Incretin-based therapy in combination with basal insulin: A promising tactic for the treatment of type 2 diabetes

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Abstract

Incretin therapies such as dipeptidyl peptidase-4 inhibitors (DPP-4Is) and GLP-1 receptor agonists (GLP-1RAs) have become well-established treatments for type 2 diabetes. Both drug classes reduce blood glucose through physiological pathways mediated by the GLP-1 receptor, resulting in glucose-dependent enhancement of residual insulin secretion and inhibition of glucagon secretion. In addition, the GLP-1RAs reduce gastrointestinal motility and appear to have appetite-suppressing actions and, so, are often able to produce clinically useful weight loss. The glucose-dependency of their glucagon-inhibiting and insulin-enhancing effects, together with their weight-sparing properties, make the incretin therapies a logical proposition for use in combination with exogenous basal insulin therapy. This combination offers the prospect of an additive or synergistic glycose-lowering effect without a greatly elevated risk of hypoglycaemia compared with insulin monotherapy, and any insulin-associated weight gain might also be mitigated. Furthermore, the incretin therapies can be combined with metformin, which is usually continued when basal insulin is introduced in type 2 diabetes. Although the combination of incretin and insulin therapy is currently not addressed in internationally recognized treatment guidelines, several clinical studies have assessed its use. The data, summarized in this review, are encouraging and show that glycaemic control is improved and weight gain is limited or reversed (especially with the combined use of GLP-1RAs and basal insulin), and that the use of an incretin therapy can also greatly reduce insulin dose requirements. The addition of basal insulin to established incretin therapy is straightforward, but insulin dose adjustment (though not discontinuation) is usually necessary if the sequence is reversed.

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Keywords: Insulin; GLP-1 analogue; DPP-4 inhibitors; Type 2 diabetes mellitus; HbA\textsubscript{1c}; Weight; Review

Résumé

Association incrétinomimétiques-insulinothérapie basale : une tactique prometteuse pour traiter le diabète de type 2.

Les thérapeutiques fondées sur les incrétines ou incrétinomimétiques (inhibiteurs de la dipeptidyl peptidase-4 [iDPP-4] et agonistes du récepteur GLP-1 [arGLP-1]) sont devenues, au cours des dernières années, des traitements bien établis du diabète de type 2 (DT2). Les incrétinomimétiques diminuent la glycémie via des voies métaboliques qui passent par le récepteur GLP-1, conduisant à une stimulation de la sécrétion d’insuline résiduelle en fonction de la glycémie et à une inhibition de la sécrétion de glucagon. En outre, les agonistes du récepteur GLP-1 ralentissent la motilité gastro-intestinale et semblent diminuer l’appétit, ce qui a pour effet de réduire le poids. Ces effets glucodépendants insulinosécréteurs et inhibiteurs du glucagon associés à une perte de poids font des incrétinomimétiques en association à une insuline basale exogène une voie thérapeutique logique et intéressante. Cette combinaison offre la possibilité d’un effet additif ou synergique de réduction de la glycémie sans risque d’hypoglycémie comparé à une monothérapie par insuline, et d’une réduction de la prise de poids liée à l’insulinothérapie. De plus, les incrétinomimétiques peuvent être associés à la metformine, habituellement poursuivie lorsque l’insuline basale est introduite pour le traitement du DT2. Même si l’association incrétinomimétiques-insuline basale n’a pas fait l’objet de recommandations internationales, plusieurs études ont évalué l’intérêt de cette association. Les résultats de ces études, qui font le sujet de la présente synthèse, sont encourageants et indiquent une
amélioration du contrôle glycémique, une limitation de la prise de poids ou une perte de poids (en particulier lorsqu’un agoniste du récepteur GLP-1 est associé à l’insuline basale) et une réduction des besoins en insuline. L’ajout d’insuline basale aux incrétinomimétiques est simple, mais l’ajustement de la dose d’insuline (et non son arrêt) est habituellement nécessaire si cette séquence est inversée.

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Mots clés : Diabète de type 2 ; Analogues du GLP-1 ; Inhibiteurs des DPP-IV ; Insulinothérapie basale ; Association ; Poids ; Revue générale

1. Introduction

Given the progressive nature of type 2 diabetes mellitus (T2DM), professional authority-based or regional treatment guidelines advocate an approach to disease management wherein intervention is escalated to keep pace with declining beta-cell function [1]. While different guidelines vary in details and in the glycemic targets recommended, there is a general consensus that intervention commences with advice on diet and exercise (maintained thereafter) and with metformin often suggested as the first-line pharmacotherapy. Metformin has well-established efficacy and is generally fairly well tolerated, weight-neutral and inexpensive [2]. It is also often perceived as having proven cardioprotective benefits, although this remains controversial [3]. When metformin monotherapy fails to maintain glycemic control, it can be used in combination with other oral antidiabetic drugs (OADs) or insulin. The traditional OADs [sulphonylureas (SUs) and thiazolidinediones (TZDs)] and insulin are associated with weight gain, however, which can compromise patients’ ongoing attempts at weight management [4]. When introducing exogenous insulin, many physicians discontinue OADs other than metformin. SUs are often discontinued due to concerns about hypoglycaemia and weight gain, while the fluid retention associated with TZDs means that they are contraindicated with insulin in many countries, as the combination can increase the risk of congestive heart failure [5]. The ultimate level of intervention is to add mealtime bolus insulin to (typically) basal insulin plus metformin, or to substitute basal insulin with a premixed insulin regimen.

