THE ROLE OF INCRETIN-BASED THERAPIES IN THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS: PERSPECTIVES ON THE PAST, PRESENT AND FUTURE

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The ever-increasing burden of type 2 diabetes mellitus (T2DM) worldwide, has led to the emergence of several antidiabetes drugs with different modes of action. Incretin hormones and their effect on glucose metabolism and pathogenesis of T2DM has been a landmark discovery in the management of this increasingly prevalent metabolic disorder. Glucagon like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are the two major classes of incretin-based therapies that regulate glucose mechanism through multiple pathways, demonstrate weight loss (GLP-1 receptor agonists) or a weight-neutral effect (DPP-4 inhibitors), and are associated with a low risk of hypoglycaemia and other adverse events. In addition, evidence reflects their possible therapeutic potential in the treatment of other clinical conditions such as obesity, cardiovascular disease and liver disorders. This review explores the availability and the impact of GLP-1 receptor agonists and DPP-4 inhibitors as potential therapeutic strategies for T2DM along with their future in the landscape of diabetes management and other clinical conditions.

KEYWORDS: cardiovascular; dipeptidyl peptidase-4 inhibitors; glucose-dependent insulinotropic polypeptide; glucagon like peptide -1; GLP-1 receptor agonists; incretin-based therapies; type 2 diabetes mellitus

РОЛЬ ТЕРАПИИ НА ОСНОВЕ ИНКРЕТИНОВ В ЛЕЧЕНИИ САХАРНОГО ДИАБЕТА 2 ТИПА: ПРОШЛОЕ, НАСТОЯЩЕЕ И БУДУЩЕЕ

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Постоянно увеличивающаяся распространенность сахарного диабета 2 типа (СД2) во всем мире привела к появлению нескольких противодиабетических лекарственных препаратов с различными механизмами действия. Инкретиновые гормоны и их влияние на метаболизм глюкозы и патогенез СД2 стали знаковым открытием в лечении этого все более распространенного нарушения обмена веществ. Агонисты рецептора глюкагоноподобного пептида-1 (ГПП-1) и ингибиторы дипептидилпептидазы-4 (ДПП-4) представляют собой два основных класса препаратов для лечения на основе инкретинов, которые различными способами регулируют механизм усвоения глюкозы, при этом снижают массу тела (агонисты рецептора ГПП-1) или не влияют на массу тела (ингибиторы ДПП-4) и связаны с низким риском гипогликемии и других нежелательных явлений. Кроме того, данные указывают на их возможный терапевтический потенциал при лечении других клинических состояний, таких как ожирение, сердечно-сосудистые заболевания и заболевания печени. В этом обзоре рассматриваются имеющиеся на сегодняшний день агонисты рецептора ГПП-1 и ингибиторы ДПП-4 и их использование в возможных стратегиях лечения СД2, а также их будущее в контексте лечения диабета и других заболеваний.

КЛЮЧЕВЫЕ СЛОВА: сердечно-сосудистая система; ингибиторы дипептидилпептидазы-4; глюкозозависимый инсулинотропный полипептид; глюкагоноподобный пептид-1; агонисты рецептора ГПП-1; терапия на основе инкретинов; сахарный диабет 2 типа

The ever-increasing prevalence of type 2 diabetes mellitus (T2DM), which currently affects 425 million individuals worldwide, is associated with deleterious long-term complications [1]. This necessitates focussed efforts to address the pathogenesis of this disease along with its outcomes. One of the hallmarks of the pathophysiology of T2DM is the progressive deterioration of pancreatic β–cells that leads to decreased insulin secretion and increased glucagon production by the α–cells of the pancreas [2, 3]. Thus, therapies aimed to increase insulin secretion and decrease glucagon secretion along with minimal adverse effects are desirable and have the potential to alter the natural progression of T2DM and eventually help achieve good glycaemic control.

