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REVIEW

Incretins beyond type 2 diabetes

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Abstract
Incretin-based therapies, in particular glucagon-like peptide-1 (GLP-1) receptor agonists, have been evaluated in other forms of diabetes, but randomised controlled trials are mainly limited to people living with type 1 diabetes. In this review we present the evidence issuing from these trials and discuss their clinical implications as well as the difficulties in interpreting the data. In type 1 diabetes, the addition of GLP-1 receptor agonists to intensive insulin therapy lowers weight and required insulin doses compared with placebo, but the effects on glucose control (HbA_{1c}, risk of hypoglycaemia) are dependent on the different study protocols. Side effects are limited to the gastrointestinal complaints of nausea, vomiting and diarrhoea. We briefly discuss the potential for using GLP-1 receptor agonists as (adjunct) therapies in other forms of diabetes, where the evidence to date is scarce.

Keywords GLP-1 receptor agonists · Glucose control · Incretins · Monogenic diabetes · Review · Type 1 diabetes · Weight

Abbreviations

CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
DKA	Diabetic ketoacidosis
GLP-1	Glucagon-like peptide-1
GLP-1RA	GLP-1 receptor agonist
LAR	Long-acting release
MDI	Multiple daily injections
PTDM	Post-transplant diabetes
SGLT2i	Sodium–glucose cotransporter 2 inhibitors

Introduction

Incretin-related therapies, dipeptidylpeptidase 4 inhibitors (DPP4i) and glucagon-like peptide receptor agonists (GLP-1RAs), have become popular tools in the treatment of people living with type 2 diabetes [1]. In particular GLP-1RAs have evolved to one of the most successful classes in the treatment of hyperglycaemia in people living type 2 diabetes, due to their robust effects on glucose control and weight and, most importantly, their direct cardiorenal protective effects. However, on the basis of their mechanism of action [2], the use of GLP-1RAs can also be envisaged in other forms of diabetes, such as post-transplant diabetes (PTDM), corticosteroid-induced diabetes, monogenic diabetes and type 1 diabetes, and potentially in the prevention of diabetes.

Over the past few years, the most detailed exploration of the potential to use GLP-1RAs outside the indication of type 2 diabetes has been in type 1 diabetes, which will be the main focus of the present review.

The treatments accessible to people living with type 1 diabetes have evolved in important ways in recent years, with the availability of insulin analogues and technological support systems for administration of insulin (pens and pumps) and, perhaps even more important, systems allowing monitoring of blood glucose levels at home, in particular the continuous glucose monitoring (CGM) systems. Embedded in intensive education, empowerment and support of the person living with type 1 diabetes by medical teams, these novel therapeutics have allowed more people with type 1 diabetes to achieve tight glycaemic control (expressed as better HbA_{1c} levels) and more stable glucose levels (expressed as more time spent in desired glycaemic ranges) and have become the new standard of care [3]. However, despite these major improvements, many people still do not manage to reach the desired glycaemic targets over the long-term or pay high prices to do so, with a higher risk of hypoglycaemia and a new phenomenon in type 1 diabetes, weight gain [4, 5].

Non-physiological replacement of insulin in people with type 1 diabetes (intermittent administration of insulin under

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the skin, with profiles that do not fully fit mealtime glucose excursions), inability of the present day insulins to adapt their activity to insulin needs varying with exercise, stress etc. and relaxation of strict diets to improve quality of life in people with type 1 diabetes lead to the growing problem of undesired weight gain with more and more people struggling with overweight and obesity. Different regions of the world report different prevalence numbers, but overall, a rising trend is reported [5].

Instinctively, clinicians have tested therapies from the type 2 diabetes arsenal in people with type 1 diabetes for their ability to yield better, more stable glucose levels, reduce insulin doses and reduce weight or prevent undesired weight gain. Metformin and sodium−glucose cotransporter 2 inhibitors (SGLT2i) have, as such, been tested, with variable success [3, 6, 7]. Metformin reduces, to a minimal extent, HbA_{1c} levels with, however, some reduction in insulin doses and a small effect on weight. The REMOVAL trial could not demonstrate an effect on carotid intima–media thickness in people with type 1 diabetes where metformin was used as adjunct therapy [8]. SGLT2i have even been indicated as adjunct therapies for people with type 1 diabetes for several years in Europe, after the European Medicines Agency's approval of use of low-dose dapagliflozin and sotagliflozin in people with type 1 diabetes with a BMI>27 kg/m^2. This approval was on the basis of study results demonstrating better glucose control (HbA_{1c}, time in range), a small weight reduction and some insulin-sparing effect [9]. The latter however, together with the mechanism of action of SGLT2i, was also the cause of the most feared side effect of SGLT2i use in type 1 diabetes: diabetic ketoacidosis (DKA) with the absence of high glucose levels (so-called euglycaemic DKA) [10]. Both RCTs and real-world evidence studies showed that, despite patient selection, training of teams and intensive education, the risk of DKA in SGLT2i users with type 1 diabetes was 2–4% per annum [10, 11]. These observations have probably contributed to the discontinuation of marketing of SGLT2i for type 1 diabetes in Europe, based on a decision by the company, but have unfortunately also led to the exclusion of people with type 1 diabetes from all outcome studies (both cardiovascular and renal) using SGLT2i, thus excluding one of the groups with the highest cardiorenal risk from evidence-gathering and thus use of these agents.

