CHAPTER 3

Does glucagon-like peptide-1 receptor agonist therapy add value in the treatment of type 2 diabetes?
Focus on exenatide

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Type 2 diabetes (T2DM) is a heterogeneous syndrome, characterized by beta-cell failure in the setting of obesity-related insulin resistance. T2DM has a progressive course and is associated with a high cardiovascular disease (CVD) risk, regardless of the treatment used. The incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP) are secreted in the gut upon meal ingestion and lower blood glucose by glucose-dependent stimulation of insulin secretion and production. Exogenously administered GLP-1 lowers postprandial glucose excursions by inhibiting glucagon secretion and delaying gastric emptying, improves beta-cell function, and promotes satiety and weight loss. Native GLP-1 is degraded rapidly by the ubiquitous enzyme dipeptidyl-peptidase (DPP)-4. Thus, injectable DPP-4-resistant GLP-1 receptor agonists (GLP-1RA) and oral DPP-4 inhibitors have been developed. Exenatide is the first GLP-1RA that became available for the treatment of T2DM patients. Exenatide has unique characteristics, as to date it is the only agent that addresses the multiple defects of the T2DM phenotype, including hyperglycaemia, islet-cell dysfunction, alimentary obesity, insulin resistance, hypertension and dyslipidaemia. In animals, exenatide also increased beta-cell mass. Long-term prospective studies in high-risk populations should address the potentially disease-modifying effect of exenatide and its effect on CVD risk, in addition to its safety and tolerability.
Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder, characterized by impaired beta-cell function and (obesity-related) insulin resistance [1], and its occurrence worldwide reaches epidemic proportions. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated gradual worsening of glycaemic control in T2DM patients, regardless of the treatment regimen [2]. Consequently, over time, T2DM patients require more therapeutic interventions to maintain metabolic control and ultimately, all will require insulin therapy (Figure 1). This progressive nature of the disease is primarily due to a relentless decline in beta-cell function, which was estimated to occur at an annual rate of 4% [3]. In addition, T2DM patients, relative to their non-diabetes age-matched peers, have a highly increased risk to develop cardiovascular disease (CVD).

In spite of the fact that current diabetes therapies lower blood glucose, thereby improving beta-cell function as they alleviate glucose toxicity, these drugs do not target causal mechanisms of beta-cell dysfunction [3,4]. As a consequence, current diabetes agents cannot alter the progressive course of the disease [5]. Also, none of these agents can favourably modify this excessive CVD risk. Taken together, presently available therapeutic options for T2DM patients should be regarded as still constituting an unmet medical need.
Since the publication of the UKPDS results in 1998, the therapeutic armamentarium for T2DM therapy has not substantially changed. According to the latest consensus statement on the treatment of hyperglycaemia of both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), in addition to lifestyle interventions, initial metformin (MET) treatment, with add-on sulfonylurea (SU) and insulin are still the main-stay therapies to lower haemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) levels to <7% in order to reduce microvascular and macrovascular complications [6,7]. If HbA\textsubscript{1c} levels rise above 7% in MET-treated patients, in addition to a SU, a thiazolidinedione (TZD) may be added. Finally, when combination therapy fails, insulin replacement therapy is initiated. Besides their lack of sustained efficacy, the use of these agents is associated with considerable side effects, including hypoglycaemia and weight gain, both of which may seriously hamper compliance.

The so-called incretin-based therapies constitute a new approach to treat T2DM, with a pathophysiological basis. These are compounds that primarily enhance the action of the incretin-hormone glucagon-like peptide (GLP)-1, that is secreted by the gut upon food ingestion, and that augments meal-related insulin secretion and production.