INCRETIN HORMONES AND MANAGEMENT OF T2DM

Incretin hormones are gastrointestinal (GI) peptides secreted after nutrient exposure that stimulate insulin secretion. The improved understanding of the incretin effect and its impact on the pathophysiology of T2DM has been instrumental in the development of incretin-based therapies. 'Incretin effect' is defined as the increase in plasma insulin levels induced by oral glucose intake as compared to intravenous infusion of glucose [4]. The two major human incretin hormones that contribute equally to the incretin effect are the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [5]. While GIP, a 42 amino acid hormone is secreted by duodenal and prox-

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imal jejunal K-cells, GLP-1 is a 36 amino acid peptide product of the proglucagon gene synthesised in L-cells primarily found in the distal small bowel and colon [5–7].

GIP plays a key role in maintaining glucose homeostasis by mediating incretin effect in healthy individuals; however, this effect is diminished in patients with T2DM. Contrastingly, the insulinotropic properties of GLP-1 are preserved in patients with T2DM, which makes it a potential therapeutic option for management of this metabolic disorder [8–10]. In addition to its insulinotropic effect, GLP-1 reduces glucagon secretion, decreases GI motility, delays gastric emptying, promotes satiety, helps in β–cell neogenesis and preservation, improves insulin sensitivity and increases glucose disposal [11]. GLP-1 has several pleiotropic effects that can be helpful for the treatment of patients with T2DM and associated comorbidities (Figure 1). Several studies have shown beneficial effects of GLP-1 on cardiovascular (CV) function, endothelial dysfunction and neurodegenerative disorders, however, long-term clinical studies are warranted to support the existing data [10].

INCRETIN-BASED THERAPIES FOR THE TREATMENT OF T2DM

In healthy individuals, the incretin effect can account for 50%–70% [12] of the insulin response after administering oral glucose, whereas this comes down to 20%–35% [13, 14] in patients with T2DM. This diminished incretin effect contributes to hyperglycaemia in T2DM. The incretin-based therapies therefore act by either mirroring or enhancing the GLP-1 activity in patients with T2DM [15].

Broadly, the incretin-based therapies currently available are GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4 inhibitors). GLP-1 receptor agonists are incretin mimetics, whereas the DPP-4 inhibitors enhance incretin levels by inhibiting their clearance. These incre-