From the early days, GLP-1RAs have also been tested as adjunct therapies in type 1 diabetes. On the basis of their mechanism of action, some benefit may be expected. In people with type 1 diabetes who have remaining beta cells, the glucose-dependent stimulation of insulin secretion may help to achieve better glycaemic control, with less exogenous insulin. However, even in those without remaining beta cells, beneficial effects are to be expected: the suppression of counteracting glucagon may improve glucose control (particularly postprandial control) and, most importantly, the effect of GLP-1RAs on appetite and weight control are desired effects in the growing population of people with type 1 diabetes struggling with weight gain and overweight/obesity [2, 12]. Moreover, direct beneficial effects on the protection of organs are also to be expected. To date, people with type 1 diabetes have also been excluded from GLP-1RA-based cardiovascular outcome studies; however, one would expect that the effects observed in people with type 2 diabetes may also translate to those living with type 1 diabetes [13].

Here we have reviewed literature in particular for randomised controlled trials where use of GLP-1RAs was evaluated in type 1 diabetes and MODY or monogenic diabetes.

Methods

A qualitative literature review was conducted to identify articles related to the effects of GLP-1RAs on type 1 diabetes and MODY or monogenic diabetes in the PubMed database, from 2005 onwards. The search strategy involved the following key terms: "diabetes mellitus, type 1", "maturity onset diabetes of the young type 1", "maturity onset diabetes of the young type 2", "maturity onset diabetes of the young type 3", "maturity onset diabetes of the young type 4", "mody type 6", "diabetes, gestational", "monogenic diabetes" and "liraglutide", "semaglutide", "exenatide", "lixisenatide", "dulaglutide" or "glucagon-like peptide 1". Two independent reviewers (CM and IA) screened and retrieved the articles. IA performed the screening of the articles based on titles and abstracts, after which CM and IA reviewed and discussed the eligible articles together.

Four hundred and fifty-nine articles were initially screened, and 16 were ultimately included in this review [14–29]. Of these, 15 were RCTs in type 1 diabetes [14–28], and one was a randomised crossover study in MODY [29]. Owing to the dearth of literature regarding the impact of incretins on diabetes types other than type 1 diabetes, we focused the review on type 1 diabetes. Specifically, 12 of the 15 articles on type 1 diabetes investigated the efficacy of liraglutide on type 1 diabetes, while three articles examined the effect of exenatide on type 1 diabetes. One additional paper explored the effect of anti-IL-21 and liraglutide on preserving beta cell function in people with recent-onset type 1 diabetes and is only covered in the Discussion [30].

Results

Ten articles described various metabolic endpoints and five studies focused on various mechanistic endpoints of liraglutide or exenatide in type 1 diabetes, all of which are summarised here [14–28]. One of the 16 included articles

was a randomised crossover study in patients with MODY, discussed in the Discussion section [29].

Table 1 shows an overview of baseline characteristics and duration of the eight trials with liraglutide [19–26] and two trials with exenatide (short-acting and long-acting release [LAR]) [27, 28]. Most studies included people with long-standing diabetes (close to 20 years), with overweight or obesity and on intensive insulin therapy. Most studies included people treated with both multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), with one study exclusively studying people with obesity [21] and another exclusively people on CSII [20]. People with hypoglycaemia unawareness were, as far as it was traceable, not excluded from any of the studies, and both ADJUNCT trials were even enriched for those with hypoglycaemia unawareness or a history of severe hypoglycaemia [19, 26].