At present, dipeptidyl-peptidase (DPP)-4 inhibitors or incretin enhancers, and GLP-1 receptor agonists (GLP-1RA) or incretin mimetics constitute the 2 classes of incretin-based therapies. The former are oral agents that increase plasma levels of endogenous GLP-1 and of the other incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), by inhibiting their degradation. The latter are DPP-4 resistant synthetic compounds that bind to G-protein coupled GLP-1 receptors in many organs, including the beta-cells, the gut, liver, muscle, heart, vasculature, and brain to exert multiple biological actions [8]. As most clinical experience to date has been obtained for the GLP-1RAs, in particular the most long-term and widely used compound exenatide, this review focuses on the latter group.

Exenatide is the first GLP-1RA that became available for the treatment of T2DM patients. Exenatide, in contrast to the currently available drugs for the treatment of T2DM, uniquely addresses the multiple defects of the T2DM phenotype, including hyperglycaemia, islet-cell dysfunction, alimentary obesity and the associated cardiometabolic abnormalities such as insulin resistance, hypertension and dyslipidaemia. In animals, exenatide also increased beta-cell functional mass (Figure 2). Thus, GLP-1RAs such as exenatide have the potential to modify the course of T2DM, by durably improving beta-cell function, and to lower the CVD risk in these patients by ameliorating the obesity-related CVD risk factors. At present, there are, however, no data from long-term prospective large-scaled studies in relevant populations to support this promising potential, nor to address issues of long-term safety and tolerability. These studies are currently being initiated and their results are eagerly awaited.
In this review, we summarize the physiological role the incretin system and its abnormalities in T2DM. Additionally, we present data from clinical studies with the GLP-1RA exenatide. Particularly, we discuss the available data describing the effects of exenatide on metabolic control, beta-cell function and CVD risk factors, in support of its potential to fulfil an important role in the treatment of T2DM.

**Figure 2. The therapeutic potential of glucagon-like peptide (GLP)-1 in type 2 diabetes.** The various actions of GLP-1 match the defects of the type 2 diabetes phenotype. Most of these effects are glucose dependent [8,10,26].

In this review, we summarize the physiological role the incretin system and its abnormalities in T2DM. Additionally, we present data from clinical studies with the GLP-1RA exenatide. Particularly, we discuss the available data describing the effects of exenatide on metabolic control, beta-cell function and CVD risk factors, in support of its potential to fulfil an important role in the treatment of T2DM.

**BIOLOGICAL ACTIONS OF INCRETIN HORMONES IN HEALTH AND DISEASE**

Following an oral glucose load insulin secretion is enhanced as compared to an intravenous glucose infusion, in the presence of similar plasma glucose concentrations [9], a phenomenon that is referred to as the incretin effect. The incretin hormones, GLP-1 and GIP, which are secreted in response to a meal from the enteroendocrine L-cells in the distal small intestine and the colon and from the K-cells in the proximal small bowel, respectively, account for 50-70% of total meal-related insulin secretion [9]. In people with T2DM, however, the incretin effect is significantly impaired and it was shown that the postprandial GLP-1, but not GIP, secretion is diminished in T2DM patients [9]. When administered exogenously, GLP-1 in a glucose-dependent manner enhances insulin secretion in both healthy and T2DM individuals, whereas the insulinotropic effect of GIP infusion in T2DM is
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lost [10]. Additionally, GLP-1 glucose-dependently lowers glucagon secretion, slows down gastric emptying and promotes satiety, all of which actions contribute to the lowering of postprandial blood glucose levels [8] To date, from the 2 incretin hormones only GLP-1 has been harnessed for the treatment of T2DM patients. Therefore, in this review we will only outline the biological actions and clinical effects of GLP-1 and GLP-1RA in healthy volunteers and T2DM patients.

GLP-1 actions on pancreatic islets
GLP-1 exerts several biological effects in the pancreas. Firstly, by binding to its membrane-bound G-protein coupled receptor located on the pancreatic beta-cell, GLP-1 stimulates glucose-stimulated insulin secretion. GLP-1 enhances glucose-mediated excretion of membrane-docked insulin granules, but also facilitates insulin secretion by stimulating mobilization of insulin-containing granules from the reserve pool into the readily releasable pool. Secondly, in addition to enhancing insulin secretion, GLP-1 stimulates insulin production, by increasing pro-insulin-gene expression and insulin biosynthesis [8,11].

