

Incretin Therapy – Present and Future

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■ Abstract

Although newer treatments for type 2 diabetes (T2D) patients have produced continual improvements in outcome, a large and growing population with prediabetes remains under-treated. In the last few years, incretin-based therapies have become an important treatment option for patients with T2D. There are two classes of incretin agents: the dipeptidyl peptidase-4 (DPP-4) inhibitors and the glucagon-like peptide 1 (GLP-1) receptor agonists. The ultimate goal of agents within both of these classes is to increase GLP-1 signaling, which results in augmented glucose-induced insulin secretion, inhibition of glucagon secretion, and decreased appetite. This should result in improved regulation of glucose homeostasis. GLP-1 receptor agonists enable patients to achieve significant weight loss. In contrast, DPP-4 inhibitors result in a less dramatic increase in GLP-1 levels; therefore,

they are weight neutral. Incretin therapies are currently recommended for use early in the treatment algorithm for T2D patients whose disease is not manageable by diet and exercise alone, but the potential for these agents may be farther reaching. Current studies are evaluating the potential benefits of combining incretin therapies with basal insulin to provide continuous glucose control before and after meals. In addition, these agents may be promising for patients with prediabetes since they effectively reduce glycosylated hemoglobin levels and fasting plasma glucose levels, enable weight control, and have the potential to preserve β -cell function. Clearly, all of these properties are desirable for patients with prediabetes.

Keywords: type 2 diabetes • hypoglycemia • glycemic control • antidiabetic • incretin • GLP-1 • DPP-4 • GLP-1 receptor agonist • prediabetes

Introduction

Although T2D represents a globally increasing social and economic burden, therapeutic outcomes are continually evolving and improving for this condition [1]. This may in part be due to an increasing disease burden giving physicians and researchers greater impetus to understand the disease, and to find improved management strategies. At present, new treatments are being introduced that take advantage of the recently discovered pathways involved in the disease process. In this article, the newer incretin therapies are reviewed, and their current and potential future therapeutic advantages are discussed.

As the physicians' armamentarium for T2D has expanded over the last 60 years, glycosylated hemoglobin (HbA1c) levels have generally improved throughout the patient population [1]. The key therapeutic agents that have been developed and used in the management of T2D are metformin, sulfonylureas, thiazolidinediones (TZDs), the α -glucosidase inhibitors, and insulin. Metformin is usually the first antidiabetic agent prescribed for patients with T2D who have not achieved glycemic control with dietary and lifestyle modifications. It has been used regularly since the second half of the twentieth century. Metformin improves the effectiveness of insulin in suppressing excess hepatic glucose production in the fasting and the

postprandial state. Also, it is effective both as monotherapy and in combination with other antidiabetic agents [2]. Sulfonylureas cause increased insulin secretion, and may render β -cells in the pancreas more glucose-sensitive. However, patients receiving sulfonylureas are at increased risk of developing hypoglycemia, which is the most severe adverse event associated with these agents [2]. Although sulfonylureas were the first-line drug of choice for many years, they have now been superseded by metformin, which was found to be more beneficial in obese patients [3]. TZDs first became available for treatment of patients with T2D in the mid-1990s. These agents increase insulin sensitivity in skeletal muscle, adipose tissue,

and liver, all of which result in increased glucose uptake and metabolism, and suppression of hepatic glucose production [2]. The enzyme α -glucosidase is situated in the epithelium of the small intestine and is required for the digestion and absorption of starch and disaccharides. α -glucosidase inhibitors were first approved in the mid-1990s. They delay the absorption of digested carbohydrates from the small intestine, ultimately lowering both postprandial glucose and insulin levels [4].

If patients do not achieve glycemic control with the above agents, insulin therapy has usually been the next choice as it replaces the deficiency in the natural hormone. Long-acting insulin is preferred because it has a sufficiently long time course to provide basal insulin coverage for a 24-hour period [2]. Although current therapies have been shown to improve overall glucose control, in the majority, they do not effectively target postprandial hyperglycemia [5]. Furthermore, sulfonylureas, TZDs, and insulin are all associated with weight gain, which is an important issue for patients with T2D [6]. Most recently, incretin-based therapies have been introduced. They are now recommended for the treatment of patients whose HbA1c levels remain uncontrolled with lifestyle modification alone and in whom metformin monotherapy is insufficient.

Although in general HbA1c levels continue to improve in patients with T2D, the number of patients who can be considered prediabetic because of obesity and/or metabolic syndrome is three times greater than those with T2D, and this population is currently under-treated [7]. Prediabetes may be classified as:

- a state of abnormal glucose homeostasis characterized by the presence of impaired fasting glucose (IFG),
- impaired glucose tolerance (IGT),
- or both.

The risk of patients with IGT to develop T2D has been reported as 5.72% per year [8], which rises to 11% per year in patients with IGT and IFG [9]. In addition to the risk of developing T2D, prediabetic patients are at increased risk of cardiovascular disease, which is itself associated with multifactorial etiologies including insulin resistance, hyperglycemia, dyslipidemia, hypertension, systemic inflammation, and oxidative stress [10]. Identifying and treating patients with prediabetes early may reduce the burden on healthcare pro-

Abbreviations:

ABCD - Association of British Clinical Diabetologists
 ACT NOW - Actos Now for the Prevention of Diabetes
 ADA - American Diabetes Association
 AGI - alpha-glucosidase inhibitor
 %B/T - rate of bound to total radioactivity
 bid - bis in die (twice daily)
 BMI - body mass index
 BP - blood pressure
 DREAM - Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
 DPP - Diabetes Prevention Program
 DPP-4 - dipeptidyl peptidase-4
 EASD - European Association for the Study of Diabetes
 FDA - Food and Drug Administration
 GIP - glucose-dependent insulinotropic peptide
 GLP-1 - glucagon-like peptide-1
 HbA1c - glycosylated hemoglobin
 HDL - high-density lipoprotein
 IFG - impaired fasting glucose
 IGT - impaired glucose tolerance
 LDL - low-density lipoprotein
 LEAD - Liraglutide Effect and Action in Diabetes
 MET - metformin
 mRNA - messenger ribonucleic acid
 NCT - National Clinical Trial
 OR - odds ratio
 PIPOD - Pioglitazone in Prevention of Diabetes
 po - per os (by mouth)
 qd - quaque die (once daily)
 qw - once weekly
 q2w - twice weekly
 SD - standard deviation
 SEM - standard error of mean
 SGLT-2 - sodium-glucose cotransporter 2
 STOP-NIDDM - Study to Prevent NIDDM
 SU - sulfonylureas
 T2D - type 2 diabetes
 TG - triglyceride
 Tid - ter in die (thrice daily)
 TRIPOD - Troglitazone in Prevention of Diabetes
 TZDs - thiazolidinediones
 XENDOS - Xenical in the Prevention of Diabetes in Obese Subjects