Table 2 shows the outcomes of the studies. Exenatide LAR [27] induced a beneficial effect on HbA_{1c} levels, with a 0.3% difference vs placebo (p=0.01) at 12 weeks, decreasing by 24 weeks (0.24%, p=0.08). None of the benefit was left 6 months after stopping therapy. This effect was most pronounced in those who still had measurable C-peptide levels. These glucose-lowering effects were achieved with less insulin (Table 2). Weight transiently decreased at 12 and 24 weeks (−2.93 kg and −2.38 kg vs placebo, p<0.0001 and p<0.01 respectively), but again, no difference in weight between people treated with exenatide LAR and placebo remained 6 months after discontinuation of therapy and weight was back to baseline values. Hypoglycaemia rates were not increased, but gastrointestinal side effects were reported more frequently in those on exenatide LAR (Table 2). The MAG1C study investigating the effect of mealtime exenatide showed no beneficial effect on HbA_{1c} but did show a reduction in (mainly mealtime) insulin doses (−9U per day, of which 8.5U mealtime insulin, p<0.0001) and in weight (4.4 kg, p<0.0001) [28]. No increase in hypoglycaemia was reported, but gastrointestinal side effects were more frequent in exenatide-treated people.

The liraglutide studies have different durations and different outcomes, and different doses have been studied, using different insulin titration protocols. Overall, a dose-dependent reduction in HbA_{1c} and increase in time in range (when reported) is observed, in particular in the shorter-duration studies (Table 2). The ADJUNCT ONE study, the only study reporting after 52 weeks of therapy, still showed a dose-dependent difference in HbA_{1c} vs placebo, with less insulin and a dose-dependent weight reduction (Table 2). This study also reported composite endpoints and showed that the numbers of people achieving a drop in HbA_{1c} levels >1% without severe hypoglycaemia were 21.2%, 18.5% and 16.8% in individuals treated with liraglutide 1.8 mg, 1.2 mg and 0.6 mg, respectively, compared with 11.1% in placebo-treated people (p<0.001, p<0.01 and p<0.05, respectively). Findings on insulin doses throughout the liraglutide studies are consistent, with insulin dose reductions (mainly mealtime insulin doses) that were liraglutide-dose dependent. Maximum differences in insulin dose reductions vs placebo were observed around 24 weeks, with differences decreasing by 52 weeks [26]. The findings are similar for weight, with consistent liraglutide-dose-dependent weight loss, peaking around 24 weeks, with differences getting smaller by 52 weeks (Table 2).

Hypoglycaemia data are very different between studies, with most not reporting an increased risk of hypoglycaemia, in contrast to the two ADJUNCT studies (Table 2).

The reporting of side effects is consistent throughout all liraglutide studies, with an increase in pulse rates (5–8 beats per min) [19–22, 24, 26] and in gastrointestinal side effect reporting (Table 2). Even at the low doses (0.6 mg) tested in the ADJUNCT studies, an increase in nausea and vomiting is reported. Higher doses lead to more gastrointestinal side effects.

No increased risk of DKA was observed, although the ADJUNCT studies found more ketosis in liraglutide-treated people [19, 26].

In smaller mechanistic studies, interesting additional data were presented. First, a significant reduction in the proinflammatory cytokine IL-6 was observed (p=0.025) following administration of liraglutide at a dose of 1.2–1.8 mg over a period of 26 weeks [14]. A dedicated study did not observe any improvement in central, autonomic or peripheral neuronal function among patients with diabetic polyneuropathy. The administration of a 1.2 mg dose of liraglutide over 12 weeks did not interfere with glycaemic recovery or gastric emptying during episodes of hypoglycaemia (p=0.96), whereas an increase in heart rate during normoglycaemia (p=0.02) was observed [15]. In a 26-week study involving overweight individuals, treatment with liraglutide at a dosage of 1.8 mg resulted in a significant decrease in fat-free mass, as well as both android and gynoid fat (all p<0.001). Additionally, reductions in waist and hip circumference were noted (p<0.001), accompanied by a decrease in the waist-to-hip ratio (p<0.018) [16]. No notable changes in subcutaneous adipose tissue composition were observed following liraglutide administration [17]. Treatment with exenatide at a dosage of 10 μg for a duration of 4 weeks led to a significant decrease in glucagon secretion during episodes of euglycaemia and hyperglycaemia. However, this decrease was not observed during episodes of hypoglycaemia [18].