However, in recent years, the ‘incretin’ therapies have become available. These act primarily to increase the physiological effects mediated via the hormone glucagon-like peptide (GLP)-1, which is rapidly secreted by intestinal L cells [along with glucose-dependent insulotropic polypeptide (GIP) from K cells], whenever food is ingested, probably via the neural and endocrine signals associated with feeding [6]. GLP-1 and GIP have multiple actions that affect nutrient handling. Nevertheless, the various physiological and pharmacological effects of GLP-1 are still being explored, and those with potential therapeutic value in T2DM are summarized in Table S1 (see supplementary material associated with this article online [71–73]). GLP-1 acts in a glucose-dependent manner to increase insulin and suppress glucagon secretion in the setting of hyperglycaemia. Moreover, counterregulatory responses to hypoglycaemia (including glucagon secretion) are fully preserved with the administration of pharmacological levels of GLP-1 [7]. Other possible effects of GLP-1 that might be of potential benefit in T2DM include satiety-inducing and weight-limiting effects [8–10], as well as potential beta-cell-sparing actions [11,12] and positive cardiovascular effects in the laboratory setting [3,13], although the latter two actions are yet to be fully proven in humans in vivo.

In T2DM, the physiological response to incretins is impaired, and while this may be a secondary manifestation of beta-cell failure [14], there is greatly reduced pancreatic sensitivity to GIP [14]. However, tissue sensitivity to GLP-1 is preserved [14,15] and thus GLP-1 signalling can be restored (or enhanced) in two ways. First, by inhibiting the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades GLP-1 in vivo, concentrations of endogenous GLP-1 are increased. Several DPP-4 inhibitors (DPP-4Is) have been developed (including vildagliptin, sitagliptin, saxagliptin, alogliptin and linagliptin) and are given orally. Relying on endogenous GLP-1 secretion, these drugs are well tolerated, and have been shown to improve glycaemia without weight gain and with low rates of hypoglycaemia in clinical trials [6,16,17].

A second approach is to give DPP-4-resistant substitutes for GLP-1 (GLP-1 receptor agonists, GLP-1RAs). Two such agents are clinically available (the incretin mimetic exenatide and the human GLP-1 analogue liraglutide), with others in development. The GLP-1RAs, being peptides, are given subcutaneously. These agents are potentially more potent than DPP-4Is, as the GLP-1 signal can be amplified to pharmacological levels with appropriate dosing [18]. GLP-1RAs reduce hyperglycaemia in T2DM when given as monotherapy or when added to various OAD regimens, and this is often achieved together with weight loss and its associated benefits (such as lower systolic blood pressure) [6,16]. Like DPP-4Is, the GLP-1RAs carry a low risk of hypoglycaemia. Gradual dose escalation is advised to minimize gastrointestinal side-effects such as nausea, which is otherwise a rather common occurrence, exceeding 40% in many of the earlier exenatide studies [6,16].

Although the optimal role of the incretin therapies is still emerging, their unique pharmacological properties oblige us to consider changes in our current treatment paradigms [19]. Most studies to date have assessed these agents as monotherapy or in combination with standard OADs [6,16]. However, there is a growing interest in (and study of) the use of incretins in combination with exogenous insulin therapy. The present review considers the potential clinical role of such regimens and looks at the available clinical data. The studies discussed here were identified by PubMed searches using the generic names of all currently available incretin-based therapies.

2. Rationale for incretin plus insulin combination therapy

Exogenous insulin replacement is used to compensate for the loss of endogenous beta-cell function. Usually, basal insulin
Basal insulin is effective in addressing fasting plasma glucose (FPG) and incretin is effective in addressing postprandial glucose (PPG), so this approach maximizes the impact on HbA1c. Basal insulin supplementation rests beta cells and relieves glucotoxicity to enable some recovery of the endogenous prandial insulin response, and incretins can maximize this response. Incretins influence alpha-cell function and, so, can potentially still improve PPG (by reducing hepatic glucose output via reduction of inappropriately elevated glucagon levels) even if beta-cell function is severely compromised. Incretins do not impair alpha-cell response to hypoglycaemia and may therefore be expected to reduce the risk of severe hypoglycaemia compared with basal + bolus insulin therapy. Use of incretins to control postprandial hyperglycaemia does not require carbohydrate counting or frequent blood glucose monitoring, as required with basal + bolus insulin therapy. Insulin tends to promote weight gain whereas incretins are weight-neutral (DPP-4Is) or weight-sparing (GLP-1RAs), thus minimizing or avoiding weight gain. Incretin actions complement those of metformin and, as metformin is usually continued alongside insulin therapy in T2DM, benefits are maintained and regimen changes are avoided.