Table 1. Comparison of approved GLP-1 receptor agonists and DPP-4 inhibitors

Feature	GLP-1 agonists	DPP-4 inhibitors
Currently marketed	Exenatide, liraglutide	Sitagliptin, vildagliptin, saxagliptin
Mode of action	GLP-1 receptor agonist, resistant to degradation by DPP-4	Inhibits degradation of GLP-1, increases endogenous GLP-1 level
Usage	Combination with metformin ± SU ± TZD	Combination with metformin ± SU ± TZD
Administration	sc injection (pen)	Oral (tablet)
Reduction in HbA1c	~1% to 1.5%	~0.5% to 1%
Beta-cell function	Possibly improved	Possibly improved
Extraglycemic benefits	↓ BP, ↓ cholesterol, ↓ LDL, ↓ TG, ↑HDL, ↑ left ventricular function, ↑ arterial vasodilation	↓ BP (sitagliptin), ↓ cholesterol, LDL, TG, ↑HDL
Hypoglycemia	Very low risk	Very low risk
Weight	Reduction	Neutral
GI adverse effects	Frequent (~35% to 50%, dose-dependent and usually self-limited)	Uncommon
Gastric emptying	Slowed (most intensive effect with exenatide)	No effect
Other adverse effects	Pancreatitis	Nasopharyngitis, upper respiratory tract infection, headache; elevated liver enzymes (vildagliptin)

Legend: BP: blood pressure. GI: gastrointestinal. HDL: high-density lipoprotein. LDL: low-density lipoprotein. SU: sulfonylureas. TG: triglycerides. TZD: thiazolidinediones. Adapted from Khoo *et al.*, 2009 [18].

viders, and may ultimately make substantial cost savings [10, 11].

A range of effective treatments is now available for T2D patients. However, a much larger population of patients at risk of developing T2D remains largely untreated. Since impaired glucose control and high body mass index are associated with increased T2D risk, strategies to assist prediabetic patients with glucose and weight control will reduce the risk of progression to T2D. Incretin therapies are effective in the treatment of T2D, and have been associated with weight maintenance or loss.

Mechanisms of incretin action

Both insulin and glucagon are abnormally regulated in the pancreatic islet cells of T2D patients, leading to dysfunctional metabolism of both carbohydrates and lipids. The term ‘incretins’ is

used to describe gastrointestinal hormones that are released during nutrient absorption, and that increase insulin secretion. The incretin effect derives from the observation that significantly more insulin is secreted in response to oral glucose than in response to intravenous glucose [5]. The incretin effect helps to regulate postprandial glucose levels and accounts for 50-70% of insulin secretion in response to an oral glucose load [12, 13]. The two most important peptides causing the incretin effect are GLP-1 and glucose-dependent insulinotropic peptide (GIP) [5]. Both of these incretins act to normalize glucagon secretion, but in diabetes only GLP-1 acts to increase glu-

ucose-induced insulin secretion [12].

GLP-1 is synthesized in L-cells primarily found in the distal small bowel and colon. It stimulates glucose-induced insulin secretion, inhibits glucagon secretion in a glucose-dependent manner, reduces appetite, and delays gastric emptying. Therefore, it regulates glucose homeostasis. GLP-1 has also been shown to enhance satiety and inhibit food intake, and may therefore help to control body weight [12, 14, 15]. GIP is secreted by duodenal and proximal jejunal K-cells. It stimulates insulin biosynthesis and secretion in a glucose-dependent manner [12]. Shortly after secretion, both GIP and GLP-1 undergo rapid metabolism (proteolytic cleavage) by the enzyme DPP-4 to become inactive metabolites [16]. This decreases the availability of GLP-1 and GIP to act on islet cells and other organs.

In patients with T2D, the insulinotropic effect of GIP is almost completely lost [14]. Unlike GLP-1,

Table 2. Maximum changes in HbA1c and effects on body weight reported with various DPP-4 inhibitors

Drug	Dose	Maximum change in HbA1c (% \pm SD)	Maximum change in body weight (kg \pm SD)
Sitagliptin + metformin [26]	100 mg qd	-0.67 \pm 0.1 [‡]	-0.6 - -0.7 [*]
Vildagliptin [27]	100 mg qd	-1.1 \pm 0.1 [‡]	-0.3 \pm 0.2
Saxagliptin + metformin [28]	5 mg qd	-0.69 \pm 0.07 ^{¶§}	-0.87
Saxagliptin +TZD [29]	5 mg qd	-0.94 ^{¶§}	+1.4
Linagliptin + metformin [30]	1 mg	-0.4 \pm 0.14 ^{†§}	-0.15
	5 mg	-0.73 \pm 0.14 ^{†§}	-0.57
	10 mg	-0.67 \pm 0.14 ^{†§}	-1.27
Alogliptin [32]	12.5 mg	-0.56 [‡]	-0.1 \pm 0.26 [§]
	25 mg	-0.59 [‡]	-0.2 \pm 0.26 [§]
Dutogliptin + metformin and/or TZD	200 mg	-0.52 [‡]	-0.36
	400 mg	-0.35 [‡]	-0.23

Legend: qd: once daily. ^{*}p < 0.05; [†]p \leq 0.006; [‡]p < 0.001; [¶]p < 0.0001; [§]SEM (each versus placebo or comparator alone).

continuous infusion of GIP does not sustain long-term insulin secretion and insulin levels [16], thus limiting its use as therapy for this condition. Similarly, because of the resistance associated with T2D, insulin has decreased efficacy in patients with T2D. In contrast to both of these agents, GLP-1 effects are not blunted in T2D. Therefore, this peptide is a useful therapeutic target in this condition [12].

Incretin-based therapeutic agents mediate their effects through mimicking or enhancing GLP-1 activity. DPP-4 inhibitors enhance incretin levels by inhibiting incretin clearance, and GLP-1 receptor agonists are incretin mimetics. The key differences between the GLP-1 receptor agonists and the DPP-4 inhibitors largely relate to differences in the degree of the resulting GLP-1 elevation. The different effects and usages are summarized in Table 1.