Discussion

Since GLP-1RAs have become available, trials have been conducted to evaluate the clinical benefit of these wmessagewgenerated from these trials is not a simple one,

Table 1 Baseline characteristics and duration of trials

	Duration, weeks	*N*	Age, years	Female, %	Duration of T1D, years	HbA_{1c}, mmol/mol; %	Weight, kg	MDI/CSII	Total insulin dose, U/day	MDI total insulin dose, U/day	CSII total insulin dose, U/day
ADJUNCT ONE Mathieu et al 2016 [26]											
Lira 1.8 mg	52	346	44±13	52	22±13	65.5±8.1; 8.1±0.7	86.3±17.3	231/115	NA	62.5	50.5
Lira 1.2 mg	52	346	44±13	52	22±12	65.7±8.5; 8.2±0.8	85.4±17.2	246/100	NA	59.6	50.7
Lira 0.6 mg	52	250	44±13	53	21±12	65.9±8.1; 8.2±0.7	86.5±17.3	279/71	NA	59.5	53.0
Placebo	52	347	43±13	52	22±12	65.5±8.0; 8.2±0.7	86.4±17.8	251/96	NA	62.4	49.2
ADJUNCT TWO Ahrén et al 2016 [19]											
Lira 1.8 mg	26	205	43	55	21	64.4; 8.0	83.6	154/51	NA	58.4	50.1
Lira 1.2 mg	26	209	43	51	21	64.7; 8.1	84.7	153/56	NA	58.8	46.8
Lira 0.6 mg	26	211	44	56	21	64.9; 8.1	83.1	158/53	NA	58.8	47.9
Placebo	26	206	43	54	21	65.2; 8.1	84.2	155/51	NA	61.7	50.3
Kuhadiya et al 2016 [25]	12							80% on CSII			
Lira 1.8 mg	12	16	42±3	69	20±3	57.0±1.6; 7.4±0.2	83±4		48.1±4.3	NA	NA
Lira 1.2 mg	12	16	42±3	31	21±3	62.0±2.0; 7.8±0.2	96±4		71.2±5.5	NA	NA
Lira 0.6 mg	12	14	45±4	64	25±2	58.0±2.0; 7.5±0.2	80±4		52.8±3.7	NA	NA
Placebo	12	17	50±3	59	30±3	61.0±2.0; 7.7±0.2	80±6		46.1±9.5	NA	NA
Dejgaard et al 2016 [21]								100% on MDI			
Lira 1.8 mg	24	50	47±13	40	20±12	71.6±7.7; 8.7±0·7	93.4±14.2		59.0	59.0	NA
Placebo	24	50	49±12	30	25±12	71.8±7.6; 8.7±0·7	94.0±12.5		60.0	60.0	NA
Dejgaard et al 2020 [20]								100% on CSII			
Lira 1.8 mg	26	22	50±14	68	21	66.0±6.0; 8.2±0.5	85±10		48.0 ± 15.0	NA	48.0 ± 15.0
Placebo	26	22	43±12	68	20	66.0 ± 6.0; 8.1±0.5	88±14		54.0 ± 19.0	NA	54.0 ± 19.0
Dubé et al 2018 [22]											
Lira 1.8 mg/placebo	24	15	36±2	53	20±2	57.0 ± 1.0; 7.4±0.1	89.0±3.8	8/7	70.9 ± 10.9	NA	NA

Table 1 (continued)

	Duration, weeks	*N*	Age, years	Female, %	Duration of T1D, years	HbA_{1c}, mmol/mol; %	Weight, kg	MDI/CSII	Total insulin dose, U/day	MDI total insulin dose, U/day	CSII total insulin dose, U/day
Ghanim et al 2020 [24]											
Lira 1.8 mg	26	37	47±2	65	27.0± 2.0	63.5± 2.0; 8.0± 0.2	94.2±3.1	12/25	61.2 ± 2.8	NA	NA
Placebo	26	27	45±3	59	28.0± 3.0	61.6±1.9; 7.8± 0.2	83.3±3.4	8/19	52.8±3.3	NA	NA
Frandsen et al 2015 [23]								100% on MDI			
Lira 1.2 mg	12	18	40±3	39	18±2	72.5±2.2; 8.8±0.2	75.8±2.9		62.0±5.9	62.0±5.9	NA
Placebo	12	18	36±2	28	20±2	71.8±1.5; 8.7±1.4	74.9±1.7		57.1±5.3	57.1±5.3	NA
Herold et al 2020 [27]								73% on CSII			
Exe LAR 2 µg/week	24	40	39±12	72	22±12	57.0±8.5; 7.4±0.8	83.7±21.7		47.0±14.3	NA	NA
Placebo	24	39	34±11	64	17±10	61.6±8.5; 7.8±0.8	84.1±22.6		52.1±15.1	NA	NA
MAG1C Johansen et al 2020 [28]								100% on MDI			
Exe 10 µg/day	26	54	50±14	25	21±11	66.8±7.9; 8.3±0.8	89.7±14.4		61.4±17.7	61.4±17.7	NA
Placebo	26	54	50±14	30	21±13	65.9±6.5; 8.2±0.6	85.8±14.3		59.3±23.9	59.3±23.9	NA