replacement is the first step in introducing insulin to patients with T2DM; the expectation is suppression of hepatic glucose production and a decrease in fasting plasma glucose (FPG) levels. Incretin drugs, on the other hand, lower blood glucose through stimulation of beta-cell function and suppression of glucagon secretion and, in the case of GLP-1RAs, through slowing of gastirc emptied. While there are pharmacological arguments for the adoption of incretin therapies earlier in the natural history of T2DM to take advantage of any remaining beta-cell function [19], glycaemic improvements have been shown in insulin-treated patients with prolonged duration of diabetes who should have markedly reduced beta-cell function [20–23]. The antihyperglycaemic effect therefore results from reductions in both postprandial glycaemia (PPG) and FPG—with the latter effect particularly evident with those agents that have a long duration of action. Given these complementary actions on the daily glycaemic burden, there is a compelling rationale for the combined use of basal insulin and incretin drugs in the management of T2DM. Furthermore, as GLP-1RAs often reduce appetite, they may also help to mitigate some of the weight gain commonly associated with insulin therapy. The potential benefits of combining insulin and incretin therapy are summarized in Table 1 and further discussed below.

Hyperglycaemia develops in T2DM as insulin secretion fails to keep pace with insulin resistance [24]. Even if insulin resistance is not profound, a progressive loss of insulin secretion can still result in hyperglycaemia. Typically, this situation first manifests with progressive elevations of PPG until, eventually, FPG levels also begin to rise [25,26]. Inadequate prandial insulin response is a fundamental pathophysiological defect in T2DM that is further exacerbated by impairments in incretin secretion and action. Moreover, glucagon secretion is inappropriately elevated in T2DM, resulting in increased hepatic glucose output, thereby further contributing to both postprandial and fasting hyperglycaemia [27–29]. This deficit in alpha-cell function is now known to emerge very early in the natural history of T2DM and, although it is possible that it is at least partly a secondary effect of reduced insulin release, it appears that the mechanism also involves decreased alpha-cell sensitivity to glucose [27]. However, the extent to which elevated PPG in T2DM reflects the three components of impaired incretin response, beta-cell exhaustion and impaired alpha-cell function is still not well understood.

Treatment of T2DM should ideally address PPG excursions as well as fasting hyperglycaemia. Elevations in PPG following oral glucose tolerance testing have been associated with increased cardiovascular risk [30] and clearly contribute to overall glycaemic exposure, as reflected by HbA1c. Under physiological conditions, the incretin system participates in the regulation of nutrient ingestion and disposal in general, and limits PPG excursions as well as fasting glycaemia. Thus, incretin-based therapies should prove to be helpful in this respect and more effective than traditional secretagogues, such as SUs, in curtailing PPG by combining glucose-dependent beta-cell stimulation with alpha-cell suppression [31,32].

PPG can, of course, be addressed with the use of short-acting mealtime insulins, which carry a higher risk of hypoglycaemia and weight gain than basal insulin [33,34], and require more frequent injection and glucose monitoring. Consequently, in T2DM, basal-only insulin supplementation added to metformin (and sometimes other OADs) has gained in popularity, particularly in primary care, as a simple tolerable approach to insulin initiation [35]. This was arguably vindicated by the Treating To Target in Type 2 diabetes (4-T) study in which the choice of basal-only insulin initiation (insulin detemir), followed by intensification with either bolus insulin, resulted in a lower percentage of patients required intensification with either bolus or premixed insulins [34]. Although basal insulin supplementation does not directly address PPG, it carries a low risk of hypoglycaemia and may help to rest beta cells and relieve glucotoxicity, thereby potentially allowing some recovery of the endogenous prandial insulin response [35–37].

However, basal insulin alone may prove insufficient to maintain control of HbA1c, obliging the addition of prandial coverage. The 4-T study illustrated this point by showing that a high percentage of patients required intensification of their initial basal regimen within the 3-year study period [34]. An alternative to adding bolus insulin might be to combine basal insulin with an incretin therapy, given the pharmacological actions of these latter drugs as outlined above. Incretin therapies would be expected to also help minimize PPG excursions through their effects on both beta- and alpha-cell function (in the case of GLP-1RAs) by slowing gastric emptied and decreasing appetite. In addition, the glucose-dependency of their pancreatic effects should pose a relatively low risk of hypoglycaemia even when combined with basal insulin. Furthermore, there is evidence that alpha-cell responsiveness to hypoglycaemia is improved by incretin therapies [27]. Placebo-controlled clamp studies have shown that both GLP-1RAs [38] and DPP-4Is [27] reduce glucagon

Table 1
Potential benefits of combining incretin-based therapies with basal insulin.

