95% CI: −1.3 to 1.1 kg; P = 0.89) in T2DM

patients treated with metformin [26]. These results were main-

tained after an open-label extension of 52 weeks (for the

complete population: HbA1c reduction least-squares mean:

−2.0%, 95% CI: −2.1 to −1.8%; weight loss: −4.1 kg, 95% CI:

−5.3 to −2.9 kg) [56]. Similar reductions of body weight have

been found in high concentrations in the hypothalamus, which is defi-


cient in blood–brain barrier (BBB) and, thus, may be accessible

through the BBB [78].

The effects on appetite reduction and gastric emptying

could also be related to GLP-1 central effects. Some rodent

studies have demonstrated that intracerebroventricular GLP-1

administration caused an anorectic response, and that repetitive

administration of GLP-1 receptor agonists resulted in negative

energy balance and weight loss [75]. However, it was also shown

that central GLP-1 and GLP-1 receptor agonists differ significan-

tly in potency and duration of action: intracerebroventricular

exenatide was 100 times more potent than GLP-1 at reduc-

ing food intake in rats [76]. Furthermore, GLP-1 receptors are

found in high concentrations in the hypothalamus, which is defi-


cient in blood–brain barrier (BBB) and, thus, may be accessible to circulating peripheral GLP-1. As the hypothalamus [77] is

involved in the control of food intake and satiety by influencing

the neuropeptide Y pathway [78], peripheral GLP-1 may have

important central effects on eating and energy balance. There is also evidence that circulating GLP-1 receptor agonists can activate

central nervous system cells [75], and that GLP-1 can cross the

BBB [78].

GLP-1 is also produced by a small group of nerve cells in the

nucleus of the tractus solitarius, and released as a neuromodula-

tor within the brainstem and hypothalamus [79]. These neuronal

GLP-1 projections probably receive signals via vagal afferents,

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antagonism, suggesting that exenatide acts partly independently of the GLP-1 receptor [81]. Yet, GLP-1 receptor

presence is required for the effect, as central exenatide has no

A substudy of the LEAD-2 and -3 trials showed that the reduction in weight with liraglutide as monotherapy or in

combination with metformin was mainly due to a reduction

in weight with liraglutide as monotherapy or in

comparison with exenatide QW compared with sitagliptin or

pioglitazone after 26 weeks of treatment (treatment differences:

−1.5 kg, 95% CI: −2.4 to −0.7 kg; P = 0.0002 vs −5.1 kg, 95% CI:

−5.9 to −4.3 kg; P < 0.0001) [57].

With liraglutide, an analysis of changes in weight throughout

the LEAD trials showed that, after stratification by BMI (≥30

vs <30 kg/m²), there was greater weight loss in those with a

higher BMI [58]. Similar results were found with exenatide BID

in the 82-week open-label extension of the three AMIGO

studies, where baseline BMI influenced the variation in weight loss:

weight reduction −2 kg (2.9% of baseline body weight) for com-

pleters with BMI less than 25 kg/m²; and greater or equal to 7 kg

with BMI greater than 40 kg/m² (5.5% of baseline body weight)

[59].

exenatide BID and was associated with reduced fasting high-

sensitivity C-reactive protein (hsCRP) and leptin levels together

in combination with metformin was found to be a reduction in

fat tissue that was significant compared with glimepiride

[60]. With liraglutide 1.2 mg and 1.8 mg, visceral adipose tissue

area was reduced from baseline by −30.6 cm² (17%) and

−30.4 cm² (16%), respectively, compared with −5.3 cm² (5%) in

the comparator group. For subcutaneous adipose tissue, the

area reductions from baseline were −23.6 cm² (8%) for the

1.2-mg dose and −26.3 cm² (9%) for the 1.8-mg dose [vs

+6.7 cm² (3%) in the glimepiride group]. A similar effect on

body fat reduction compared with insulin glargine was seen with

exenatide BID, and was associated with reduced fasting high-

sensitivity C-reactive protein (hsCRP) and leptin levels together

with an increase in fasting total adiponectin concentration [61].