Interestingly, GLP-1 does not only enhance insulin secretion, in several studies GLP-1 treatment was shown to increase beta-cell mass as well. In (human) cell lines, primary rodent islets and in vivo studies in different rodent species, GLP-1 induced beta-cell mass expansion through reduced apoptosis and enhanced proliferation and differentiation [12,13,14,15,16]. To date, there are no data available to show that similar effects also occur in humans.

In addition to beta-cell specific actions, GLP-1 also acts upon pancreatic alpha-cells. GLP-1 suppresses glucagon secretion at plasma glucose concentrations above 3.7 mmol/L [17]. Whether GLP-1-induced reduction of glucagon secretion is mediated by direct stimulation of GLP-1-receptors on the alpha cells, or through paracrine regulation via enhanced insulin or somatostatin secretion, currently remains inconclusive [10].

Thus, by affecting both alpha and beta-cells, GLP-1 may help to restore the natural homeostatic balance between insulin and glucagon secretion during hyperglycaemic conditions.

Extra-pancreatic actions of GLP-1
GLP-1 has many biological actions in multiple organ systems besides the pancreas, many of which lead to its glucometabolic effects [10]. GLP-1 has a plasma half-life time of just several minutes as it is readily degraded by the ubiquitous enzyme DPP-4. As a consequence, only a small proportion of secreted GLP-1 will ultimately reach the pancreatic islets in its active form [18]. Therefore, GLP-1 is believed to also indirectly affect pancreatic islet function. GLP-1 receptors are expressed on cells in the central and peripheral nervous system. GLP-1-mediated activation of neuronal pathways, such as the autonomic nerve endings originating from the gut and the enteric nervous system,
contributes to the metabolic actions of the incretin hormone. The exact proportion of the neuronal contribution to GLP-1-induced insulin secretion is yet unknown [10,19].

GLP-1 delays gastric emptying, thus contributing to lowering of postprandial glucose levels. The GLP-1-induced delay in gastric emptying is thought to be mediated through peripheral stimulation of abdominal vagal afferent nerves, however, since GLP-1 molecules can easily pass the blood-brain barrier, it may also be regulated through more centrally located mechanisms [10]. GLP-1 acts centrally to affect satiety but the satiety promoting effects may also be a result of gastric distension, secondary to delayed gastric emptying. Nevertheless, the fact that appetite is reduced also in the postabsorptive state, favours a direct central effect of GLP-1 on regulation of satiety [10]. This reduction in appetite by GLP-1 results in markedly reduced food intake and weight loss following prolonged treatment (discussed below). GLP-1-associated weight loss has in turn beneficial effects on various CVD risk factors, including insulin resistance and dyslipidaemia, however these conditions may also improve through direct GLP-1 actions. As such, it was recently demonstrated in dogs that activation of GLP-1 receptor-mediated pathways enhance postprandial glucose turnover, by increasing insulin-mediated whole-body glucose disposal and uptake of exogenous glucose by the liver [20]. In rats, GLP-1 infusion resulted in decreased triglyceride (TG) absorption and apolipoproteinB particle production by the intestine [21].

**GLP-1 AS A THERAPEUTIC OPTION FOR THE TREATMENT OF T2DM**

As both the incretin effect [9] and postprandial GLP-1 concentrations are markedly reduced in T2DM, relative to healthy individuals [22], the first clinical studies addressed the question whether raising GLP-1 levels by exogenous administration of the incretin hormone, could restore its glucoregulatory actions. Due to its short circulating half-life time, GLP-1 was given continuously (subcutaneously or intravenously) to achieve effective plasma concentrations.