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Hyperglycaemia is

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secretion in conditions of either hyperglycaemia or euglycaemia, but increase it during hypoglycaemia. Ahren and colleagues [39] reported an increased pancreatic polypeptide response to hypoglycaemic clamp in the presence of vildagliptin, suggesting that GLP-1 was at least partly influencing alpha-cell responsiveness to glucose via vagal signalling rather than through a direct endocrine action. Whatever the mechanism, the observation of an enhanced counterregulatory response was consistent with clinical reports of low hypoglycaemia rates with these drugs [6,16], and raises the prospect of an incretin + insulin regimen providing glucose control with a lower risk of hypoglycaemia than insulin alone.

Intensifying basal insulin with the addition of an incretin-based drug instead of prandial insulin should result in less weight gain. Insulin therapy, particularly prandial insulin replacement, promotes weight gain through reduction of glycosuria and inappropriately high exposures of adipocytes to systemically administered insulin [40]. Incretins, on the other hand, stimulate endogenous insulin secretion and, in the case of GLP-1RA, additionally promote satiety and weight loss. This offers the prospect of improved glycaemia without weight gain. The use in insulin-treated T2DM patients of metformin intensified by an incretin drug offers several advantages: metformin not only directly inhibits hepatic glucose and improves tissue sensitivity to insulin [41], but also increases GLP-1 levels [42], and there is evidence that this reflects both metformin-mediated increased GLP-1 production [43] and DPP-4 inhibition by metformin [44,45]. Thus, metformin is likely to act additively with both DPP-4Is and GLP-1RAs. Indeed, DPP-4Is have been found to be significantly more effective when combined with metformin than when introduced as monotherapy to previously drug-naïve patients [46,47]. In short, a regimen of incretin therapy plus basal insulin might mimic some of the pharmacological benefits of basal-bolus insulin therapy, but in a less complex regimen associated with lower risks of hypoglycaemia and weight gain.

A comparison of exenatide and insulin glargine found that insulin sensitivity and first-phase glucose-stimulated insulin secretion were improved after 3 years of exenatide treatment, but not with insulin glargine, thus supporting both the ability of incretins to address PPG and their potential beneficial effect on beta-cell health [48].

3. Clinical performance of incretin + insulin therapy

3.1. Adding incretins to insulin: data for GLP-1RAs

Despite being a theoretically appealing treatment approach, few prospective trials have been published on insulin + incretin combination therapy at the time of writing, although it is currently the subject of several ongoing studies. One of the first published studies was an uncontrolled retrospective analysis of 188 patients in whom exenatide was added to insulin [23]. The authors reported considerable heterogeneity in the results, but highlighted the long duration of disease in the cohort (~70% had T2DM for >10 years). Despite this and a baseline HbA1c of 8.05% with insulin therapy, HbA1c was further reduced by a mean −0.66% (P < 0.001) with exenatide addition, with evidence of this decrease being sustained beyond 2 years, albeit only in a restricted subset of patients. The improvement in glycaemia occurred in the setting of an initial 15% decrease in insulin dose and ongoing weight loss averaging −2.4 kg (P < 0.001) at 6 months and −6.2 kg (P < 0.001) at 12–18 months. These data support the idea of the ability of an incretin-based therapy added to insulin even in cases of late-stage disease to improve glycaemic control and facilitate weight loss despite continued insulin treatment. The authors highlighted a dropout rate of 26% due to adverse events, the vast majority of which were due to nausea and other related gastrointestinal side-effects commonly seen with GLP-1RAs. While the authors did not report any concerns about hypoglycaemia, it would be prudent to escalate the dose of GLP-1RA gradually when adding it to ongoing insulin therapy.

A prospective 30-week, placebo-controlled, randomized, double-blind study of 261 patients with T2DM (disease duration: 12 years) assessed the addition of either exenatide or placebo to insulin glargine (± OADs) [21]. The glargine dose was decreased by −20% if HbA1c was less or equal to 8.0%, or maintained if HbA1c was greater than 8.0%, then titrated to an FPG target of less than 100 mg/dL (5.6 mmol/L). The addition of exenatide decreased HbA1c by −1.74% (baseline: 8.3%), while placebo was associated with a reduction of −1.04% from a baseline of 8.5% (P < 0.001 between treatments). This difference was achieved despite an average 7-U greater increase in final insulin dose in the placebo group. End-of-trial FPG and self-monitored glucose data showed that the HbA1c difference was explained by a greater reduction in PPG with exenatide, but with no difference in the final FPG values (6.5–6.6 mmol/L). Weight increased by +1.0 kg in the placebo group, but decreased by −1.8 kg following the addition of exenatide (P = 0.001 between treatments). Hypoglycaemia event rates for exenatide and placebo were low at 1.4 and 1.2 events/patient/year, respectively, with two severe hypoglycaemic events reported, both in the placebo group. Gastrointestinal side-effects were more frequent in the exenatide group, with nausea experienced by 41% (vs 8% with placebo).