DPP-4 inhibitors

DPP-4 inhibitors are taken orally. They block DPP-4 activity, and thereby prevent GLP-1 metabolism, and increase the free levels of GLP-1. As GLP-1 enhances insulin secretion in response to a meal, DPP-4 inhibitors have been reported to cause a 0.5-1% HbA1c reduction [17, 18]. Also, DPP-4 inhibitors lead to reduced appetite and de-

creased gastric emptying, and are not associated with hypoglycemia or weight gain [18]. DPP-4 inhibitors are formulated to allow once daily dosing, and the pharmacokinetics are not affected by age, gender, ethnicity, or body mass index. Also, no significant drug interactions have been documented [19]. Common adverse events associated with DPP-4 inhibitors include upper respiratory infections, nasopharyngitis, and headache [16]. An overview of maximum changes in HbA1c and effects on body weight reported with various DPP-4 inhibitors is provided in Table 2.

Approved DPP-4 inhibitors

Four DPP-4 inhibitors are approved for the treatment of T2D. The key clinical data have been reviewed substantially elsewhere [5, 18, 20-25]. Sitagliptin (Januvia[®], Merck and Co.) was the first DPP-4 inhibitor approved, gaining its marketing license in 2007. In combination with metformin, it has been associated with reductions in HbA1c of 0.67% and mild reductions in body weight (0.6-0.7 kg) [26]. Following successful clinical trials, the dose of 100 mg was selected as the optimal dose. Sitagliptin is taken once daily, orally, with or without food.

Vildagliptin (Galvus[®], Novartis) was subsequently approved in Europe in 2007 for use in combination with metformin, sulfonylurea, or TZDs, but it is not currently licensed in the USA. The Food and Drug Administration (FDA) requested further assessment of vildagliptin in patients with renal impairment early in 2007. The current plans for vildagliptin in the USA remain unclear. In clinical trials, vildagliptin monotherapy was associated with reductions in HbA1c of 1.1% and weight neutrality or minor loss (-0.3 \pm 0.2 kg) [27]. Each tablet contains 50 mg vildagliptin, and recommended doses are once daily (in combination with a sulfonylurea) or twice daily (in combination with metformin) orally, with or without food.

Saxagliptin (Onglyza[™], Bristol Myers Squibb and AstraZeneca) was approved in 2009. It has shown comparable efficacy in combination with metformin or TZDs (reduction in HbA1c of 0.69% and 0.94%, respectively) [28, 29]. Generally, saxagliptin has been shown to be weight neutral.

Weight changes reported in the clinical trials are predominantly attributable to the combination agent rather than to saxagliptin itself. A dose of 5 mg is taken once daily as add-on combination therapy to metformin, a TZD, or a sulfonylurea, with or without food.

In 2011, linagliptin (Boehringer Ingelheim, and Eli Lilly and Company) was approved for use in the USA (Tradjenta™), Europe (Trajenta®), Japan (Trazenta), and Mexico and Brazil (Trayenta) as monotherapy or in combination with other medications for type 2 diabetes. Approval was granted in response to positive data that showed significant and clinically relevant improvements in glycemic control (reductions in HbA1c of 0.73%) and non-significant reduction in body weight (loss of 0.57 kg) at a dosage of 5 mg once daily [30]. Following previous concerns expressed by the FDA with regard to vildagliptin, linagliptin has been studied in patients with renal impairment, and no dose adjustments were required [31].

Developmental DPP-4 inhibitors

There are several other DPP-4 inhibitors in clinical development but some have limited clinical data reported. In a phase III study with alogliptin (SYR-322, Takeda), reductions in HbA1c were reported as 0.56% at 12.5 mg once daily and 0.59% at 25 mg once daily. Body weight remained approximately constant [32]. However, the FDA did not approve this agent, citing insufficient data on cardiovascular risks. Takeda is now conducting long-term safety trials to evaluate cardiovascular risks [33], and has notified the European Medicines Agency of its intention to submit marketing approval application upon completion of these trials.

Several DPP-4 inhibitors have either been discontinued or have no data reported. Although positive phase III data were reported for dutogliptin (PHX1149, Phenomix Corporation), with reductions in HbA1c of 0.52% versus placebo and no notable changes in weight [34], all clinical studies have now been terminated. Similarly, development of denagliptin (GSK) has been terminated because of toxicity issues. No data have been reported on either teneligliptin (Mitsubishi Tanabe) or gemigliptin (LG Life Sciences).

Table 3. Maximum changes in HbA1c and effects on body weight reported with various GLP-1 receptor agonists

Drug	Dose	Maximum change in HbA1c (% ± SD)	Maximum change in body weight (kg ± SD)
Exenatide + sulfonylurea [42]	10 µg bid	-0.86 ± 0.11 [†]	-1.6 ± 0.3 [†]
Exenatide + metformin [43]	10 µg bid	-0.78 ± 0.10 [†]	-2.8 ± 0.5 [†]
Liraglutide + metformin +/ sulfonylurea [45]	1.8 mg qd	-1.12 (1.2) [†]	-3.2 ± 0.3
Taspoglutide + metformin [49]	20 mg qw	-1.2 ± 0.1 [¶]	-2.8 ± 0.3 [¶]
	10 mg q2w	-1.0 ± 0.1 [¶]	-1.9 ± 0.3 [§]
Lixisenatide + metformin [62]	30 mg qd	-0.76 [§]	-3.5 ± 0.4 [§]
	30 mg bid	-0.87 [§]	-3.9 ± 0.4 [§]
Albiglutide (phase II) [107]	30 mg qw	-0.87 ± 0.65 [†]	-1.1 to -1.7
	50 mg q2w	-0.79 ± 0.98 [†]	(details not provided per dosing)
	100 mg qm	-0.87 ± 0.87 [†]	

Legend: bid: twice daily. qd: once daily. qw: once weekly. q2w: twice weekly. qm: once monthly. [†]p < 0.05; [§]p < 0.01; [¶]p < 0.002; [‡]p < 0.001; [¶]SEM p < 0.0001 (each versus placebo or comparator alone).

GLP-1 receptor agonists

By mimicking the effects of GLP-1, GLP-1 receptor agonists inhibit glucagon and stimulate insulin secretion in a glucose-dependent manner, reduce the gastric emptying rate, and suppress appetite [35]. GLP-1 agonists, which are administered by subcutaneous (sc) injection, are a good alternative to insulin therapy in patients not achieving glucose control with oral therapies. This therapy combines effective glycemic control with weight loss [36, 37]. The licensed agents are formulated into a pen-type prefilled syringe, and are self-administered once or twice daily. Agents with longer half-lives, requiring less frequent injection, are in clinical development. The main adverse events associated with GLP-1 receptor agonists are gastrointestinal in nature, most commonly nausea. An overview of maximum changes in HbA1c and effects on body weight reported with various GLP-1 receptor inhibitors is provided in Table 3.