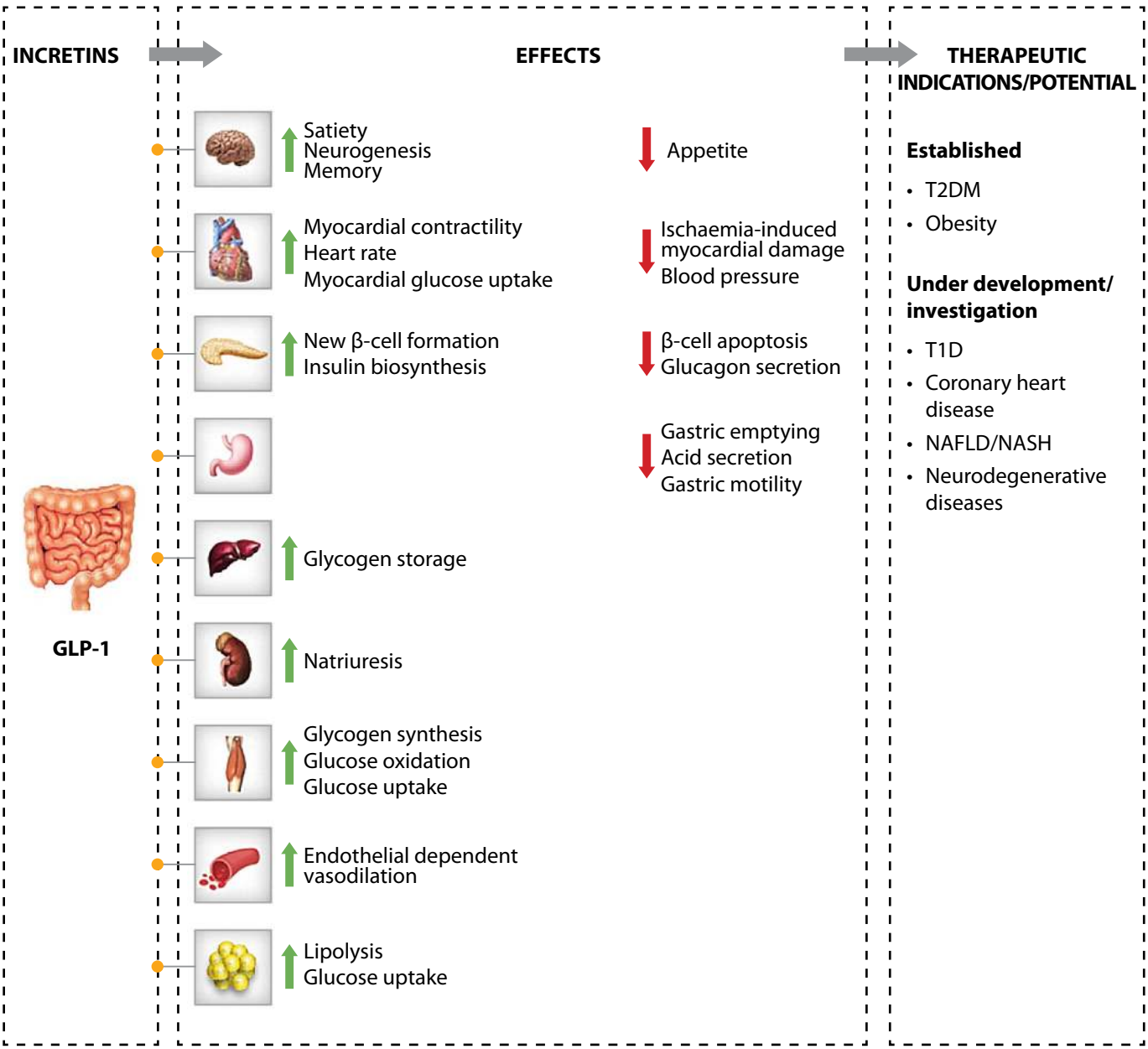

Figure 1. Effect of GLP-1 on different tissues and organs, and the therapeutic potential of incretin-based therapies: GLP-1, glucagon-like peptide-1; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T1D, type 1 diabetes; T2DM, type 2 diabetes mellitus

tin-based therapies also help overcome the short half-life (1–2 minutes) of native GLP-1 by preventing its inactivation by DPP-4 enzymes [15].

GLP-1 receptor agonists

GLP-1 receptor agonists are peptide-based therapies administered subcutaneously to prevent degradation by GI enzymes. They are resistant to inactivation by DPP-4 enzymes and have a high affinity towards the GLP-1 receptors, which leads to long-standing receptor activation. Primarily, they are categorised as short- and long-acting compounds based on their pharmacokinetic profile providing intermittent or continuous exposure, respectively. The GLP-1 receptor agonists based on the structure of native GLP-1 are termed as GLP-1 analogues [15].

Short-acting GLP-1 receptor agonists such as exenatide and lixisenatide are resistant to inactivation by the DPP-4 enzyme, however have a plasma half-life of 2–3 hours, because they are eliminated via renal route. Long-acting GLP-1 receptor agonists such as exenatide LAR (long acting release), liraglutide, semaglutide, albiglutide, dulaglutide, efpeglenatide and ITCA 650 (subdermal release of exenatide) have been modified technically to avoid renal elimination and maintain continuous activation of GLP-1 receptors [10, 16] (Table 1).

Short-acting GLP-1 receptor agonists display intermittent stimulation of the GLP-1 receptor, with slowing of gastric emptying being one of the main effects by which they reduce postprandial glucose excursions. Long-acting GLP-1 receptor agonists mediate their glucose-lowering effect mainly through their constant glucagonostatic and insulinotropic properties, with substantial reductions in fasting plasma glucose and glycated haemoglobin (HbA_{1c}). Both short- and long-acting GLP-1 receptor agonists demonstrate a reduction in appetite and body weight [10, 16].

DPP-4 inhibitors

An alternative approach to overcome the short half-life of the native GLP-1 is the inhibition of the DPP-4 enzyme that results in enhancing and prolonging the action of GLP-1. The DPP-4 inhibitors are orally active small molecules that inhibit the catalytic site of the DPP-4 enzyme and increase GLP-1 and GIP levels. They are also known to increase insulin secretion, reduce glucagon secretion and improve glycaemic control. Sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin are the commonly used DPP-4 inhibitors that have been effective in lowering HbA_{1c} levels both as monotherapy and in combination with other classes of antidiabetic drugs such as metformin, sulphonylureas, thiazolidinediones and insulin. In studies up to 52 weeks, DPP-4 inhibitors demonstrated a reduction of HbA_{1c} by 6–11 mmol/mol (0.6%–1.1%) from the baseline with no weight gain and fewer hypoglycaemic events and/or adverse events [17].