Continuous intravenous infusion (from 22.00 hr to 17.00 hr the following day) of native GLP-1 reduced fasting and postprandial glucose concentrations and improved beta-cell function in 8 T2DM subjects, compared with saline infusion. Moreover, infusion with exenatide almost normalized the diurnal glucose profile in these patients [23].

Short-term studies with subcutaneous administration of GLP-1 demonstrated similarly beneficial effects on fasting and postprandial glucose levels [24]. Subcutaneous preprandial self-injection of GLP-1 injections over a period of 3 weeks, improved postprandial glucose levels by 58% and reduced plasma glucagon concentrations in 6 T2DM patients [25].

Subcutaneous infusion of GLP-1 during six weeks via an insulin-pump, decreased HbA1c by a mean 1.3%, fasting glucose by 4.3 mmol/L and daytime mean plasma glucose levels by 5.5 mmol/L, and
improved beta-cell function in 10 T2DM patients [26]. Bodyweight was reduced by 1.9 kg in the GLP-1 treated group, satiety was increased and gastric emptying was significantly delayed.

The beneficial clinical effects of GLP-1 were evident, however, the necessity of continuous infusion of the incretin hormone hampered its broad clinical application. The development of synthetic DPP-4 resistant long-acting GLP-1RA with an affinity for the GLP-1 receptor comparable with native GLP-1, enabled harnessing of the incretin concept in clinical practice [10].

CLINICAL USE OF THE GLP-1 RA EXENATIDE

Exenatide (Byetta®) was the first GLP-1RA to be approved by the Food and Drug Administration (FDA) in 2005 and by the European Medicines Agency (EMeA) in 2006. This therapeutic agent is based on exendin-4, a peptide derived from the saliva of the Gila lizard that shares 53% amino-acid homology with native GLP-1. Exenatide is injected subcutaneously at a recommended dose of 10µg twice daily (BID), prior to breakfast and dinner. In this section we will discuss clinical data of exenatide BID, in particular with regard to glycaemic control, beta-cell function, body weight, CVD risk factors and safety aspects.

4 The effects of exenatide on glycaemic control

The efficacy of exenatide BID was first demonstrated in three large, phase-3, randomized controlled trials [27,28,29]. These trials were followed by an open-label uncontrolled extension, up to approximately 3-3.5 years [30,31]. In the phase-3 trials, T2DM subjects, not achieving adequate glycaemic control with MET alone [29], SU alone [27] or combination treatment with MET+SU [28], received exenatide 5 or 10 µg BID or placebo as add-on therapy. Compared to placebo, exenatide showed a reduction in HbA1c of ~ 1% over a 30 week period. From the exenatide-treated patients, 34-46 % reached the target HbA1c ≤ 7 %, compared to 9-13 % of the placebo-treated group. Exenatide reduced fasting plasma glucose (FPG) by 0.3-0.5 mmol/L and 0.6 mmol/L for the 5 mg and 10 mg arms, respectively, as compared to a 0.4-0.8 mmol/L increase in the placebo group.

In contrast to its relatively moderate effect on FPG, exenatide significantly reduced postprandial glucose excursions in the 30-week phase-3 studies. The decrease in the area under the curve for glucose (AUC\textsubscript{gluc}) after a standardized breakfast was 34 % in subjects using exenatide as added to MET, versus 9 % in the placebo group [29]. Moreover, in subjects using exenatide as add-on to MET+SU, postprandial AUC\textsubscript{gluc} declined by 87 % versus <1 % in the placebo arm [28].

A relatively small number of participants of the phase-3 randomized studies were enrolled in the open-label extension [30,31]. After a run-in period all patients received exenatide 10 µg BID as add-on treatment to their ongoing MET and/or SU therapies. A sustained effect on glycaemic control was
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demonstrated after 2 (n=283) to 3 years (n=217) exposure to exenatide, with mean HbA1c reduction by 1.0 % from baseline, and with 46-50 % of the subjects achieving the target HbA1c ≤ 7 % [30,31].