One issue in need of resolution when incretin therapy is added to insulin is whether, and how, to make compensatory adjustments in the insulin dose. Some light on the issue was shed by a British clinical audit of patients initiating exenatide that included a subgroup of more than 1500 in whom the drug was added to insulin [the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial] [49,50]. The trial data suggested a trade-off between glycaemic control and weight reduction when the insulin dose was adjusted: weight reduction was positively correlated with insulin dose reduction, while improvement in HbA1c was negatively correlated. Overall, the 26% of insulin-treated patients who discontinued insulin upon initiation of exenatide showed no change in glycaemic control, but did experience clinically significant weight loss of −6.6 kg (P < 0.001) [49]. However, in 48.4% of patients, substitution of exenatide for insulin was associated with worsening glycaemic control, with 27.7% of patients having an HbA1c increase of greater or equal to 1% [49]. These observations indicate that, while the two drugs can act additively or synergistically, a GLP-1RA cannot be regarded as an equivalent substitute for insulin.
and therefore, insulin should not be discontinued in insulin-dependent patients. Patients continuing insulin with exenatide initiation did, however, reduce their mean daily insulin doses from 1.0 U/kg to 0.7 U/kg ($P < 0.001$), with 16.6% discontinuing insulin treatment altogether by the end of the 1-year audit [50]. Reassuringly, this audit suggested very low incidences (2/1257 patients) of severe hypoglycaemia when using exenatide together with insulin. Total hypoglycaemia rates were low, but were higher with insulin + exenatide than with exenatide alone (8.9% vs 6.1%, respectively; $P < 0.001$) [50].

The major insulin dose reductions (and even discontinuations) revealed by the above audit suggested that some doctors were using exenatide as an insulin-sparing therapy—and possibly even as a tool to manage obesity in T2DM patients. Although this is currently not an approved indication for incretin-based therapy, the idea was specifically investigated in a study of 160 consecutive insulin-treated obese patients with T2DM followed for up to 12 months after initiation of exenatide [51]. Fourteen withdrew early (out of an original cohort of 174) due to gastrointestinal side-effects, with eight further withdrawals within 6 months. However, the addition of exenatide allowed a mean insulin dose reduction in the cohort of ≈63% from a baseline of 144 U/d (with ≈25% having at least temporarily discontinued insulin at the 3- and 6-month assessment points). There was a mean 10.7 kg weight reduction at 6 months (representing 9% of the original body weight) and, in the subset whose data were available at 12 months, there was a 12.8 kg weight reduction. These changes were achieved without an increase in mean HbA1c, although HbA1c control tended to remain poor (8.6% and 9.1% at 6 and 12 months, respectively), underscoring the need for continued active insulin management.

Similar findings were made in a recently reported retrospective Swedish clinical audit of T2DM patients in whom either liraglutide ($n = 40$) or exenatide ($n = 21$) had been added to insulin therapy [52]. For the total cohort of 61 patients, after a mean period of 7 months, HbA1c decreased from a mean 8.9% to 7.9% ($P < 0.001$), weight decreased by 7 kg ($P < 0.001$), and hypoglycaemic event rates remained low and did not lead to discontinuation. Thus, in this study, the clinically important improvement in HbA1c came despite a substantial insulin dose reduction from 91.1 U to 52.2 U ($P < 0.001$). In addition, assessment of a change version of the Diabetes Treatment Satisfaction Questionnaire (DTSQc) showed a significant increase in treatment satisfaction compared with previous regimens.

The potential for insulin dose reduction was further highlighted in a small-scale observational study of 15 overweight T2DM patients with very high insulin requirements (initial mean daily dose: 192 ± 77 U) who were given a combination of 500-U insulin and liraglutide for at least 12 weeks [53]. The insulin dose was reduced by 0–30% upon initiation of liraglutide, with subsequent dose adjustments based on the clinician’s judgement rather than a specific algorithm. After 12 weeks, HbA1c decreased by 1.4% from a baseline mean of 8.48%, with a mean weight reduction of 5.1 kg. The total daily insulin dose was reduced by 28%, and there were no reports of severe hypoglycaemia.

These studies all demonstrate that GLP-1RAs can be added to insulin therapy during relatively late-stage T2DM with the benefit of achieving substantial weight reduction and insulin dose reduction. In addition, pilot studies have shown that similar outcomes can be achieved in type 1 diabetes (T1DM) patients [54–56]. Although appealing, however, insulin reduction in T1DM carries the risk of acute loss of glycaemic control, which is why protocols need to be developed to enable individualized optimal outcomes; in fact, there is currently no incretin-based therapy indicated for use in T1DM. The ability to make large insulin dose reductions without loss of glycaemic control in T2DM might be largely dependent on a high initial insulin requirement plus the scope for major weight loss [51,52].