In patients treated with exenatide BID vs insulin-treated patients,

body weight decreased (−4.0 ± 1.0 kg vs +0.4 ± 1.0 kg, 95% CI

difference: −6.8 to −2.1 kg; P = 0.0004), with significant

reductions in body fat mass (−2824 ± 774 g vs +288 ± 797 g,

95% CI: −4938 to −1285; P = 0.0012) and waist circumference

(−5.3 ± 1.0 cm vs +1.0 ± 1.0 cm, 95% CI: −8.7 to −4.0 cm;

P < 0.0001) [61]. These results were confirmed by the European

Exenatide (EUREXA) study, a long-term, prospective, open-

label study comparing the effects of exenatide and glimepiride on

the maintenance of glycaemic control after 9 months of treat-

ment [62].

Furthermore, these weight benefits were not associated with

gastrointestinal adverse events. Indeed, data from the liraglutide

and exenatide BID trials have reported no significant association

between weight loss and nausea in GLP-1 receptor agonist-
treated patients [22,23,25,29,30]. This finding suggests that the

effects on weight loss are mediated by other mechanisms. In

some studies, weight loss tends to be higher in patients with

nausea compared with patients without nausea, but the difference

remained non-significant [22,23,25,29,30].
effect on food intake or weight in GLP-1-receptor-deficient mice [82]. In their meta-analysis, Bradley et al. [83] found that exenatide decreases energy intake and increases energy expenditure in humans. However, the relative importance of each mechanism on weight loss is difficult to determine, as studies in this field are not consistent.

Weight loss may be beneficial in terms of improvement of insulin resistance. As insulin resistance is one of the key mechanisms of T2DM, it is important to act on this parameter. However, how this effect occurs is unknown: does it involve weight loss itself, endogenous GLP-1 secretion or a direct effect of GLP-1 receptor agonists? Weight loss may significantly impact glucose metabolism and insulin resistance through decreases in body mass and changes in the release of circulating levels of adipocytokines, such as leptin and adiponectin [84,85]. The investigation of insulin resistance changes in insulin-resistant obese patients after a 6-month restricted-calorie and exercise program showed weight loss (−6.9 ± 0.1 kg) associated with a significant reduction in plasma leptin (27.8 ± 3 vs 23.6 ± 3 ng/mL), and an improvement in sensitivity index from 1.8 ± 0.3 10−4 min−1 (mU/mL)−1 to 2.9 ± 0.4 10−4 min−1 (mU/mL)−1 [86]. However, weight loss from lifestyle modifications is generally short-lived. As a result, the net improvement in glucose metabolism and insulin resistance generally disappears within 1 year of weight loss [87].

After bariatric surgery, patients lose 50 to 70% of body weight, and their incretin secretion is improved [88–90]. Furthermore, in those with T2DM, 87% achieve at least better glucose control with a need for fewer antidiabetic medications, and an average of 78% achieve normal glycemic control without the need for any antidiabetic medications at all [88–90]. Many studies have suggested that the improvement in insulin secretion after bariatric surgery occurs rapidly [91–94]. Thus, it may not be wholly accounted for by weight loss, but may perhaps be a consequence of changes in incretin secretion. Indeed, robust increases in postprandial levels of GLP-1, occurring prior to marked weight loss, have been demonstrated [95–98].

The potential effect of GLP-1 receptor agonist on insulin resistance in animal models has been investigated, but the molecular mechanisms of the effects of GLP-1 on β-cell mass are still poorly understood [99,100]. In patients with T2DM, the effects of exenatide BID on insulin resistance have also been studied [6]. Beta-cell function and insulin sensitivity were measured during an arginine-stimulated hyperglycemic clamp at week 0, week 52 and after a 4-week off-drug period in T2DM patients treated with metformin and exenatide BID or insulin glargine. Treatment with exenatide and insulin glargine improved insulin sensitivity to a similar extent (0.9 ± 0.3 and 1.1 ± 0.3 mg/min/kg, respectively; P = 0.49). After a 4-week discontinuation of study medication, the M value was not significantly different from pretreatment values in the insulin-glargine-treated group, whereas it remained significantly higher in the exenatide-treated group (between-group difference: 0.8 ± 0.4 mg/min/kg; P = 0.03). After 52 weeks of treatment, the exenatide group demonstrated a significant increase in all measures of β-cell function.

Accordingly, exenatide treatment significantly increased first- and second-phase glucose-stimulated C-peptide secretion by 1.53 ± 0.11 times and 2.85 ± 0.22 times, respectively (P < 0.0001), compared with insulin glargine. The C-peptide response to arginine during hyperglycaemia increased by 3.19 (± 0.24) times from pretreatment in the exenatide group compared with a 1.31 (± 0.07)-fold increase in the insulin-glargine group (between-group difference: 2.46 ± 0.20 times; P < 0.0001). At 4 weeks after discontinuation of the study medication, measures of β-cell function returned to pretreatment values in both groups [6].