Data are presented as mean ± SD or *N*, unless otherwise indicated

Exe, exenatide; Lira, liraglutide; NA, not available; T1D, type 1 diabetes

Table 2 Effects of GLP-1RA in type 1 diabetes vs baseline

	HbA_{1c} change, mmol/mol	HbA_{1c} change, % *p* vs Pbo	Body weight, kg *p* vs Pbo	Total insulin dose, U/day	Basal, U/day	Bolus, U/day	Risk of hypoglycaemia	Gastrointestinal side effects
ADJUNCT ONE Mathieu et al 2016 [26]								
Lira 1.8 mg	−5.9	−0.54 *p*=0.0019	−4 *p*<0.0001	−2.2	NA	NA	50.2[a]	2.7[a]
Lira 1.2 mg	−5.4	−0.49 *p*=0.0164	−2.7 *p*<0.0001	−0.9	NA	NA	49.4[a]	1.9[a]
Lira 0.6 mg	−4.8	−0.43 *p*=0.1299	−1.3 *p*<0.0001	+1.8	NA	NA	45.4[a]	1.3[a]
Placebo	−3.8	−0.34	+0.9	+1.7	NA	NA	42.7[a]	0.76[a]
ADJUNCT TWO Ahrén et al 2016 [19]								
Lira 1.8 mg	−3.8	−0.35 *p*<0.0001	−5.1 *p*<0.0001	0.90[b]	NA	NA	54.1[a]	2.0[c]
Lira 1.2 mg	−2.5	−0.23 *p*<0.0021	−4.0 *p*<0.0001	0.93[b]	NA	NA	58.7[a]	1.3[c]
Lira 0.6 mg	−2.6	−0.24 *p*<0.0011	−2.5 *p*<0.0001	0.95[b]	NA	NA	47.9[a]	0.8[c]
Placebo	+0.1	+0.01	−0.2	NA	NA	NA	50.6[a]	0.4[c]
Kuhadiya et al 2016 [25]								
Lira 1.8 mg	−4.6	−0.42 *p*=0.39	−5 *p*<0.001	−10	−1.7	−8.2	13/16[d]	9/16[e]
Lira 1.2 mg	−8.5	−0.78 *p*<0.01	−5 *p*<0.001	−12	−6.3	−6.1	16/16[d]	10/16[e]
Lira 0.6 mg	−2.8	−0.26 *p*=0.81	−3 *p*=0.006	−2.8	−1.4	−1.4	13/14[d]	11/14[e]
Placebo	−3.3	−0.30	=	−1.9	+0.4	−1.5	14/17[d]	3/17[e]
Dejgaard et al 2016 [21]								
Lira 1.8 mg	−6	−0.5 *p*=0.18	−5.9 *p*=0.0145	+4.1	+3.8	+0.5	1.3[f]	58[g]
Placebo	−4	−0.3	+0.2	+13.4	+8.1	+5.4	1.8[f]	10[g]
Dejgaard et al 2020 [20]								
Lira 1.8 mg	−5	−0.5 *p*=0.001	−6.8 *p*<0.001	−4.9	−1.8	−3.1	2.5[h]	73[g]
Placebo	+2.3	+0.2	−0.4	+2.8	−0.5	+3.3	2.1[h]	41[g]
Dubé et al 2018 [22]								93[i]
Lira 1.8 mg	NA	−0.3 NS	−5.6 *p*=0.0001	−4.2	+0.6	−4.7	NS	
Placebo	NA	−0.2	−0.7	+2.4	+2.5	+0.1	NA	
Ghanim et al 2020 [24]								
Lira 1.8 mg	−4.5	−0.41 *p*=0.1	−3.9	−5.3	−1.4	−3.7	8[j]	NA
Placebo	−1.3	−0.12	+0.4	+1.9	+1.0	=	9[j]	NA

Table 2 (continued)

	HbA_{1c} change, mmol/mol	HbA_{1c} change, % *p* vs Pbo	Body weight, kg *p* vs Pbo	Total insulin dose, U/day	Basal, U/day	Bolus, U/day	Risk of hypoglycaemia	Gastrointestinal side effects
Frandsen et al 2015 [23]								
Lira 1.2 mg	−6.2	−0.6 *p*=0.62	−3.1	NA	−0.1	−3.9	2.6[k]	13/18[e]
Placebo	−5.6	−0.5	+1.1	NA	−0.1	+0.1	1.4[k]	9/18[e]
Herold et al 2020 [27]								
Exe LAR 2 µg/week	NA	+0.16 *p*=0.08	−2.38 *p*=0.0078	NA	NA	NA	3.89[l]	56.4[m]
Placebo	NA	+0.40	NA	NA	NA	NA	4.59[l]	22.9[m]
MAG1C Johansen et al 2020 [28]								
Exe 10 µg/day	−3.2	−0.3 *p*=0.36	−4.3 *p*<0.0001	−7.0	+1.2	−8.2	0.3[n]	185[p]
Placebo	−2.2	−0.2	+0.1	+2.0	+1.8	+0.2	0.2[n]	115[p]