Approved GLP-1 receptor agonists

Two GLP-1 receptor agonists are approved for the treatment of T2D, namely exenatide and liraglutide. The clinical data have been reported extensively elsewhere [5, 18, 21, 23-25, 35, 37-40]. Briefly, Exenatide (Byetta®; Amylin Pharmaceuti-

cals and Eli Lilly and Company) was approved as add-on therapy with metformin, or sulfonylureas, or TZDs, or a combination, in 2006. It is administered by twice daily sc injection at doses of 5-10 µg before meals [38, 41]. Exenatide reduced HbA1c levels by approximately 0.8-1.0% from baseline, and resulted in weight loss of 2-3 kg after 30 weeks [42, 43]. Also, exenatide was associated with improvements in fasting plasma glucose levels of approximately 1.4 mmol/l [35].

Liraglutide (Victoza®; Novo Nordisk) received marketing approval for use as add-on therapy with metformin, or sulfonylureas, or TZDs, or a combination, in 2009. For improved patient convenience, liraglutide 1.8 mg is a once-daily formulation that can be taken independently of meal times [44]. In a head-to-head comparison of liraglutide and exenatide in combination with metformin and/or sulfonylurea [45], liraglutide reduced HbA1c by significantly more than exenatide ($1.12 \pm 0.08\%$ vs. $0.79 \pm 0.08\%$, $p < 0.0001$), and patients achieved weight loss of 3.24 ± 0.33 kg, which was similar to the weight loss achieved with exenatide (2.87 ± 0.33 kg). Moreover, liraglutide was associated with significantly greater reductions in mean fasting glucose levels than exenatide ($p < 0.001$) [45].

Generally, therapeutic proteins/peptides with low structural similarity to endogenous proteins/peptides have more immunogenicity, which in turn can lead to increased risk of adverse events or reduced efficacy. Exenatide is a synthetic exendin-4 xenopeptide and shares 53% homology with human GLP-1, whereas liraglutide is a recombinant human GLP-1 analog, sharing 97% homology with human GLP-1. The Liraglutide Effect and Action in Diabetes (LEAD)-6 trial, was an open-label, head-to-head study designed to compare immunogenic responses in patients receiving liraglutide or exenatide in combination with metformin and/or sulfonylurea [46]. After 26 weeks of treatment, 8.7% and 8.3% of patients receiving once daily liraglutide (1.2 mg and 1.8 mg respectively) had anti-liraglutide antibodies (range 1.6-10.7 antibody-bound radioactivity out of total radioactivity, %B/T) compared with 61% of patients receiving exenatide with anti-exenatide antibodies (range 2.4-60.2, %B/T). The levels of anti-liraglutide antibodies observed were not found to correlate with negative effects on glycaemic efficacy of liraglutide. However, high levels of anti-exenatide antibodies were correlated with significantly smaller reductions in HbA1c in patients treated with exenatide ($p = 0.0022$).

Developmental GLP-1 receptor agonists

GLP-1 receptor agonists are administered subcutaneously. Long-acting formulations are in development. These may improve the rates of patient treatment compliance. A once-weekly formulation of exenatide (Bydureon®) is undergoing clinical development. Data were recently released from an open-label 26-week, multicenter clinical study, comparing exenatide 2 mg weekly with liraglutide 1.8 mg daily (DURATION-6) [33]. As once-weekly exenatide showed reductions in HbA1c of 1.3% and liraglutide showed reductions of 1.5%. Exenatide did not meet its primary endpoint of non-inferiority compared with liraglutide. Also, injection site nodules were reported in 10% of patients receiving once-weekly exenatide compared with 1% of patients receiving liraglutide. However, there were more GI adverse effects with liraglutide than exenatide [47].

Taspoglutide (R1583/BIM51077; Hoffmann-La Roche) is another long-acting GLP-1 agonist, which has 97% homology with human GLP-1 [48]. Taspoglutide is administered once weekly sc, but has also been shown to have efficacy when given biweekly [49]. The once-weekly dose resulted in HbA1c decreases of 1.2% and weight loss of 2.8 ± 0.3 kg [49]. However, taspoglutide is currently undergoing reformulation because of a high incidence rate of unspecified adverse events that may have been immunologic in nature [50].

Lixisenatide (AVE0010; Sanofi-Aventis) and albiglutide are other GLP-1 receptor agonists currently undergoing clinical evaluation. Lixisenatide is an exendin-4 analog with a modified C-terminus containing six Lys residues, meaning it is able to withstand physiological degradation by DPP-4 [51]. In a phase III trial, metformin plus lixisenatide 5, 10, 20, and 30 µg once or twice daily significantly improved mean HbA1c in a dose-dependent manner versus placebo ($p < 0.01$). Once or twice daily doses of lixisenatide 30 mg were associated with weight loss of 3-4 kg [49]. It has recently been announced that the primary efficacy endpoint (significant reduction in HbA1c versus placebo, $p < 0.0002$) was met in a phase III trial in which lixisenatide was used as an add-on therapy to basal insulin (with or without metformin) [52]. Also, lixisenatide treatment resulted in a significant reduction in body weight ($p < 0.0001$), significantly improved post-prandial plasma glucose ($p < 0.0001$), and no significant increase in symptomatic hypoglycemia ($p = 0.14$). Additionally, lixisenatide is undergoing phase III evaluation in

combination with other antidiabetic agents and as monotherapy [33]. It is also being developed with insulin glargine (Lantus®) as a combination product [53].

Albiglutide is an albumin-fusion peptide, which has a prolonged half-life as a result of its fusion with albumin and associated resistance to DPP-4 degradation, meaning that it can be administered once weekly via sc injection. When compared with placebo in a phase III trial, mean HbA1c was significantly reduced from baseline by albiglutide by approximately 0.8% with various dosing schedules (each $p < 0.05$), and weight losses of 1.1-1.7 kg were reported [54]. Further phase III trials with albiglutide are currently in progress [33, 55, 56].

Current applications of incretin therapy

Incretin therapy has a range of therapeutic benefits for patients with T2D, including improvement of β -cell function, stimulation of insulin secretion, and inhibition of glucagon secretion. Moreover, incretin therapy has been shown to reduce appetite, which has been associated with stabilization of body weight and/or promotion of weight loss in patients with T2D [1]. As the various incretin therapies have been approved over the last 5 years, the treatment algorithm for T2D has evolved to incorporate both GLP-1 receptor agonists and DPP-4 inhibitors. Because of their weight-neutral or weight-reducing effects, incretin therapies can easily be combined with more traditional therapies. They now play an important role in the early management of T2D [2]. The currently recommended applications of incretin therapies as monotherapy and in combination with metformin, TZDs, or sulfonylureas are shown in Figure 1.