For this reason, the effects of an additional 2 years of therapy have also been studied [101]. Exenatide BID and insulin glargine sustained HbA1c over 3 years of treatment, while exenatide BID reduced, and insulin glargine increased, body weight. Compared with insulin glargine, exenatide improved glucose- and arginine-stimulated C-peptide secretion [results for exenatide BID vs insulin glargine: C-peptide iAUC260–270 min ratio to pretreatment, 1.02 ± 0.11 vs 1.06 ± 0.10 (P = 0.665); first-phase C-peptide AUC180–190 min ratio to pretreatment, 0.88 ± 0.09 vs 1.08 ± 0.10 (P = 0.038); and second-phase C-peptide AUC190–260 min ratio to pretreatment, 0.97 ± 0.08 vs 1.17 ± 0.08 (P = 0.017)]. Following cessation of both 3-year treatments, β-cell function, measured as the disposition index, remained significantly improved in the exenatide-treated patients vs insulin glargine (+1.43 ± 0.78 for exenatide BID vs −0.99 ± 0.65 for insulin glargine; P = 0.028). These results suggest that prolonged treatment with exenatide may be necessary to achieve any beneficial effects on β-cell function.

Weight loss by itself could be beneficial in terms of CV outcomes [102]. However, GLP-1 receptor agonists may also have direct CV effects that are not attributable to weight loss alone [103].

### 2.2. GLP-1, GLP-1 receptor agonists, cardiovascular risk factors and cardiac function

Exenatide BID has been associated with significant improvements in cardiometabolic risk factors and anthropometric parameters in patients with the metabolic syndrome [104].

#### 2.2.1. GLP-1, GLP-1 receptor agonists and blood pressure

Regarding blood pressure (BP), the clinical effect of GLP-1 in animal models is not clear: some studies demonstrated an increase [79,105], while another reported a reduction in BP [85]. Measurable changes in kidney function have been observed during treatment with GLP-1: in healthy subjects as well as in insulin-resistant obese men, GLP-1 was associated with natriuresis and a reduction in H+ excretion and glomerular hyperfiltration with a potential renoprotective effect [106].

In human trials, GLP-1-receptor-agonist treatment was associated with a reduction of BP associated with a slight increase in heart rate [27,28,49,107]. Some studies of longer duration of exenatide BID use have also suggested improvement in BP [49,52,108–110], notably in patients with abnormally high baseline systolic BP [108]. In shorter-term trials, clinical pharmacology studies demonstrated small increases in heart rate

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[111,112], which have also been specifically described in a recent study [113]. The results of that study, which included patients with T2DM taking metformin and/or thiazolidinedione randomized to receive either exenatide BID or a placebo, suggested that 12 weeks of exenatide BID had no significant effect on 24-h heart rate, whereas a trend towards lower 24-h daytime and night-time systolic BP was observed [113].

Over 82 weeks of exenatide BID treatment, a significant reduction vs baseline in systolic/diastolic BP in 314 overweight patients with T2DM averaged −1.3/−2.7 mmHg (95% CI: −3.1 to +0.5/−3.8 to −1.7 mmHg), with even greater changes observed in the quartile of patients who lost more weight (on average: −3.9/−4.4 mmHg) [59].

In a study combining exenatide BID or placebo with a lifestyle-modification programme in 194 overweight or obese patients with T2DM treated with metformin and/or sulphonylurea, those treated with exenatide over a 24-week period observed a greater decrease vs placebo in both systolic (−9.44 ± 1.40 vs −1.97 ± 1.40 mmHg; P < 0.001) and diastolic (−2.22 ± 1.00 vs 0.47 ± 0.99 mmHg; P = 0.04) BP [49].

However, a larger analysis of six exenatide BID trials, including 2171 patients treated for at least 6 months, showed no differences in diastolic BP compared with placebo or insulin, but a significant change in systolic BP compared with placebo (−2.8 ± 0.75 mmHg; P = 0.0002) and insulin (−3.7 ± 0.85 mmHg; P < 0.0001); these differences reached −3.8 ± 1.08 mmHg (P = 0.0004) and −4.0 ± 1.01 mmHg (P < 0.0001), respectively, in patients with systolic BP greater or equal to 130 mmHg [108].