Data are presented as mean ± SD or *N*, unless otherwise indicated

[a]Event rate per year of exposure; [b]Estimated treatment ratio with placebo; [c]Event rate per year of exposure (nausea); [d]Number of patients with events <3 mmol/l); [e]Number of people with nausea; [f]Hours of hypoglycaemia on CGM per day; [g]Per cent of people with nausea; [h]Per cent of time spent in 'low' on CGM (level 1 [3.0–3.9 mmol/l] and level 2 [<3.0 mmol/l]); [i]Per cent people in lira + placebo group with nausea; [j]Per cent of time spent <3.89 mmol/l on CGM; [k]Hours of hypoglycaemia on CGM per day; [l]Event rate per person per month; [m]Per cent of people with gastrointestinal disorders; [n]Weekly incidence rate (<3 mmol/l); [p]Total events

Exe, exenatide; Lira, liraglutide; NA, not available; Pbo, placebo; T1D, type 1 diabetes

withwresults varying according to the baseline characteristics of the population, the product and dose tested, the duration of the intervention and the study protocol. A major difficulty with fully exploring the potential of these agents is that, in the background of the intervention, clinicians and patients are adapting insulin doses and changing behaviour (eating, exercise), which makes interpretation of outcomes difficult.

When collating all studies with a duration of 12 weeks or longer, beneficial effects on glucose control, expressed as HbA_{1c} lowering from baseline, compared with placebo, are emerging for the longer-acting GLP-1RA (liraglutide once daily, and exenatide LAR once weekly), with no effect seen in the MAG1C study investigating mealtime short-acting exenatide [28]. The reduction in HbA_{1c} was most impressive in shorter term studies (12–26 weeks), with the effect progressively waning in the one study where the intervention lasted 52 weeks [26]. Explanations of study fatigue are given, but interpretations are not easy as, in most studies, insulin doses were allowed to be adapted in the background, and most studies show a rise in insulin doses after the initial lowering of insulin in the first months of the study. Thus, to fully evaluate the direct effect of adding a GLP-1RA for the treatment of people with type 1 diabetes, the effect on HbA_{1c} should be corrected for insulin dose adaptation in the background. Most studies did report an insulin-dose-sparing effect, in particular for mealtime insulin doses. This dose reduction was also seen in the MAG1C study with mealtime short-acting exenatide without, however, any effect on HbA_{1c} [28]. The study that allowed the best assessment of the direct glucose-lowering effect of GLP-1RA adjunctive therapy in people with type 1 diabetes was the ADJUNCT TWO study, where the protocol capped the insulin dose during the study to the starting dose. In that 26 week study, all doses of liraglutide led to HbA_{1c} lowering from baseline, ranging from 0.33% with 1.8 mg to 0.23% with 0.6 mg liraglutide vs 0.01% with placebo. However, in this study differences in background insulin doses were also seen, with up to 15% lower insulin doses in liraglutide-treated people, whereas doses were almost back at baseline levels in those treated with placebo.

When discussing glucose control, HbA_{1c} and insulin doses should be considered together with glucose variability and hypoglycaemia risk. Here again, data differ from trial to trial, depending on the aggressiveness of insulin dose reduction at the initiation of the trial and the protocol for insulin up- or down-titration. In the trials with the 'lightest touch', as regards pushing physicians to adapt insulin doses, no increased risk for hypoglycaemia was observed, in contrast to the industry-driven ADJUNCT ONE and TWO trials, in which stricter protocols for titration were present. In these ADJUNCT trials, higher rates of symptomatic hypoglycaemia were reported, as well as higher rates of ketosis (although without any increase in risk of full DKA) in the highest liraglutide-dose arm (1.8 mg). This increased risk

in hypoglycaemia also needs to be considered with the perspective that these two studies were enriched for people with hypoglycaemia unawareness and a history of severe hypoglycaemia, both risk factors for hypoglycaemia [31]. Of importance, no evidence for altered counter-regulatory defences or prolonged recovery in cases of hypoglycaemia was found in those treated with a GLP-1RA [15, 18]. In those studies where CGM was introduced, the data reflected effects on HbA_{1c} and the clinically observed hypoglycaemia rates.