As reviewed above, the two subtypes of incretin therapy have different advantages and disadvantages in terms of reductions in HbA1c and body weight, and route of administration. In a multinational internet-based survey [57], patients were asked to consider their preferences regarding the route of administration and other factors determining the therapeutic drug profile for incretin therapies. Most patients reported that on balance they would prefer to receive an oral drug such as sitagliptin (83.2%) over a sc product such as liraglutide (16.9%). Eighty percent of patients would find it more straightforward and achievable to take an oral drug as directed by their physician for a longer period than a sc agent. The likelihood of preferring the sitagliptin-like profile signifi-

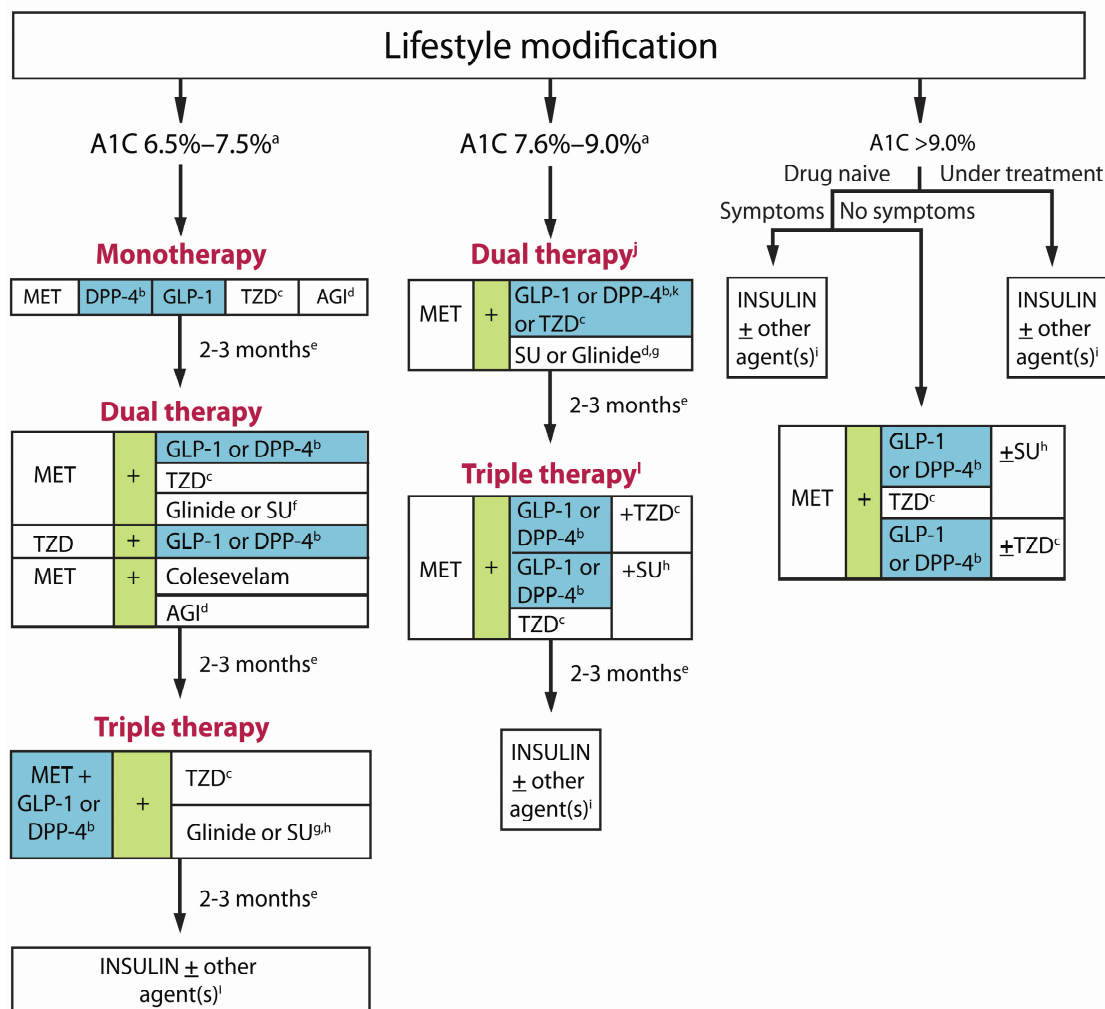
cantly increased with patient age (OR = 1.02) and with the importance placed on the method of administration (OR = 1.32, $p < 0.05$). Conversely, patients ranking glycemic efficacy and weight loss as the most important factors preferred the liraglutide-like profile [57-59].

The ADA/EASD Consensus Panel [60] placed greater emphasis on GLP-1 receptor agonists than DPP-4 inhibitors, based on their associated beneficial weight loss. However, these benefits should be balanced against patients' feelings regarding daily self-injection and their sensitivity to gastrointestinal side effects. Therefore, DPP-4 inhibitors may be more suitable for some patients [1]. In patients for whom GLP-1 receptor agonists are the preferred choice, long-acting agents provide multiple benefits over short-acting ones, and these benefits are not solely related to the need for less frequent sc injections. Indeed, long-acting agents have been associated with increased glucose control and reduced incidence of adverse events in addition to improved compliance.

The more traditional therapies for T2D such as TZDs, sulfonylureas, and insulin often result in body weight increments, which are clearly not desirable in patients who may already be overweight or obese. As mentioned above, the DPP-4 inhibitors are considered to be weight neutral, and can be combined with these other therapies without compounding weight gain. However, DPP-4 inhibitors may mitigate or counteract treatment-induced weight gain. In contrast, GLP-1 receptor agonists have been associated with reductions in body weight of approximately 3.0 kg when administered as monotherapy or in combination with metformin [43, 45, 61, 62]. These benefits were obviously recognized by certain subsets of patients who participated in the multinational internet-based patient preference survey. Those participants who were obese, had experienced weight gain with previous therapies, had HbA1c values above target, and exercised, reported a preference for the liraglutide-like profile ($p < 0.05$) [57]. For these patients, the benefits relating to body weight of the GLP-1 receptor agonists appeared to outweigh the inconvenience of the sc administration.

Other potential applications of incretin therapy

As the range of benefits associated with incretin therapy has been recognized, treating physicians are looking at other potential applications in patients with T2D and beyond. For example, it has been suggested that incretin therapy may be



A1C indicates glycosylated hemoglobin; AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; AGI, alpha-glucosidase inhibitor; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; MET, metformin; PPG, postprandial glucose; SU, sulfonylurea; TZD, thiazolidinedione.

^aFor patients with diabetes and A1C <6.5%, pharmacologic treatment may be considered.

^bDPP-4 if ↑ PPG and ↑ FPG or GLP-1 if ↑ PPG.