As for trials of liraglutide, this GLP-1 receptor agonist was also associated with systolic BP reduction, but no changes in diastolic BP. In the LEAD-2 study, liraglutide 1.2 mg and 1.8 mg for 26 weeks led to significant reductions in systolic BP compared with placebo and glimepiride in T2DM patients taking metformin: liraglutide 1.2 mg, −3.2 mmHg (P = 0.0128); liraglutide 1.8 mg, −2.7 mmHg (P = 0.0467) [29]. A study comparing liraglutide with insulin glargine and placebo in T2DM patients treated with metformin plus glimepiride also showed a significant reduction in systolic BP with liraglutide vs insulin glargine (−4.51 mmHg, 95% CI: −6.82 to −2.20 mmHg; P = 0.0001), but not vs placebo (−2.53 mmHg, 95% CI: −5.36 to 0.29 mmHg; P = 0.0791) [28]. However, liraglutide 1.2 mg and 1.8 mg in association with metformin and rosiglitazone were associated with significant reductions in systolic BP compared with placebo [placebo-corrected difference: liraglutide 1.2 mg, −5.6 mmHg (P < 0.001); liraglutide 1.8 mg, −4.5 mmHg (P = 0.0009)] [29]. Minor, but significant, changes in pulse rate with all doses of liraglutide were shown vs placebo (liraglutide: +2 to +4 bpm; placebo: −1 to +0.9 bpm) [27,28].

Trials with exenatide QW also reported a reduction in BP in T2DM patients. After 30 weeks of treatment, patients treated with exenatide QW showed similar, significant improvements in systolic and diastolic BP as those treated with exenatide BID (systolic BP changes from baseline: exenatide QW, −4.7 ± 1.1 mmHg; exenatide BID, −3.4 ± 1.1 mmHg; diastolic BP changes from baseline: exenatide QW, −1.7 ± 0.7 mmHg; exenatide BID, −1.7 ± 0.7 mmHg) [26]. These results with exenatide QW were maintained at 52 weeks (systolic BP: −6.2 mmHg, 95% CI: −8.5 to 3.9 mmHg; diastolic BP: −2.8 mmHg, 95% CI: −4.3 to −1.3 mmHg) [56]. After 26 weeks of treatment, the reduction in systolic BP was significantly greater with exenatide QW than with sitagliptin in T2DM patients treated with metformin (difference: −4 mmHg, 95% CI: −6 to −1 mmHg) [57].

Exenatide BID and liraglutide have both been associated with reductions in BP, and no significant differences between these two treatments were observed in a comparative study [26]. Weight loss may have contributed to the BP decrease. However, systolic BP changes occurred early in the trials and preceded weight loss. Thus, it is unlikely that BP decreases can be attributed to body-weight reductions only [23,112–116].

2.2.2. GLP-1, GLP-1 receptor agonists and lipids

In healthy volunteers, GLP-1 infusion in the fasting state has been associated with improvements in postprandial triglycerides presumably as a result of delayed gastric emptying [117]. Indeed, after test-meal ingestion, gastric emptying was delayed by GLP-1 compared with placebo, and the postprandial increase in triglyceride levels was completely eliminated by GLP-1 (change in triglycerides: −0.023 ± 0.045 mmol/L; P < 0.05) [118].

Variations in lipid parameters have also been observed in T2DM patients treated with GLP-1 receptor agonists. After a 3.5-year open-label extension study, lipid parameters improved: the reduction in total cholesterol was −5% (P = 0.0007); low-density lipoprotein (LDL) cholesterol was reduced by −6% (P < 0.0001) and triglycerides by −12% (P = 0.0003); and high-density lipoprotein (HDL) cholesterol increased by +24% (P < 0.0001) in completers treated with exenatide BID (age: 57 ± 9 years; duration of diabetes: 8 ± 6 years; baseline HbaA1c: 8.2 ± 1.0%; baseline BMI: 33.4 ± 5.4 kg/m²) [50].