Of interest, for both exenatide LAR and liraglutide, the best effect of adjunct GLP-1RA on glucose control (combining HbA_{1c} lowering, insulin dose reductions and lower risk of hypoglycaemia and ketosis) was observed in those people with type 1 diabetes who still showed preserved residual insulin production, as measured by C-peptide positivity [26, 32]. Unfortunately, this parameter is not available in most trials for evaluation, but pathophysiologically it makes sense, as direct effects of GLP-1RAs on beta cell function and health have been described [2, 33]. These observations also provided a rationale to test liraglutide in individuals newly diagnosed with type 1 diabetes for its potential to actually preserve beta cell function, both alone or in combination with immune modulation. von Herrath et al demonstrated a transient preservation of C-peptide levels in individuals with newly diagnosed type 1 diabetes using a combination of liraglutide and anti-IL-21 [30]. In this study, a possible role for liraglutide, and incretins in general, in modifying the course of type 1 diabetes is suggested. Recently, a protocol for evaluating beta cell preservation using liraglutide in people with multiple diabetes-related autoantibodies, with or without dysglycaemia (stage 1 and 2 of type 1 diabetes), as well as in people with clinically symptomatic stage 3 type 1 diabetes, has been presented (INVESTDIA trial) [34].

The observation that stands most clearly throughout all trials studying GLP-1RAs in people with type 1 diabetes is the weight reduction induced by GLP-1RAs. This reduction is dose dependent, but again seems to reach its maximum at around 6 months after initiation of the GLP-1RA, as demonstrated for exenatide LAR, exenatide at mealtimes and liraglutide. In the ADJUNCT ONE study, liraglutide-dose-dependent reductions in body weight were observed vs placebo, but some weight regain happened between 6 months and 1 year of therapy. The magnitude of weight loss is quite comparable to what has been observed with the doses of GLP-1RA studied in people living with type 2 diabetes, when correcting for baseline weight. Short-term studies investigating the impact of GLP-1RAs on body composition suggest a selective loss of fat tissue compared with muscle [16, 22, 24]. One study suggested a change in food preference (lower sugar intake) [16].

A recent meta-analysis of the two ADJUNCT studies with liraglutide showed that the dose-dependent effects of liraglutide on glucose control, insulin dose and weight were independent of the baseline characteristics of those included in the study [32].

A final point of interest emerging from the studies of GLP-1RAs in people with type 1 diabetes is the observation that the side effect profile is similar to that observed in those with type 2 diabetes, with nausea, dyspepsia, diarrhoea and vomiting being the most prominent; however, numbers tend to be higher and side effects seem to appear at lower doses than in type 2 diabetes studies. Reports for both the short- and long-acting GLP-1RAs show that, at the highest doses, more than two thirds of individuals experienced these side effects. Transient delays in gastric emptying were reported, but these do not seem to persist long-term or interfere with glycaemic recovery during hypoglycaemia [15, 21].

One of the studies included in this review showed how liraglutide therapy can lower IL-6 levels, raising the possibility of a potential anti-inflammatory effect [14]. Liraglutide treatment also resulted in a significant decrease both in fat and fat-free mass. This may also be explained by the lower sugar intake of the liraglutide group vs the placebo group ($p<0.004$) [16]. Another 4-week crossover study [35], utilising lixisenatide instead of exenatide (as investigated in the study by Jiang et al [18]), revealed non-significant alterations in glucagon levels during episodes of hypoglycaemia. In contrast to the majority of liraglutide studies, this study did not demonstrate a significant decline in HbA_{1c} with lixisenatide. A significant decrease in mealtime insulin dose was the only observed outcome. Notably, gastrointestinal side effects were reported most frequently as adverse events following hypoglycaemic episodes.

When performing the literature review, the absence of RCTs in people living with type 1 diabetes using the newer GLP-1RAs (semaglutide and dulaglutide) was striking, although off-label use in real-world settings, in particular for weight loss, is happening, despite lack of clear data on cost-effectiveness. The reluctance of pharmaceutical companies to embark in these trials is probably inspired by the attitude of regulatory agencies, who demand HbA_{1c} as an endpoint when using the lower doses of GLP-1RA approved in type 2 diabetes, thus making the design and conduct of such RCTs difficult in these times of hybrid closed loop systems. When weight loss is the endpoint, the doses of GLP-1RA approved for obesity should be used (higher than those in type 2 diabetes), and these may not be tolerated by people living with type 1 diabetes, putting the field in a conundrum. Again, as these therapies are now off-label for the treatment of type 1 diabetes, no reimbursement of these agents is foreseen for people living with type 1 diabetes, resulting in a major financial burden.