While both GLP-1 receptor agonists and DPP-4 inhibitors do not vary in their potential to lower HbA_{1c} levels, the former therapy results in weight loss whereas the latter has a weight-neutral effect. One of the common adverse effects associated with GLP-1 receptor agonists is nausea, which is not experienced in patients receiving DPP-4 inhibitors [18].

THE FUTURE OF INCRETIN-BASED THERAPIES

In addition to the existing incretin-based therapies, there has been focused research on developing potential avenues for future development of this class of therapy to overcome the existing challenges such as prolonged GLP-1 receptor activation, reducing associated adverse events and for optimising treatment.

The first oral GLP-1 analogue under clinical development is a combination of semaglutide with sodium N-[8-(2-hydroxybenzoyl) aminocaprylate] (SNAC), an absorption enhancer absorbed via the transcellular route. Semaglutide tablets are absorbed in the stomach, where SNAC causes a localised increase in pH, this in turn leads to higher solubility and prevents proteolytic degradation. This new oral formulation may lead to patient acceptance and adherence versus the injectable forms [19].

Other developments include osmotic minipumps that release exenatide for a long duration (~6 months), and fixed-ratio combinations of GLP-1 analogues and basal insulin that are effective and have reduced GI side effects [20].

Another approach to enhance the metabolic effects of GLP-1 receptor agonist is its combination with GIP. A 26-week study of a dual GIP and GLP-1 receptor agonist, LY3298176, showed significantly better efficacy in terms of glucose control and weight loss versus dulaglutide, with an acceptable safety and tolerability profile [21]. Similarly, a balanced dual GLP-1 and glucagon-receptor agonist, MEDI0382, has demonstrated clinically meaningful reductions in blood glucose levels and body weight in obese or overweight individuals with T2DM. Adverse events such as GI disorders, nausea and vomiting were associated with MEDI0382, which may be due to the use of glucagon [22]. The currently available and emerging incretin-based therapies are listed in Table 1.

THERAPEUTIC BENEFITS OF INCRETIN-BASED THERAPIES BEYOND GLYCAEMIC CONTROL

CV outcome studies

CV risk is higher among patients with T2DM and serious concerns around CV safety prompted the US Food and Drug Agency to mandate CV outcome trials for new T2DM treatments [23] including incretin-based therapies.

GLP-1 receptor agonists such as liraglutide [24], semaglutide [25] and albiglutide [26] reduce the risk of major adverse cardiac events (MACE). In the LEADER (liraglutide) trial, the CV benefit was driven by a significant reduction in death from CV causes (hazard ratio [HR] 0.78; 95% confidence interval [CI]: 0.66–0.93; P=0.007) whereas in SUSTAIN-6 (semaglutide), there was a significant reduction in nonfatal stroke (HR 0.61; 95% CI: 0.38–0.99; P=0.04) [24, 25]]. The recently reported HARMONY trial (albiglutide) demonstrated superiority to placebo with respect to MACE (HR 0·78; 95% CI: 0·68–0·90; P=0.0006) [26].

On the other hand, lixisenatide [27] and extended-release exenatide [28] had a neutral effect (lixisenatide: HR 1.02; 95% CI: 0.89–1.17; P<0.001, and exenatide: HR 0.91, 95% CI: 0.83–1.00; P<0.001) on the CV outcomes. These findings have translated into the updated T2DM guidelines where emphasis is on the presence of CV disease as a key element to guide the selection of a GLP-1 receptor agonist