As for liraglutide, patients treated with 1.2 mg of liraglutide, metformin and rosiglitazone reported reductions in LDL cholesterol (−0.28 ± 0.07 mmol/L; P < 0.05), triglycerides (−0.38 ± 0.10 mmol/L; P < 0.05) and free fatty acids (FFA; −0.03 ± 0.02 mmol/L; P < 0.05) vs placebo, whereas the 1.8-mg dose significantly reduced only FFA levels vs placebo (−0.05 ± 0.02 mmol/L; P < 0.05) [29]. A meta-analysis of six trials of liraglutide reported reductions in total cholesterol (−0.13 mM; P < 0.01), LDL cholesterol (−0.20 mM; P < 0.0001), FFA (−0.09 mM; P < 0.0001) and triglycerides (−0.20 mM; P < 0.01) compared with baseline in the intention-to-treat population [119].

The LEAD-6 study, comparing exenatide BID 10 µg and liraglutide 1.8 mg, reported similar reductions in total (−0.20 ± 0.07 vs −0.09 ± 0.07 mmol/L; P = 0.0946) and LDL (−0.44 ± 0.06 vs −0.40 ± 0.06 mmol/L; P = 0.4412) cholesterol, and a greater reduction in triglycerides (−0.41 ± 0.10 vs −0.23 ± 0.10 mmol/L; P = 0.0485) in the liraglutide group [27].

With exenatide QW in the DURATION-1 study, significant reductions from baseline were seen in total cholesterol, LDL cholesterol and triglycerides. The improvement in total and LDL cholesterol was significantly greater with this formulation than with exenatide BID [56]. However, the greatest improvements in lipid profiles were observed in patients with the greatest weight
reductions [59]. Nevertheless, the relationship between weight loss and effect on lipid parameters during use of GLP-1 receptor agonists has not yet been studied.

It appears that, in the postprandial state, exenatide BID may have direct effects on the lipid profile. The effects on postprandial lipidaemia of 1-year treatment with exenatide (vs insulin glargine), followed by a 5-week off-drug period, have been investigated [120]. No between-group differences in fasting lipid parameters were observed after the 1-year intensified treatment, although changes in lipid profiles were observed with exenatide administration following a mixed-meal test, with between-group differences in least-squares mean iAUC0–4 h ± SEM changes from pretreatment in triglycerides [2.3 ± 0.4 mM/h (P < 0.001)] and in FFA [−897 ± 294 μM/h (P = 0.004)] [120]. Results for lipids across studies with both GLP-1 receptor agonists revealed no detrimental changes [27,28,50,56,119].

By lowering glucose, systolic BP and lipid concentrations, treatment with GLP-1 receptor agonists might reduce the CV risk in patients with T2DM. Beneficial CV effects with GLP-1 receptor agonists could also involve their effects on oxidation. Exenatide BID therapy for 1 year was shown to significantly decrease the oxidative marker malondialdehyde (MDA) compared with insulin glargine, although there were no effects on either oxidized LDL or LDL particle size [120].

2.2.3. GLP-1, GLP-1 receptor agonists and endothelium

GLP-1 effects on the CV system may include a direct action on endothelium, as GLP-1 receptors are present in the heart and endothelial tissue [121,122]. It is also possible that incretins have indirect effects on endothelium through BP reduction. Nyström et al. [122] demonstrated that acute administration of GLP-1 can improve endothelial dysfunction in T2DM patients with coronary heart disease. However, the explanation of why and how GLP-1 may have such an action on the CV system is still unknown.

In animal models, GLP-1 has been shown to induce endothelial-dependent relaxation of pulmonary artery vessel rings [123,124], an effect that is nitric oxide (NO)-dependent [124]. Nyström et al. [125] demonstrated an independent NO vasodilatory effect of GLP-1 in rats, indicating a direct action on vascular smooth muscle cells through the GLP-1 receptor.