### 3.2. Adding incretins to insulin: data for DPP-4Is

Several studies have evaluated the addition of DPP-4Is to insulin and, although protocols have varied, the results reported have been remarkably similar. The first such study randomized 296 patients with T2DM (mean disease duration: 14.7 years) that was poorly controlled by high-dose insulin (mean HbA1c: 8.4% with ≥30 U/d of insulin) to receive an additional 50 mg of vildagliptin twice daily or a matching placebo [57]. Insulin dose adjustment was permitted, but changes in the type of insulin were not allowed. After 24 weeks, HbA1c was reduced by −0.5% and −0.2% in patients receiving vildagliptin and placebo, respectively ($P = 0.01$). There was no difference in adverse event rate between placebo and vildagliptin and, interestingly, both mild (1.95 vs 2.96 events/patient/year, $P < 0.001$) and severe hypoglycaemia (0 vs 0.1 events/patient/year, $P < 0.05$) was less frequently seen in association with vildagliptin than with placebo. In addition, 200 of these patients consented to take part in a study extension and were followed up for an additional 28 weeks [58], with patients from the original placebo group given 50 mg/d of vildagliptin. In patients continuing with vildagliptin 100 mg/d plus insulin, the 24-week HbA1c reduction was sustained over 52 weeks (−0.5%), whereas patients switching from placebo to vildagliptin 50 mg/d had a mean reduction of −0.4%, with the benefit most marked in patients aged more than 65 years. Hypoglycaemia rates in these two groups of patients over 52 weeks were 1.8 and 1.78 events/patient/year, respectively, with no discontinuations due to hypoglycaemia. Weight remained stable.

Another study randomized 390 patients with a mean baseline HbA1c of 9.3% (mean T2DM duration: 12–13 years) to receive once-daily 12.5-mg or 25-mg doses of alogliptin or placebo added to stable insulin therapy ± metformin for 26 weeks [22]. In the setting of unchanged insulin doses, alogliptin reduced HbA1c (by −0.63% and −0.71% with 12.5 mg and 25 mg, respectively, vs −0.13% with placebo; $P < 0.001$). No differences were observed in the percentages of patients reporting hypoglycaemia (27% for each alogliptin arm, 24% in the placebo group) or other adverse events. There was minimal weight gain in the cohort with a baseline body mass index (BMI) greater than 32 kg/m², and weight change did not differ between the alogliptin groups (+0.7 kg and +0.6 kg, respectively) and placebo (+0.6 kg).

Although the absolute level of glycaemic control achieved in this study (and the earlier vildagliptin study) fell short of...
guideline targets, the authors noted that, as insulin dosing had not changed (thus, they were not optimized), the effect of DPP-4Is was isolated. They also noted that reductions in HbA1c were proportional to baseline values, which was consistent with other studies of DPP-4 inhibition and, indeed, of other OADs [59–61]. Another relevant observation was that changes in FPG with alogliptin (+0.1 and −0.6 mmol/L, respectively) were minimal. This implies the HbA1c reduction (∼−0.5–0.6%) was primarily attributable to PPG reduction, consistent with the drug’s pharmacology. Given that these patients had poor baseline control and a diabetes duration of more than 12 years, it is tempting to speculate that they had retained only limited beta-cell function, in which case, the additional efficacy provided by alogliptin could be largely attributed to improved alpha-cell function. This hypothesis could also apply to the studies described above of GLP-1RAs added to insulin, and is worthy of further investigation. While the theory remains speculative, the concept and clinical data support an argument for not dismissing incretin-based therapies in advanced T2DM.

Very similar results to the vildagliptin and alogliptin studies were obtained in a placebo-controlled 24-week study of sitagliptin 100 mg added to insulin (restricted to basal only or premix regimens) ± metformin [20]. Again, the study cohort (n = 641) had long-standing T2DM (>12 years) with poor baseline control (HbA1c > 8.6%), and a BMI of 31.4 kg/m². Insulin and metformin doses were kept constant and, after 24 weeks, the addition of sitagliptin had reduced HbA1c by −0.6% vs no change in the placebo group (P < 0.001). FPG was again quite modestly reduced by the DPP-4I (−0.8 mmol/L) compared with a 2-h post-meal glucose reduction of 2.0 mmol/L (values relative to placebo). C-peptide-based indices confirmed that sitagliptin was primarily acting to increase prandial insulin response, although an increase in fasting insulin output was also observed. Hypoglycaemia was more common with sitagliptin than with placebo (16% vs 8%, respectively), but few events were considered severe (two vs one, respectively). However, no significant change in body weight was associated with sitagliptin.