Exenatide showed similar reductions in HbA1c levels compared to insulin treatment as add-on therapy in T2DM patients sub-optimally controlled with MET and/or SU in a number of clinical studies. The first study, according to a non-inferiority design, compared treatment with long-acting insulin glargine (titrated to FPG ≤ 5.6 mmol/L), to exenatide 10 μg BID for a period of 26 weeks in MET and/or SU-treated T2DM. Patients receiving exenatide achieved a similar reduction in HbA1c (of 1.11 %) as those receiving insulin glargine. FPG levels decreased more in the insulin-treated group, from 10.4 mmol/L to 7.5 mmol/L, than in the exenatide group (FPG fell from 10.1 mmol/L to 8.7 mmol/L). In addition, exenatide reduced postprandial glucose levels, measured as incremental AUC_{gluc}(iAUC_{gluc}), by 6.6 fold, as compared with insulin glargine [32].

In a cross-over study, comparing 16 weeks treatment with exenatide versus insulin glargine, HbA1c levels decreased in both groups by 1.36 %. In agreement with the previously-mentioned study, a greater reduction in FPG was observed in the insulin-treated group (-4.1 mmol/L versus -2.9 mmol/L) [33]. More recently, these results were confirmed in a study in 69 T2DM patients on MET treatment. Both exenatide and insulin glargine showed a reduction in HbA1c levels of 0.8 % following one-year treatment, and FPG was more reduced in the insulin glargine-treated group (-2.9 mmol/L versus -1.6 mmol/L) [34]. In this study, one year treatment of exenatide reduced postprandial iAUC_{gluc}, by 54 % during a standardized meal-test, while glargine had no effect [35]. The reduced postprandial glucose concentrations are most likely the result of exenatide-related increased insulin secretion, delayed gastric emptying and suppression of endogenous glucose output [20,36].

Interestingly, when exenatide was compared to biphasic insulin aspart, HbA1c levels after one year of therapy were similarly reduced by 1.04 % and 0.89 % for exenatide and biphasic insulin aspart-group, respectively (non significant), and no difference was observed in change of FPG between both groups [37].

The effects of exenatide on beta-cell function

In the phase-3 clinical trials, 30-week exenatide therapy versus placebo improved beta-cell function, measured as fasting pro-insulin to insulin ratio [27,29]. In the open-label extension, exenatide treatment was associated with an increase in HOMA-B from baseline by approximately 50 % at 2 year and by approximately 70 % at 3 years [30,31]. In a subset of the studied population, additional beta-cell parameters were obtained from modelling analysis of glucose and C-peptide concentrations during standardized meal tests. Exenatide improved a number of beta-cell function parameters, including glucose sensitivity [38].
The above-mentioned beta-cell parameters have their limitations, since insulin secretion is related to prevailing insulin sensitivity, insulin plasma levels depend on both secretion and clearance, and mathematical modelling may not be fully compatible with biological processes. Therefore, the gold-standard clamp method, using hyperglycaemia and a non-glucose stimulus, i.e. arginine, as insulin secretagogues, with additional assessment of insulin sensitivity during a hyperinsulinaemic euglycaemic clamp, may be the preferred method to evaluate beta-cell function. In the one-year trial comparing exenatide to insulin glargine treatment in 69 MET-treated T2DM subjects, we used a combined clamp procedure and the beta-cell secretory response was derived from C-peptide levels [34]. Both first- and second-phase C-peptide secretion improved from baseline at 52 weeks in exenatide-treated patients compared to those on insulin glargine (1.53 and 2.85 fold respectively). Additionally, arginine-stimulated C-peptide secretion during hyperglycaemia increased 2.46 fold with exenatide treatment (Figure 3).