In humans, GLP-1 has several potential effects on endothelium. First, it has been shown in vitro that, in advanced glycation end-product (AGE)-exposed human umbilical vein endothelial cells (HUVECs), GLP-1 decreased reactive oxygen species (ROS) generation and subsequently reduced vascular cell adhesion molecule-1 (VCAM-1) mRNA levels [126,127]. Furthermore, in HUVECs, native GLP-1 attenuates the expression of tumour necrosis factor (TNF)-α, induced by plasminogen activator inhibitor (PAI)-1 [128]. In T2DM patients with stable coronary artery disease (but not in healthy subjects), GLP-1 vs placebo infusion improved endothelial dysfunction by increasing flow-mediated vasodilatation in the brachial artery (3.1 ± 0.6% vs 6.6 ± 1.0%, respectively; P < 0.05) [122]. In another study, Basu et al. [121] showed that, in humans, infused GLP-1 may have direct beneficial effects on endothelium-dependent vasodilatation that are differentially modulated by sulphonylureas. Indeed, changes of GLP-1 in forearm blood flow, as measured by venous occlusion plethysmography using graded brachial artery infusions of acetylsalicylic acid and nitroprusside, were seen before and after IV infusion of GLP-1 in healthy, non-diabetic subjects randomized to receive placebo, glyburide or glimepiride. Patients treated with GLP-1 experienced significantly enhanced acetylsalicylic acid-mediated vasodilatation and changes from baseline in forearm blood flow compared with subjects given a placebo (P < 0.03). In contrast, glyburide abolished GLP-1-induced acetylsalicylic acid-mediated vasodilatation, whereas glimepiride did not alter the ability of GLP-1 to enhance acetylsalicylic acid-mediated vasodilatation (P < 0.04). Also, neither GLP-1 nor sulphonylurea altered nitroprusside-induced vasodilatation [121].

So far, there have been few studies on the effects of liraglutide and exenatide on endothelium. With liraglutide, beneficial effects on markers of endothelial dysfunction have been observed. In cultured HUVECs in vitro, Hattori et al. [129] demonstrated an anti-inflammatory effect of liraglutide in vascular endothelial cells. Indeed, this GLP-1 receptor analogue dose-dependently increased NO production in HUVECs, and inhibited nuclear factor-kappa-B (NF-kB) activation, at least partly, through AMP-activated protein-kinase (AMPK) activation. Yet another study in vitro revealed, in the same culture model, that liraglutide inhibited expression of TNF-α and hyperglycaemic-mediated induction of expression of PAI-1 and VCAM-1 [130].

In rodents, exenatide treatment produced a significant reduction in carotid artery intima/media ratio (a surrogate marker of CV disease) that was associated with a trend towards NF-kB reduction [131]. In mice, exenatide can also reduce monocyte/macrophage accumulation in the arterial wall, and attenuate mRNA levels in TNF-α and monocyte chemoattractant protein (MCP)-1 [132]. In subjects with impaired glucose tolerance or recent onset T2DM (less than 3 years), acute administration of exenatide following a high-fat meal improved endothelial function, as assessed by peripheral arterial tonometry [133].

2.2.4. GLP-1, GLP-1 receptor agonists and myocardium

Experimental exenatide BID was shown to reduce myocardial infarct (MI) size and to improve cardiac function in a porcine model [134]. A study in the same animal model, but using liraglutide, failed to confirm MI size reduction [135]. However, liraglutide-induced GLP-1 receptor activation was shown to confer cardioprotection and survival advantages in mice over metformin, despite achieving equivalent glycaemic control; this effect lasted up to 4 days after treatment cessation [136]. The animal model used, as well as the timing and dosages of the various compounds, may account for the discrepancies between studies. It should be noted that, in rats, IV administration of GLP-1 receptor agonists has been associated with increased BP and heart rate [79,104,137,138]. Nevertheless, recombinant GLP-1 dramatically improved left ventricular (LV) function and systemic haemodynamics in dogs with advanced dilated cardiomyopathy: the insulinotropic and glucagonostatic properties resulted in increased myocardial glucose uptake [139].
The mechanisms underlying the myocardial action of GLP-1 are also complex. In rats, GLP-1 has direct effects on myocardial muscle, thus protecting it against MI [140]. Mice with genetic deletion of GLP-1 receptors displayed increased LV thickness, impaired LV contractility and diastolic dysfunction after insulin administration, as well as reduced LV contractility after epinephrine infusion [141].

A few small trials have evaluated the efficacy of GLP-1 infusion in patients with chronic heart failure (with or without concomitant T2DM) and with LV dysfunction. Thrainsdottir et al. [142] examined six patients with diabetes and congestive heart failure of ischaemic aetiology treated by subcutaneous infusion of 3 to 4 pmol/kg/min of recombinant GLP-1 for 72 h. Significant improvements in the glycaemic state were noted, as well as a non-significant trend towards myocardial improvement (reduced resting heart rate, lowered systolic BP). In one exploratory study, a 72-h GLP-1 infusion improved regional and global LV function in 10 patients with acute MI and severe diastolic dysfunction after successful primary angioplasty, increasing ejection fraction from 29±2% to 39±2% (P<0.01) [143]. In a recent study, infusion of GLP-1 reduced ischaemic LV dysfunction after supply ischaemia during coronary balloon occlusion (delta dP/dtmax: −13.1% vs −25.3%; P=0.01) [144]. Sokos et al. [145] studied the effects of GLP-1 infusion (1.5 pmol/kg/min) before and after coronary artery bypass grafting (CABG) in patients with heart disease and preserved LV function. Compared with the controls, these patients needed fewer inotropic and vasoactive drug infusions postoperatively to achieve the same haemodynamic results, and presented less frequently with arrhythmias.