3.3. Adding incretins to insulin: data for GLP-1RAs vs DPP-4Is

That incretin-based therapies act in part by improving PPG control when added to basal insulin therapies was further supported by a single-centre proof-of-concept study in which PPG increments after a standard meal were measured [62]. This small-scale, short-duration study also provided useful early insights into the comparative performances of a GLP-1RA and a DPP-4I added to basal insulin plus metformin. In this study, 48 patients were randomized to receive 4 weeks of either exenatide (5–10 μg twice daily) or sitagliptin (100 mg once daily), or no further treatment, in addition to a regimen of metformin plus insulin glargine titrated to an FPG target of less or equal to 100 mg/dL. The 6-h PPG excursion (AUC0–6h) following a standard mixed-meal challenge was significantly lower with both exenatide (606 mg/dL/h, P = 0.0036) and sitagliptin (612 mg/dL/h, P = 0.0008) compared with the non-incretin-intervention group (728 mg/dL/h). FPG levels did not differ between groups at the end of the trial, having been significantly reduced from baseline during a run-in period with insulin plus metformin. In this short study, HbA1c decreased by −1.9% in the exenatide group, by −1.5% in the sitagliptin group and by −1.2% in the group not receiving incretin, but from different baseline values of 8.39%, 7.89% and 7.91%, respectively. HbA1c less than 7.0% was achieved by 80.0%, 87.5% and 62.5% of subjects, respectively, with such high percentages most likely reflecting the simultaneous use of incretins alongside optimization of insulin doses. Hypoglycaemia rates were low, although numerically higher in the incretin groups (10.1, 3.3 and 1.6 events/patient/year, respectively), but no nocturnal or severe episodes were reported. A weight decrease of 0.9 kg seen in the exenatide group was significantly different from the slight weight gain noted in the non-incretin group (+0.4 kg, P = 0.0377).

3.4. Adding insulin to incretins: data for GLP-1RAs

To date, fewer data have been published concerning the addition of insulin to incretins than *vice versa*, which probably reflects the historical availability of suitable study cohorts. Nevertheless, there are sound theoretical arguments for a treatment algorithm that establishes patients on incretin therapies before the addition of insulin (Table 2). With increasing numbers of patients being given incretin therapies over the past few years, however, it has become possible to study the addition of insulin to incretins and thus, accordingly, the study data are now becoming available.

One such important study, the largest prospective study of incretin plus insulin reported, assessed the sequential addition of liraglutide and basal insulin in 988 insulin-naïve T2DM patients who were not adequately controlled with metformin ± SU [63]. All patients received metformin (≥ 1500 mg/d) plus liraglutide (titrated to 1.8 mg once daily) during a 12-week run-in period, with discontinuation of SU therapy at study initiation. At the end of the run-in period, patients whose HbA1c remained greater than 7.0% (n = 323) were randomized to either continue treatment with metformin + liraglutide 1.8 mg or have insulin detemir (titrated to maintain FPG at 4.0–6.0 mmol/L) added to their ongoing metformin + liraglutide therapy for a further 26 weeks. Patients treated with insulin detemir plus liraglutide achieved a 0.6% HbA1c reduction during the metformin + liraglutide
run-in, with a further 0.51% HbA1c reduction following the addition of detemir, whereas those continuing without added insulin sustained, but did not further decrease, their HbA1c level from the end of the run-in period. This study demonstrated the ability of a GLP-1RA to achieve target HbA1c levels in patients not controlled with metformin, as 61% of those completing the run-in period achieved the glycaemic target of HbA1c less than 7% in 12 weeks. The study also confirmed that the addition of basal insulin to those patients still not achieving target with the GLP-1RA could further improve glycaemic control and bring more patients to their glycaemic targets. Hypoglycaemia was infrequent in both groups, with no severe events, and both groups experienced weight reductions from baseline. Notably, the weight reduction obtained with metformin + liraglutide during the run-in period was sustained following the addition of detemir. Based on this study, it appears that, with at least this particular combination of insulin and GLP-1RA, two of the traditional barriers to insulin therapy—hypoglycaemia and weight gain—may be less evident when basal insulin and GLP-1RAs are used together.

3.5. Adding insulin to incretins: data for DPP-4Is

The addition of insulin to established DPP-4I therapy is less well reported, although one recent 26-week study compared the simultaneous addition (to metformin background therapy) of sitagliptin plus once-daily insulin detemir (with discontinuation of SU) with the introduction of sitagliptin alone with SU continued in 217 insulin-naïve patients who were no longer well controlled by metformin ± SU [64]. The estimated HbA1c decrease (baseline mean: 8.5%) was −1.44% with once-daily detemir plus sitagliptin and −0.89% with sitagliptin ± SU (P < 0.001). Predictably, FPG was decreased significantly more when detemir was used (−3.7 vs −1.2 mmol/L, P < 0.001). HbA1c less or equal to 7.0% was achieved by 45% of SU-treated patients, respectively (P = 0.001), with these percentages achieved with hypoglycaemia rates of only 16% and 20%, respectively (P = 0.008). Interestingly, self-monitored plasma glucose profiles suggested that 2-h PPG levels were significantly lower with detemir + sitagliptin than with sitagliptin ± SU, thereby demonstrating that basal insulin supplementation can improve mealtime as well as fasting glucose levels, an effect that can then be maximized by incretin therapy. Indeed, the lower FPG and PPG values (culminating in lower HbA1c) suggest that the incretin plus insulin combination was working as intended. This was further supported by the observation of a low incidence of hypoglycaemia, with no severe episodes and no significant difference between treatments, as reflected by an event rate of ∼0.5 episodes/patient/year. Body weight decreased by a mean −1.6 kg with sitagliptin ± SU and by −0.8 kg with insulin detemir + sitagliptin (NS).