Figure 3. One year of exenatide versus glargine therapy improves various aspects of clamp-measured beta-cell function. Data are geometric mean ±SE of the ratio of C-peptide concentration during different phases of the hyperglycaemic clamp at 52 week of therapy with exenatide (black bars) and insulin glargine (white bars) to pre-treatment. AIR(arg) denotes C-peptide response to a 5 g. arginine bolus at 15 mmol/L glucose concentration, calculated as the incremental area under the curve during 10 min following arginine administration. 1st and 2nd phase are first- and second phase C-peptide secretion in response to 15mmol/L hyperglycaemia, calculated as area under the curve during 0-10 and 10-70 min following glucose infusion [34].

Taken together, exenatide improved various measures of beta-cell function in a number of studies, however, at present, it needs to be determined whether this effect is sustained in long-term studies and whether exenatide is able to change the progressive decline in beta-cell function in T2DM patients.
The effects of exenatide on body weight
Established blood-glucose lowering therapies, such as SU, TZDs and insulin, are effective in reducing HbA1c levels, however, these effects are accompanied by body weight gain, which overtime, may offset the metabolic benefits [39]. In contrast, MET-therapy and DPP-4 inhibitors are considered to be weight-neutral. GLP-1 RAs, however, in spite of their blood-glucose lowering effects, showed weight-reducing properties in all clinical trials. After 30 weeks of exenatide 10 μg BID therapy as add-on to MET, mean body weight decreased from baseline by 2.8 kg [29], by 1.6 kg when added to ongoing SU-monotherapy or MET and SU combination [27,28]. Weight loss was progressive at 2 years of the extension study, with an average decline of 4.7 kg from baseline. Again, when exenatide was used with ongoing MET therapy, average weight loss was most prominent (5.9 kg), whereas it was less in patients taking SU (3.9 kg) or MET+SU combination (4.1 kg) [30,31,40]. Twenty-six weeks of exenatide 10 μg BID resulted in a weight reduction of 2.3 kg, whereas subjects treated with titrated insulin glargine showed a weight gain of 1.8 kg [32]. One-year treatment with exenatide compared to either titrated biphasic insulin or insulin glargine, resulted in a weight difference between the treatment arms of 5.4 kg and 4.6 kg respectively, in favour of exenatide [34,37].

Importantly, weight loss appeared to be independent of gastro-intestinal side effects, with similar weight reduction observed in subjects who did not experience nausea and/or vomiting as those experiencing these side effects. Importantly, while nausea and vomiting were mostly reported during the first eight weeks of treatment, weight loss continued during the entire treatment period [27,28,29,30,31]. Therefore, the favourable effects of exenatide on body weight may possibly be rather related to its central action on satiety and food intake.

In separate analyses of the 3-year open-label extension data, no association was found between changes in body weight and glycaemic control, however, 68% of the participants (n=217) experienced both weight loss and decrease in HbA1c [31].

The effects on exenatide on body fat distribution
Using Dual-Energy X-ray Absorptiometry (DEXA) we found that at 44 weeks, exenatide, in addition body weight reduction, significantly reduced total body fat, limb fat mass and truncal fat mass as compared to insulin glargine [41]. In addition, GLP-1RA treatment might also have beneficial effects on fatty liver, the key feature of the metabolic syndrome and independent predictor of CVD [42]. Recently, a case report described a reduction of liver fat content, quantified by proton-magnetic resonance spectroscopy (1H-MRS), in a T2DM male following 10-month exenatide therapy [43]. In the extension study, exenatide therapy was associated with a decrease in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), both markers for hepatic steatosis, at two years [30].

In obese mice, exenatide altered the expression of hepatic genes associated with lipid metabolism,
thus providing a potential pathophysiological mechanism explaining these GLP-1RA-related anti-steatotic effects [44].