Table 1. Current and emerging incretin-based therapies

Drug class		Drug name
Current therapies		
GLP-1 RA:	*Short-acting compounds*	Exenatide and lixisenatide
	Long-acting compounds	Liraglutide, exenatide LAR, albiglutide, dulaglutide, and semaglutide
DPP-4 inhibitors		Sitagliptin, vildagliptin, alogliptin, saxagliptin, and linagliptin
Emerging or future therapies		
GLP-1 RA: *Long-acting compounds*		ITCA 650 (subdermal exenatide release) and efpeglenatide
GLP-1 analogue/basal insulin		Insulin degludec/liraglutide and insulin glargine/lixisenatide
Triple peptide agonists or antagonists		HM15211 and NN9423 (GLP-1/glucagon/GIP)
GLP-1/other gut hormones (glucagon, GIP, PYY, gastrin, etc.)		MEDI0382 (GLP-1/glucagon) and LY3298176 (GLP-1/GIP)
Oral enhancers of GLP-1		SNAC, G-protein-coupled receptors, nuclear farnesoid-receptor X, and the G-protein coupled bile acid-activated receptor (TGR5)

Sources: Andersen et al. 2018; Meier and Nauck 2015. DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; LAR, long acting release; PYY, Peptide YY; RA, receptor agonist; SNAC, sodium N-[8-(2-hydroxybenzoyl) aminocaprylate]

as the second glucose-lowering agent to be added to metformin. The addition of a GLP-1 receptor agonist is recommended in patients with atherosclerotic CV disease if HbA_{1c} is above the target level [29].

DPP-4 inhibitors such as sitagliptin (HR 0.98; 95% CI: 0.88–1.09; P<0.001) [30], saxagliptin (HR 1.00; 95% CI: 0.89–1.12; P<0.001) [31] and alogliptin (HR 0.96 [95% upper limit ≤1.16]; P<0.001) [32], and the recently reported trial with linagliptin (HR 1.02; 95% CI: 0.89–1.17; P<0.001) [33], have demonstrated neither a decrease nor increase of CV events. Although not associated with any increase in mortality, saxagliptin demonstrated an increased risk of hospitalisation for heart failure. While no CV outcome trials were planned for vildagliptin, a meta-analysis of MACE (consisting of adjudicated nonfatal myocardial infarction, nonfatal stroke and CV death) that included data from all of the randomised Phase III–IV trials reaffirmed the CV safety of vildagliptin versus comparators (risk ratio [RR] 0.82; 95% CI: 0.61–1.11) [34].

Overall, the underlying mechanisms for the CV benefit are not well elucidated; the potential factors may include changes in insulin resistance, weight loss, reduction in blood pressure, improved lipid profile and direct effects on the heart and vascular endothelium [35], which require further in-depth studies for conclusive evidence.

Other clinical indications

A meta-analysis including patients with nonalcoholic fatty liver disease (NAFLD) and T2DM treated with either a GLP-1 receptor agonist or DPP-4 inhibitors, demonstrated reductions in biochemical markers of NAFLD and decreased signs of inflammation, steatosis and fibrosis in biopsy samples and imaging [36]. Liraglutide resulted in biopsy-confirmed resolution of nonalcoholic steatohepatitis (NASH) in 39% of patients, compared with 9% in the placebo group in a 48-week Phase II study of 52 patients [37].

Neurodegenerative diseases such as Parkinson's disease (PD) have been linked to impaired insulin signalling, which resulted in an interest in utilising GLP-1 receptor agonists as a potential therapeutic intervention for PD. Exenatide once weekly has been shown to halt disease progression after 48 weeks of treatment and a 12-week washout period [38].

There have also been ongoing studies to utilise incretin-based therapies to treat type 1 diabetes mellitus, prediabetes, obesity and psoriasis (Meier and Nauck 2015; Andersen et al. 2018). Although the preliminary results are promising, further long-term clinical trials are warranted to support the use of incretin-based therapies in these clinical conditions (Figure 1).

CONCLUSION

In summary, incretin hormones play a crucial role in the pathophysiology of glucose regulation in T2DM. The incretin-based therapies are effective in treatment of the key underlying islet dysfunction of T2DM accompanied by a low risk of adverse events and hypoglycaemia along with no weight gain. The recently completed and ongoing studies have also revealed a strong potential of this class of drugs to broaden the therapeutic indications beyond glycaemic control. Although there exists a wealth of evidence of incretin-based therapies, it will be rather interesting to witness a promising future with regard to further development of this class of antidiabetes drugs.

ADDITIONAL INFORMATION

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