^cTZD if metabolic syndrome and/or nonalcoholic fatty liver disease.

^dAGI if ↑ PPG.

^eIf A1C goal not achieved safely.

^fLow-dose secretagogue recommended.

^gGlinide if ↑ PPG or SU if ↑ FPG.

^hDecrease secretagogue by 50% when added to GLP-1 or DPP-4.

ⁱa) Discontinue insulin secretagogue with multidose insulin; b) can use pramlintide with prandial insulin.

^jIf A1C <8.5%, combination pharmacologic treatment with agents that cause hypoglycemia should be used with caution.

^kGLP-1 not approved for initial combination pharmacologic treatment.

^lIf A1C >8.5%, in patients on dual therapy, insulin should be considered.

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Figure 1. The ACCE/ACE diabetes treatment algorithm [2].

more appropriate for use early in the treatment algorithm for T2D patients [21], potentially even at diagnosis [36], to maximize residual β -cell function. Furthermore, liraglutide has been evaluated in a phase III trial, which showed successful weight loss in obese patients who did not have

T2D [63]. Liraglutide also improved certain obesity-related risk factors, and reduced levels of pre-diabetes in these patients.

Some authors have suggested that combining incretin therapies with basal insulin may be an advantageous treatment approach to enable pa-

tients with T2D to avoid the need for meal-time insulin [36]. These therapies may be complementary to each other for a variety of reasons, particularly as they have distinct mechanisms of action. Therefore, they have the potential for a synergistic effect [36]. GLP-1 therapies have been shown to reduce elevated postprandial glucose levels [43, 61, 64], which would be complemented by the better fasting plasma glucose-lowering activity of basal insulin. In addition to providing consistent glucose control, the combination of these two classes of antidiabetic agents has the potential to positively affect weight management in patients with T2D. Insulin use is commonly associated with weight gain, but the addition of a GLP-1 receptor agonist may counteract this, and thus offer weight neutrality for patients. Indeed, a retrospective analysis of off-label exenatide used in combination with insulin and oral agents in 188 patients showed reductions in HbA1c of 0.54% and weight loss of 5.5 kg over a course of 2 years [65].

Arnolds *et al.* have reported findings from a proof-of-concept study, in which insulin glargine plus metformin with or without exenatide 5-10 µg bid or sitagliptin 100 mg qd were co-administered in an attempt to determine whether the theoretical advantages of combining these agents could be practically demonstrated [66]. Data showed that HbA1c was significantly decreased from baseline in all three groups ($p < 0.001$), but the exenatide-containing regimen resulted in a significantly larger decrease in HbA1c than insulin glargine plus metformin alone ($p = 0.0154$). The addition of an incretin-based therapy substantially decreased postprandial glucose increments (exenatide $p = 0.0036$ and sitagliptin $p = 0.0008$). Also, the exenatide-containing combination (but not the sitagliptin-containing combination) resulted in weight loss of 0.9 ± 1.7 kg ($p = 0.0396$), as hypothesized.

Another study by Buse *et al.* examined whether administration of exenatide (10 µg bid) further reduced HbA1c levels in patients receiving insulin glargine was conducted [67]. Over a period of 30 weeks, exenatide treatment resulted in a significant ($p < 0.001$) decrease in HbA1c versus placebo in patients receiving insulin glargine. Also, 60% of patients who received exenatide (versus 35% in the placebo group) achieved the target HbA1c value of 7.0% or less. The proportion of patients reporting hypoglycemia was unaffected by exenatide treatment. However, exenatide treatment resulted in a modest (but significant) weight loss compared with placebo ($p < 0.001$), as observed previously.

The Association of British Clinical Diabetologists (ABCD) conducted a nationwide audit to assess the use of exenatide in the UK [68]. It showed that of the 4857 patients for whom baseline and follow-up data were provided, 1921 (39.6%) were receiving exenatide off-label in combination with insulin therapy.

In addition to the modulation of incretin signaling, another important emerging therapeutic approach is the inhibition of the sodium-glucose cotransporter 2 (SGLT-2) [69]. SGLT-2 is situated in the kidney and plays an important part in controlling renal glucose reabsorption. Inhibition of SGLT-2 causes inhibition of this glucose reabsorption. Therefore, it has the potential to reduce hyperglycemia in patients with T2D. A recent meta-analysis of randomized trials concluded that, while dapagliflozin treatment resulted in significant reductions in HbA1c and fasting plasma glucose, it also led to an increased risk of urinary and genital tract infections [70]. A number of SGLT-2 inhibitors are currently in development for the treatment of T2D. Dapagliflozin, tagatose, and succinbucol are all in late-stage development [33, 71, 72].

Prediabetic patients

According to ADA and EASD consensus statements, IFG (plasma glucose concentration of 100-125 mg/dl and a 2-hour post-challenge plasma glucose concentration of <200 mg/dl) and IGT (fasting plasma glucose concentration of <126 mg/dl and a 2-hour post-challenge plasma glucose concentration of 140-199 mg/dl) characterize abnormal glucose metabolism and define a prediabetic state, in which the risk of developing T2D is increased [73, 74]. These states of abnormal glucose control form part of a continuum of risk; patients initially suffer from obesity and/or metabolic syndrome that leads to the prediabetic state and ultimately results in the development of T2D. Indeed, even lower glucose concentration cut-offs may be appropriate for diagnosing some patients with equal levels of risk for developing T2D and its cardiovascular sequelae [7].

Obese patients are at increased risk of developing insulin resistance and subsequent T2D as adipose cells release non-esterified free fatty acids, hormones, adipocytokines, and other substances that contribute to insulin resistance in these patients [75]. Under normal conditions, pancreatic islet β -cells respond to glucose by increasing insulin production, which counteracts increased blood glucose concentrations and maintains normal

blood glucose levels. However, in genetically predisposed patients, β -cells eventually become dysfunctional, perhaps because of the increased activity required to counteract prolonged levels of high blood glucose, and this ultimately leads to T2D. Prediabetes is frequently diagnosed in patients who are obese or have metabolic syndrome [76]. While prediabetes and metabolic syndrome are two distinct conditions, there are clinical similarities, and there is some overlap as metabolic syndrome also increases equally the risk for T2D and cardiovascular disease [77]. Importantly, arresting the progression of the risk continuum in individuals with obesity by encouraging them to lose weight can delay or sometimes prevent the development of T2D [75, 78].