The effects of exenatide on blood pressure
Exenatide was shown to lower blood pressure, albeit to a modest extent. In the two-year extension, exenatide reduced systolic blood pressure by 2.6 mmHg, diastolic blood pressure by 1.9 mmHg in T2DM patients, who had a mean baseline blood pressure of 130/79 mmHg [30]. This reduction was sustained at 3 years, with blood pressure lowering of 3.5 mmHg (systolic) and 3.3 mmHg (diastolic) [31].

The effects of exenatide on lipids and lipoprotein levels
In the 82-week analysis of the extension study, exenatide improved several aspects of diabetic dyslipidaemia, including a mean increase in high-density lipoprotein (HDL)-cholesterol by 0.12 mmol/L, while TG levels decreased on average by 0.43 mmol/L. Total cholesterol, low-density lipoprotein (LDL)-cholesterol and apolipoprotein B trended towards improvement. When stratified according to weight-change quartile, subjects with the greatest weight reduction had greater beneficial changes in lipid profiles (HDL-cholesterol + 0.19 mmol/L; TG - 1.04 mmol/L) [40]. In a subset of patients (n=151), followed for up to 3.5 years in the open-label extension study, exenatide reduced TG by 12% and increased HDL-cholesterol by 24% [31].

In the one-year exenatide versus insulin glargine study in MET-treated T2DM subjects, postprandial lipid profiles were studied at baseline and at 52 weeks of treatment. After ingestion of two consecutive standardized high-fat mixed test-meals, TG iAUC decreased by 4.2 fold, while HDL-cholesterol iAUC increased by 7.4 fold in the exenatide, as compared to the insulin glargine-treated group [34,35]. No effect of exenatide treatment on LDL particle size was observed [45]. Although the exenatide-related postprandial TG-lowering effects may be partly explained by delayed gastric emptying, GLP-1 administration in rats was shown to reduce intestinal lymph flow, TG absorption and production of apolipoprotein B, all of which could potentially affect lipid metabolism [21].

The effects of exenatide on markers of inflammation and oxidative stress
One year treatment with exenatide significantly reduced fasting high sensitive C-reactive protein (hs-CRP) levels compared to insulin glargine, with a post-treatment to baseline ratio of 0.47 for exenatide versus 0.80 for insulin glargine [41]. In the same study, malondialdehyde (MDA) and oxidated LDL-cholesterol (ox-LDL), both markers of oxidative stress, were measured during a 4-hour standardized meal test. After 1-year treatment, MDA levels were decreased in the exenatide- versus the insulin glargine-treated group, while ox-LDL levels remained unchanged [45].
In conclusion, with regard to CVD risk factors, exenatide therapy is associated with reductions in body weight, truncal adipose tissue, blood pressure and improvement of dyslipidaemia, low-grade inflammation and (postprandial) oxidative stress. Whether the improvements in lipid metabolism, inflammation and blood pressure are direct effects of exenatide treatment or secondary to improved in metabolic control and/or weight loss, requires further study. Also, at present, it is unknown whether these beneficial changes on CVD risk factors will translate into less CVD outcomes on the long term.

**Side effects, safety and tolerability of exenatide**

As indicated above, due to their relatively short time on the market, long-term safety and efficacy data for incretin-based therapies, including exenatide, are largely lacking. Large-scaled long-term prospective studies are currently underway to address these issues.

In general, treatment with exenatide is well-tolerated in T2DM [27,28,29,30,31,34]. The most frequently occurring side effects of exenatide include nausea, abdominal distension and occasional vomiting, which are generally mild and transient in nature [27,28,29]. During the first eight weeks of treatment the frequency of reported nausea and gastro-intestinal side-effects is highest, up to ~30% with exenatide 10 μg BID as add-on to MET and/or SU, thereafter it gradually declines during further treatment, with an average of reported nausea of ~10% at 26-weeks [27,28,29]. After two years of treatment with exenatide, 8% of the study population still experienced nausea. Overall, 3% of the intention-to-treat study population withdrew from further treatment due to nausea [30]. Similarly, when compared to insulin treatment, exenatide-treatment was related to higher incidence rates of mild-to-moderate nausea (42.6% with exenatide vs. 3.1 % with insulin) and vomiting (9.6% with exenatide vs. 3.1% with insulin), both occurring mostly during initiation of treatment [33].