This review has focused on use of GLP-1RAs in type 1 diabetes, but this is not the only form of hyperglycaemia outside type 2 diabetes where GLP-1RAs could be of use. However, only very few trials have been performed as most other forms of hyperglycaemia have circumstances where use of GLP-1RAs may not be optimal.

A first population are those with pancreatic causes of diabetes, such as those with a history of pancreatitis. Although beneficial metabolic effects could be expected, a history of pancreatitis is probably still the most accepted contraindication for GLP-1RA use. Real-world evidence and the large GLP-1RA cardiovascular outcome trials conducted in people with type 2 diabetes have put to rest concerns about pancreatic cancer risk, but contradicting signals on the risk of pancreatitis remain. Whether this is a direct effect, or a consequence of weight loss and increased risk of biliary calculus and thus biliary pancreatitis, is unclear [36]. At present, large trials investigating GLP-1RAs in people with a history of pancreatitis are lacking.

PTDM and steroid-induced diabetes, which are related to type 2 diabetes, have been explored as potential hyperglycaemia situations in which GLP-1RAs might be used. Evidence regarding PTDM is mainly based on uncontrolled, retrospective studies, but effects on glucose control, insulin-sparing, weight and side effects were comparable with those reported in people with type 2 diabetes [37]. For those receiving high-dose or chronic corticosteroids, no clear clinical guidance is given, except the use of insulin if needed on top of healthy lifestyle behaviours and metformin. Few studies are available in this population. van Raalte et al showed the rationale for using GLP-1RA in corticoid-induced hyperglycaemia in a small, short-term study in healthy individuals receiving corticosteroids, where an infusion of exenatide reduced postprandial glucose excursions [38]. One Japanese retrospective case–control report in people with steroid-induced diabetes receiving dulaglutide (dose of 0.75 mg) showed better glucose control with less (mealtime) insulin requirements, without increased reporting of gastrointestinal symptoms [39].

Originally, we included in our literature search monogenic diabetes, but only a single randomised crossover study was identified in patients with MODY. This study focused on *HNF1A*-MODY (MODY3), which is the most common form of MODY and is caused by alterations in the *HNF1A* gene [29]. Although sulfonylureas are frequently used in the treatment of MODY, they can also be associated with hypoglycaemia (in people with MODY) owing to their glucose-independent mechanism of action. The small study (n=16) compared liraglutide 1.8 mg with glimepiride (a sulfonylurea; 1.0 mg) over a total duration of 14 weeks and demonstrated slightly lower fasting glucose levels during liraglutide treatment, but no difference in HbA_{1c}. More patients (67%) experienced hypoglycaemic episodes while on glimepiride, while only one patient (7%) experienced hypoglycaemia while receiving liraglutide (the same patient had three episodes while on glimepiride). These data have not led to alterations in clinical guidance on the treatment of hyperglycaemia in people with monogenic diabetes, but more evidence would be welcomed.

With the recent extension of evidence on the prevention of type 2 diabetes by GLP-1RAs in those living with overweight and obesity, and with new generations of incretin-based therapies (like multi-incretins) becoming available, a whole new population of people with dysglycaemia who could benefit from GLP-1RAs and related agents is emerging. We specifically want to highlight a small double-blind, randomised, placebo-controlled study in women with previous gestational diabetes and persistent metabolic abnormalities, where those randomised to a combination of metformin and liraglutide (on top of healthy lifestyle measures) had better metabolic outcomes than those on metformin only [40]. Our institution is currently sponsoring a large intervention trial using semaglutide in women with previous gestational diabetes, assessing the impact on progression to type 2 diabetes (SERENA study, NCT05569772).

Finally, we look forward to emerging trials assessing the effect of incretins on nephropathy and cardiovascular disease in populations other than people living with type 2 diabetes.

Our conclusion on use of incretins in other forms of diabetes is that for type 1 diabetes their benefit to clinicians and those living with the disease is obvious, with beneficial effects on glucose control (lower HbA_{1c}, with lower insulin needs) and less weight gain (or weight loss), but that expressing these effects in outcomes that are acceptable to regulators is not a given. For other forms of hyperglycaemia, the potential benefits are also there, on the basis of retrospective or small prospective studies. The clinical community, together with pharmaceutical companies and regulators, should now design and execute robust prospective randomised studies to demonstrate (or refute) the benefit of incretins in the treatment of other forms of diabetes, in order to guide clinicians on how these agents could be used to help people with non-type 2 forms of diabetes.

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