A series of studies have been conducted to investigate the effects of lifestyle intervention on prevention of T2D. These interventions include healthy eating and moderate intensity exercise programs leading to weight loss. The programs have shown reasonable levels of success in reverting patients from a prediabetic state and normalizing glucose tolerance. The first study was reported by Eriksson and Lindgärde [79]. They conducted a 6-year follow-up of lifestyle intervention strategies in patients newly diagnosed with, or considered high risk for the development of, T2D. Lifestyle interventions included: dietary treatment and/or increase of physical activity or training. After 6 years, >50% of patients achieved normal glucose tolerance and >50% of patients with diabetes reverted to a non-diabetic state.

A similar 6-year study by Pan *et al.* randomized patients to diet modifications, or an exercise program, or both [80]. Diet modifications included increased consumption of vegetables, controlled alcohol intake, and reduced intake of simple sugars. Subjects with BMI ≥ 25 kg/m² were encouraged to reduce their calorie intake and gradually lose 0.5-1.0 kg per month until they achieved a BMI of 23 kg/m². Subjects assigned to exercise were encouraged to increase the amount of physical exercise by at least one level per day (such as mild activity to moderate or strenuous to very strenuous) or by two levels per day (such as mild to strenuous), if possible, for those <50 years of age with no evidence of cardiovascular disease or arthritis. After 6 years, the risk of diabetes was reduced by 36% in the diet group, 47% in the exercise group, and 39% in the combined intervention group, although it was difficult to confirm how effectively subjects had maintained the lifestyle modifications over the 6-year period.

Patients in the Diabetes Prevention Program (DPP) with elevated fasting and post-load plasma glucose concentrations undertook lifestyle modifications (diet and exercise) or received placebo or metformin (850 mg bid) [9]. The lifestyle modifications were substantially more effective than metformin at reducing the risk of T2D. The former resulted in a 58% decrease in the incidence of diabetes versus placebo at an average follow-up of 2.8 years, whereas the latter resulted in a 31% decrease. Another successful study of intervention strategies including dietary and exercise counseling was reported by Tuomilehto *et al.*, [81, 81]. In this study, middle-aged, overweight patients with impaired glucose tolerance were randomized to intervention or control. Median follow-up was 3.2 years. The risk of progression to T2D was significantly reduced in the intervention group compared with the control group ($p < 0.001$).

However, despite these promising findings and clear evidence that lifestyle changes can prevent or reduce the risk of patients with obesity, prediabetes, and/or metabolic syndrome from developing T2D, experience shows that many T2D patients find it difficult to maintain lifestyle changes over prolonged periods, and subsequently go on to require pharmacotherapy [82]. The difficulty in maintaining lifestyle changes may prove to be particularly important in prediabetic patients, as these individuals may not consider themselves to have an illness, and may therefore place a lesser value on the benefit and importance of maintaining lifestyle changes. In many cases, therefore, patients with prediabetes may benefit from antidiabetic medications and to date, several other studies have assessed the benefit of prescribing these agents in an attempt to prevent or delay the progression to T2D.

The TRIPOD study followed patients for a median of 2.5 years and reported a 55% relative risk reduction of progression to T2D with the TZD troglitazone 400 mg/day versus placebo [83]. The subsequent PIPOD study was conducted with the TZD pioglitazone 30 mg/day, and followed patients for a further median of 3.0 years. There was no comparator arm in this study, but a rate of diabetes incidence was recorded at 4.6% per year, which is comparable to the incidence with troglitazone in the TRIPOD study [84].

The XENDOS study evaluated orlistat 120 mg tid in this setting, and followed patients for a median of 4.0 years [85]. Orlistat is an anti-obesity drug that inhibits gastric and pancreatic lipases; consequently triglycerides from the diet are not

hydrolyzed into absorbable free fatty acids, and are excreted in an undigested state. The data showed that orlistat was associated with a 37% relative risk reduction of progression to T2D versus placebo.

Similarly, in the DREAM study, use of TZD rosiglitazone 8 mg/day resulted in a 60% relative risk reduction of developing T2D versus placebo at a median follow-up of 3.0 years [86]. More recently, data from the ACT NOW study with pioglitazone 45 mg/day, which followed patients for a median of 2.4 years, reported a 72% relative risk reduction of progression to T2D versus placebo. However, pioglitazone treatment was found to result in significant weight gain (3.9 kg, $p < 0.001$) and increased incidence of edema compared with placebo [87, 88].

Patients were followed for a median of 3.2 years in the STOP-NIDDM study, which evaluated the efficacy of acarbose in this setting [89]. Acarbose inhibits α -glucosidase, which releases glucose from larger carbohydrates. The study findings showed that acarbose 100 mg tid led to a 36% relative risk reduction of progression to T2D versus placebo.

In summary, substantial evidence exists that supports the introduction of lifestyle (diet and exercise) and/or pharmacological measures in the prevention of progression to T2D [74, 90]. Indeed, diet and exercise leading to weight loss, and pharmacological interventions, associated with improvements in IFG and IGT have been shown to have comparable effects in the reduction of progression to T2D [91].

Potential applications of incretin therapy in prediabetic patients

Treatments that assist with management or maintenance of body weight in addition to glucose control may be particularly beneficial in patients with prediabetes. Since DPP-4 inhibitors have been shown to maintain body weight, and GLP-1 receptor agonists have been shown to reduce body weight, incretin therapies appear to be logical and promising in this setting.

Furthermore, as the onset of T2D is preceded by a marked deterioration in pancreatic β -cell function [92], agents that can preserve β -cell function in addition to controlling glucose levels and body weight would appear particularly promising in this population. GLP-1 is supposed to improve the function of pancreatic β -cells by promoting neogenesis and proliferation, and by decreasing apoptosis signals [93, 94]. Therefore, the incretin

agents, which utilize GLP-1 receptor signaling, may have the potential to improve β -cell function. Indeed, in cultured β -cells and in a rodent model of diabetes, GLP-1 receptor agonists have been shown to cause an increase in β -cell mass [95].

The effects of liraglutide on obese patients with prediabetes have been evaluated in the clinic [63]. In this study, liraglutide (1.2, 1.8, 2.4, and 3.0 mg sc once daily) was compared with the anti-obesity agent orlistat (120 mg po tid) or with placebo (sc qd). The authors reported that liraglutide was associated with significantly greater weight loss than placebo ($p < 0.0001$ at 1.8-3.0 mg) or orlistat ($p < 0.0001$ at 3.0 mg), and an 84-96% reduction in the prevalence of prediabetes with 1.8-3.0 mg per day was observed. Furthermore, patients receiving liraglutide experienced reductions in blood pressure at all doses [63].