In the clinical studies, the occurrence of hypoglycaemic events in the exenatide arm equalled those in the placebo group (5.3%) [29], and was lower to those in the insulin-treated group (8.3% versus 24.2%) [34], when exenatide was used as add-on to MET alone. As expected, when exenatide was added to ongoing SU or SU+MET, hypoglycaemic events were reported more frequently (mild-to-moderate hypoglycaemia-rates up to 36%) [27,28], as concomitant use of SU-derivates seems to off-set glucose-dependent mode of action of GLP-1RA.

In almost half of the patients receiving exenatide treatment (10 μg BID), anti-exenatide antibody titres were detectable (incidence 41%-49%) [27,28,29,32], although mostly at low titres, at which levels, the antibodies did not affect the metabolic effects of exenatide. The clinical significance of these antibodies remains uncertain.
There are recent reports regarding the occurrence of acute pancreatitis in connection with treatment with GLP-1RA [46,47]. This was also observed for DPP-4 inhibitors [48, 49]. Although there is as yet no proof that the incidence of pancreatitis is causally related to GLP-1RA use, these data should be taken seriously and health-care providers should be alert to symptoms in patients that could possibly indicate this serious event.

Conclusions and future perspectives

GLP-1RA are promising new drugs for the treatment of T2DM, based both on their working mechanism, that has a (patho-)physiological basis, and the currently available data obtained from clinical trials. In contrast to present therapies, GLP-1RA improve glycaemic control while additionally inducing weight loss and causing minimal hypoglycaemia in the majority of subjects treated. Additionally, exenatide improves CVD risk factors, such as an adverse lipid profile, visceral adiposity and high blood pressure, all of which effects seem to be mainly related to the changes in body weight.

Current clinical data indicate that exenatide may improve various aspects of beta-cell function, however, at present it is unclear whether these effects are durable and whether on the long term, exenatide-treatment could modify the natural course of T2DM. Although current guidelines recommend that in T2DM the injectable GLP-1RA should be started prior to insulin, one may argue that, if part of their action is mediated by beta-cell protection and preservation, earlier initiation of these therapies may be warranted, i.e. when there is still sufficient beta-cell function to be salvaged (Figure 1). Also, since postprandial, rather than fasting hyperglycaemia contributes to the HbA1c value when HbA1c is just above the target of 7.0%, exenatide, by mainly lowering postprandial glucose, should be started early, i.e. when HbA1c is just off target [50].

Although GLP-1RA are promising regarding their added value to T2DM therapies, long-term safety and tolerability data of these agents are largely lacking. Taking into account that incretin-receptors are expressed on cell surfaces on a broad range of tissues in the human body, thus potentially implementing a wide range of different (side) effects, patients using these new drugs must be observed carefully in large-sized longitudinal studies.

Despite these uncertainties, further development of this new drug class, i.e. by introducing once weekly formulations with improved efficacy and tolerability and less side effects [51], is still needed to expand the possibilities of the current T2DM treatment paradigm. Particularly when taking into account the heterogeneity of the disease, the high CVD risk, and the inappropriate response of a considerable proportion of T2DM patients to the available therapies. Future studies of sufficiently long duration, in which currently recommended agents are used as a comparator, performed in a large number of high-risk individuals should investigate 1) whether using GLP-1RA as an initial step
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in T2DM treatment, whether as mono- or combination therapy, would durably preserve pancreatic islet function and halt the progression of the disease and 2) whether the hitherto observed beneficial effects on CVD risk factors indeed translate into long-term reduction in CVD outcome.
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