Unfortunately, these benefits in myocardial function were not confirmed in a recent study of 20 patients without diabetes, but with heart failure and ischaemic heart disease, who received 48-h GLP-1 (0.7 pmol/kg/min) [146]. In another study, GLP-1 treatments were associated with improvements in LV function, functional status and quality of life (as measured by the Minnesota Living with Heart Failure Questionnaire, quality-of-life score) in patients with chronic heart failure [147]. In addition, the in-hospital mortality rate was reduced in patients with acute MI and LV dysfunction (27% vs 10%, respectively) after successful reperfusion [143]. Furthermore, GLP-1 may have a direct effect on myocardium: positive inotropic and chronotropic changes, unmodifiable by beta-adrenergic blockers, have been reportedly attributed to GLP-1 actions in an exploratory study [79].

Cardiovascular studies with GLP-1 receptor agonists are currently underway to evaluate their risks/benefits on CV endpoints in T2DM patients [148,149], although recent meta-analyses have retrospectively examined the CV safety of GLP-1 receptor agonists [150,151]. Monami et al. [150] analyzed 36 randomized trials of exenatide BID or liraglutide (vs placebo or other comparators) with a duration greater or equal to 12 weeks involving T2DM patients. The results suggested no detrimental effects of GLP-1 receptor agonists on CV events (Mantel–Haenszel odds ratio [95% CI]: for exenatide BID, 0.85 [0.50–1.45]; P=0.55; for liraglutide, 0.69 [0.40–1.22]; P=0.20). Ratner et al. [151] retrospectively examined the CV safety of exenatide BID vs pooled comparators treated with either placebo or insulin in 12 controlled, randomized trials (duration of 12 to 52 weeks) in T2DM patients. The primary major adverse CV events (MACE) suggested that exenatide use did not increase CV risk (Mantel–Haenszel relative risk: 0.7; 95% CI: 0.38–1.31). Finally, a retrospective analysis of the LifeLink™ database (medical and pharmaceutical insurance claims) reported a reduction in the relative incidence of cardiovascular disease (CVD) events and lower rates of CVD-related hospitalization in T2DM patients with exenatide BID vs other glucose-lowering agents [hazard ratio (HR): 0.81, 95% CI: 0.68–0.95 (P=0.01) vs HR: 0.88, 95% CI: 0.79–0.98 (P=0.02), respectively] [152].

However, more studies are needed to better understand these emerging CV actions of GLP-1 receptor agonists and their potential benefits as a treatment of CVD in patients with T2DM.

3. Conclusion

GLP-1 receptor agonists—namely, exenatide BID and, more recently, liraglutide once daily—have been widely prescribed in patients with T2DM. They have the advantage of offering better blood glucose control compared with DPP-4 inhibitors, while not significantly increasing weight gain or the risk of hypoglycaemia in patients treated with metformin with or without thiazolidinediones. In addition, they have shown promising results in inducing weight loss, and may be associated with improvements in CV risk factors in patients with T2DM. However, the underlying mechanisms have yet to be clearly established, and further experimental and clinical prospective studies are required to identify and understand the potential benefits in order to establish the definitive place of these drugs in the management of patients with T2DM.

Disclosure of interest

B. Vergès received, during the 3 previous years, honoraria for advisory boards and lectures from the following companies: AstraZeneca/Bristol-Myers Squibb, Bayer Pharma, Lilly France, Merck Sharp Dohme-Chibret, Novartis Pharma, Novo Nordisk, Sanofi-Aventis, Servier and Takeda.

E. Renard is a member of consultant and educational boards for Eli Lilly and Company, Novo Nordisk and Sanofi-Aventis.

C. Bonnard is employed by and is a shareholder of Eli Lilly and Company.

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