It was hypothesized that the combination of the α -glucosidase inhibitor voglibose and the DPP-4 inhibitor alogliptin would prevent the inactivation of intact GLP-1, and enhance its release, resulting in increased levels of active GLP-1 in circulation. Moritoh *et al.* conducted a study of alogliptin (0.03%) and voglibose (0.001%) alone or in combination in prediabetic db/db mice [96]. After 3-4 weeks, the combination increased active GLP-1 circulation, increased insulin secretion, and decreased glucagon secretion substantially more than either agent alone. Furthermore, the combination was also associated with prevention of T2D, and preserved pancreatic β -cells and islet structure.

A range of further studies is currently ongoing or planned with DPP-4 inhibitors (sitagliptin, saxagliptin, and alogliptin) and with GLP-1 receptor agonists (exenatide and liraglutide) in the setting of prediabetes [33]. These include:

1. A randomized, open-label study to compare the effects of sitagliptin, glimepiride and exenatide on functional β -cell mass in patients with prediabetes or early type 2 diabetes in (NCT0775684).
2. A randomized, double-blind study to determine the effects of sitagliptin (alone or in combination with pioglitazone) on insulin secretion and response in patients with IGT (NCT01006018).
3. A phase IV, randomized, open-label study to assess the vascular effects of exenatide versus metformin in obese patients with IGT (NCT00546728).
4. A phase III, randomized, double-blind trial

to evaluate the potential of liraglutide to induce and maintain weight loss, and to delay the onset of type 2 diabetes in non-diabetic obese patients, or overweight patients with comorbidities (NCT01272219).

Safety of incretin therapy

The long-term safety of incretin therapy is yet to be determined. Concern has been expressed regarding the potential of incretin-based therapies to result in complications such as acute pancreatitis, C-cell hyperplasia, and medullary thyroid cancer.

Acute pancreatitis

Patients with T2D exhibit significantly increased rates of acute pancreatitis compared with the general population [97]. Also, there are many known risk factors and predisposing factors for acute pancreatitis, and a wide range of drugs has been found to be associated with development of the condition [98]. Therefore, it is perhaps not surprising that acute pancreatitis has been observed in patients with T2D receiving incretin therapies. Data collected from drug safety surveillance systems and pooled analyses of clinical trials indicate that rates of pancreatitis are no higher for sitagliptin or exenatide compared with other antidiabetic agents [99-101]. Data from the LEAD clinical trial program indicated that treatment with liraglutide may result in slightly higher rates of acute pancreatitis, but the number of reports/patients was not sufficient to draw clear conclusions as to the cause of the pancreatitis cases observed [102].

In response to the cases of acute pancreatitis observed in both clinical studies and postmarketing reports, the FDA required the manufacturers of liraglutide, exenatide, and sitagliptin to prominently address the possible increased risk of pancreatitis in the product labeling; for example, all patients should be monitored closely during treatment for signs or symptoms of acute pancreatitis, and these treatments should be used with caution in patients with a history of pancreatitis [103].

C-cell hyperplasia and medullary thyroid cancer

In rodents, C-cell hyperplasia is regarded as a preneoplastic lesion leading to medullary thyroid cancer [104]. Preclinical studies of liraglutide at

doses resulting in plasma drug levels similar to those seen in humans at approved doses have shown an increase in occurrence of benign C-cell adenomas. Doses of liraglutide resulting in 8-fold plasma levels compared with those seen in humans receiving the maximum approved dose resulted in a significant increase in the incidence of malignant C-cell carcinomas [103].

Knudsen *et al.* investigated the species-specific differences in C-cell number, GLP-1 receptor expression, and effects of GLP-1 receptor agonists in the thyroid [105]. In rats and mice, C-cell densities in the thyroid glands were found to be 22- and 45-fold higher, respectively, than that reported for humans, whereas C-cell densities in the thyroid glands of cynomolgus monkeys were comparable to those in humans. In rodents, exposure to liraglutide resulted in calcitonin secretion, upregulation of calcitonin mRNA, C-cell proliferation, and tumor formation. In comparison, 20 months' dosing of liraglutide in monkeys at more than 60-fold the clinical exposure resulted in no calcitonin secretion, and no evidence of C-cell hyperplasia. The authors concluded that, in response to GLP-1 receptor activation, thyroid C cells in rodents differ markedly from those in primates. These results for GLP-1 receptor expression are supported by a further study conducted by Waser *et al.* [106]. However, this study also examined incretin receptors for GIP in normal thyroid glands, C cell hyperplasia, and medullary thyroid carcinomas in rodents and humans. GIP receptors were not detected in normal rodent thyroid glands or in C cell hyperplasia, but were found in all rat medullary thyroid carcinomas. GIP receptors were greatly overexpressed in neoplastic C cells in both rodents and humans. No GIP receptors were detected in normal human thyroids, but up to 89% of the human medullary thyroid carcinomas tested were found to express GIP receptors in a high density. The authors concluded that the presence of incretin receptors in thyroid C cell lesions suggests that the thyroid should be monitored both before and during incretin-based diabetes therapy.

Based on the data available at the time of approval of liraglutide, the FDA concluded that the increments in the incidence of carcinomas among rodents translated into a low risk in humans [103]. However, additional studies are required to further explore possible associations between liraglutide use and medullary thyroid cancer. A long-term cancer registry has been established to monitor the incidence of medullary thyroid cancers in patients receiving liraglutide [102].

Conclusions

Incretin therapy is established as an important treatment option for patients with T2D. It may be prescribed as monotherapy or in combination with metformin, TZDs, or sulfonylureas in line with recommended treatment algorithms [7]. GLP-1 receptor agonists may be particularly suitable for use in patients with early disease who retain some residual β -cell function [36]. Although both the DPP-4 inhibitors and the GLP-1 receptor agonists are effective in the reduction of HbA1c levels without weight gain in patients with T2D, GLP-1 receptor agonists have the additional benefit of effectively reducing body weight. Other potential applications of incretin therapy include combination with basal insulin in patients with diabetes, which would complement their distinct mechanisms of action; GLP-1 therapies reduce postprandial increments in glucose levels [43, 61, 64], and basal insulin lowers fasting plasma glucose levels.

Prediabetes is a substantial and growing problem that should be addressed more comprehensively than has been done in current clinical practice. Preventing individuals from experiencing dis-

ease progression to T2D has considerable clinical and pharmacoeconomic benefits. Although dietary and/or exercise lifestyle modifications are effective in reducing the risk of progression to T2D, they are difficult for patients to maintain over prolonged periods. Therefore, pharmacological treatment options may be recommended for these patients in the future [82].

Incretin therapy may be an appropriate pharmacological intervention for patients with prediabetes as it is associated with glucose control and weight control. They also have the potential to preserve β -cell function. Early data in this setting with liraglutide and alogliptin have shown promising efficacy. The outcomes from further studies and safety monitoring are eagerly anticipated.

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