4. Unanswered questions and the need for future studies

It has been shown that the introduction of an incretin can maximize the therapeutic benefits (including minimizing hypoglycaemia and reducing weight) when insulin is introduced [63]. However, at present, except for a single pilot study [62], there have been no trials comparing (a) different incretin therapies in combination with insulin or (b) different insulins combined with an incretin therapy. Also, it would be unwise to draw too many conclusions by making indirect comparisons across different studies, given the wide heterogeneity of the study protocols and cohorts. Nevertheless, the data presented in the present review suggest that GLP-1RAs are more effective at mitigating insulin-associated weight gain than DPP-4Is and that GLP-1RAs have also generally tended to provide somewhat greater reductions in hyperglycaemia. These observations are consistent with our understanding of these drugs’ pharmacological profiles, and with head-to-head comparisons of GLP-1RAs and DPP-4Is in clinical trials involving patients not receiving insulin; both liraglutide [65] and extended-release exenatide [66] have been shown to lower HbA1c and reduce weight to a greater extent than sitagliptin when added to metformin. However, against these efficacy advantages of the GLP-1RAs must be weighed the possible tolerability advantages of the DPP-4Is, including their oral administration and the reduced likelihood of gastrointestinal side-effects [6]. These issues require further testing in future trials as, indeed, do the relative performances of incretin + basal insulin regimens vs basal + bolus insulin regimens at various stages in the T2DM disease process. Another interesting concept that might be mechanistically evaluated is the combination of DPP-4Is with GLP-1RAs (with and without insulin). This might at first seem to be a strange idea, but as DPP-4 plays a role in the metabolism of at least some of the GLP-1RAs, such as liraglutide [67], the two drug types could potentially be combined synergistically.

It is also unclear how the efficacy of various incretin + insulin regimens will change over the course of the T2DM disease process, and thus, whether and how dosages will need to be adapted. Studies that provide specific guidance on dose adjustments for established insulin regimens when an incretin is added are especially welcome. Another related question is whether there will be a continuing role for incretin therapies when prandial insulin becomes necessary. An ongoing effect on alpha-cell function would imply that there could be a useful role for incretin therapies in late-stage T2DM or even in T1DM [68,69]. The prospect of prolonged use of incretin therapies also obliges us to study the long-term safety profiles of these agents and regimens [70]. Many useful new insights are already beginning to emerge from epidemiological and observational studies, and data are also expected from randomized trials currently in progress.

5. Where and when should incretin + insulin therapy be used?

Theoretically, it may be more appropriate to start with an incretin and then add insulin than vice versa, as this would avoid the complexity of having to down-titrate insulin; in addition, any nausea issues with GLP-1RAs are likely to have subsided by the time of insulin initiation. While the introduction of incretin therapy prior to insulin can be advocated, it should also be emphasized that patients suboptimally controlled by
high-dose basal insulin and those struggling to manage their weight can nevertheless still benefit from the addition of an incretin. This might permit substantial insulin dose reduction, although incretin therapies should not be regarded as a substitute for insulin. The impact of nausea with GLP-1RAs can be minimized with patient counselling, gradual GLP-1-RA dose escalation and perhaps mealtime administration of the drug [16].

In conclusion, incretin plus basal insulin therapy has a logical rationale, and may provide improved efficacy and tolerability in the treatment of T2DM. Indeed, there is already enough evidence to advocate this approach in patients who do not have contraindications and who have reached the point of requiring treatment intensification from metformin ± other OADs, or metformin plus basal insulin.

Disclosure of interest

J.V. has received support for research and attendance at national and international educational meetings, and honoraria for lecturing and sitting on advisory boards from Novo Nordisk, Eli Lilly, Sanofi Aventis, MSD Takeda, Novartis, Boehringer Ingelheim and Abbott Laboratories. S.C.B. reports having received lecture fees and research, educational and clinical grants from Boehringer Ingelheim, Diartis Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi Aventis, Schering-Plough, Servier and Takeda. T.D. has received consulting fees from AstraZeneca, Novo Nordisk and Sanofi Aventis. G.D. consults for LifeScan and Novo Nordisk, and has received lecture fees from Bioton, Eli Lilly, Novo Nordisk, Sanofi Aventis and Servier. L.F.M. has received consulting fees from Novo Nordisk and Sanofi Aventis, and has received grants or has grants pending with Boehringer Ingelheim, MannKind, Medtronic, Novo Nordisk and Pfizer. P.H. has consulted for Novo Nordisk. S.A.R. has received research funding and/or honoraria from Novo Nordisk, Eli Lilly, MSD, Boehringer Ingelheim, Sanofi Aventis and Bristol-Myers Squibb.

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Appendix A. Supplementary data

Supplementary material (Table S1) associated with this article can be found at http://www.sciencedirect.com, at http://dx.doi.org/10.1016/j.diabet.2012.08.002.

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