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Incretin-based medications (GLP-1 receptor agonists, DPP-4 inhibitors) as a means to avoid hypoglycaemic episodes

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ABSTRACT

Hypoglycaemia is common in both type 1 and type 2 diabetes and has both acute and long-term consequences. Therefore, a key to proper glucose-lowering therapy in diabetes is to avoid or prevent hypoglycaemia. Incretin therapy (DPP-4 inhibitors and GLP-1 receptor agonists) offers an advantage in this respect, because it reduces glucose with a low risk of hypoglycaemia, both in monotherapy and in combination with other therapies. The reason for this low risk of hypoglycaemia is the glucose dependency of action of incretin therapy and the sustainment of glucose counter-regulatory hormone responses to hypoglycaemia, in particular the glucagon response. Incretin therapy is also associated with a low risk of hypoglycaemia in patient groups which are especially vulnerable and susceptible for hypoglycaemia, e.g., subjects with renal impairment, elderly subjects and subjects with on-going insulin therapy. This review summarizes how incretin therapy may meet the challenges of hypoglycaemia and suggests that incretin therapy is a therapy of choice to avoid hypoglycaemia, both in the general diabetes population and in subjects with increased risk or vulnerability for hypoglycaemia.

1. Hypoglycaemia – the clinical challenge

1.1. Background and symptoms

Hypoglycaemia is the adverse event during glucose-lowering therapy of both type 1 and type 2 diabetes which is a major limitation for a good glycemic control [1,2]. Symptoms associated with hypoglycaemia usually start when glucose levels fall below 3.6 mmol/l, but sometimes already at 3.9 mmol/l (Fig. 1). The acute symptoms are either neuroendocrine (autonomic) symptoms (tachycardia, shakiness, anxiety, irritability and sense of hunger) or neuroglycopenic symptoms (difficulties to concentrate, weakness, dizziness, headache, confusion, blurred vision, slurred speech and coma).

1.2. Long-term consequences

Hypoglycaemia has also consequences beyond the acute symptoms. These consequences include fear of future hypoglycaemia, which may result in deteriorated glucose control, since the patient may loosen the glycemic control [3,4], weight gain due to eating in self-defense against the risk of hypoglycaemia, accidents or other injuries. If hypoglycemic episodes are repeated, the cardiovascular system may be particularly affected and result in increased risk for cardiovascular diseases [5]. Repeated hypoglycaemia may also result in cognitive dysfunction and dementia, particularly in older patients [6].

1.3. Incidence rate

The incidence rate of hypoglycaemia is difficult to estimate because glucose levels are not always measured, documented or reported in clinical studies, and because many hypoglycemic episodes are unrecognized. It is also difficult to compare different studies since the criteria for hypoglycaemia vary [7]. To grasp the incidence, a summary of 15 different studies estimated a frequency of ≈0.1–0.7 episodes of severe hypoglycaemia (a hypoglycaemic event requiring assistance of another person) per patient per year in type 2 diabetes [2]. Mild, non-severe hypoglycaemia was estimated to have an incidence of ≈0.3–0.7 episodes per patient per week in insulin treated subjects with type 2 diabetes [2,8,9].

1.4. High-risk groups

There is an increased risk of hypoglycaemia in certain high-risk patient groups [7,10]. Long duration of diabetes and insulin therapy [11,12], high age [1,13] and tight glycemic control are important risk factors. Reduced awareness of hypoglycaemia [14,15], socioeconomic deprivation [16], renal impairment [17,18] and cognitive dysfunction and dementia [19] are additional risk factors. This information is important when considering glucose-lowering therapy in various subgroups of patients.

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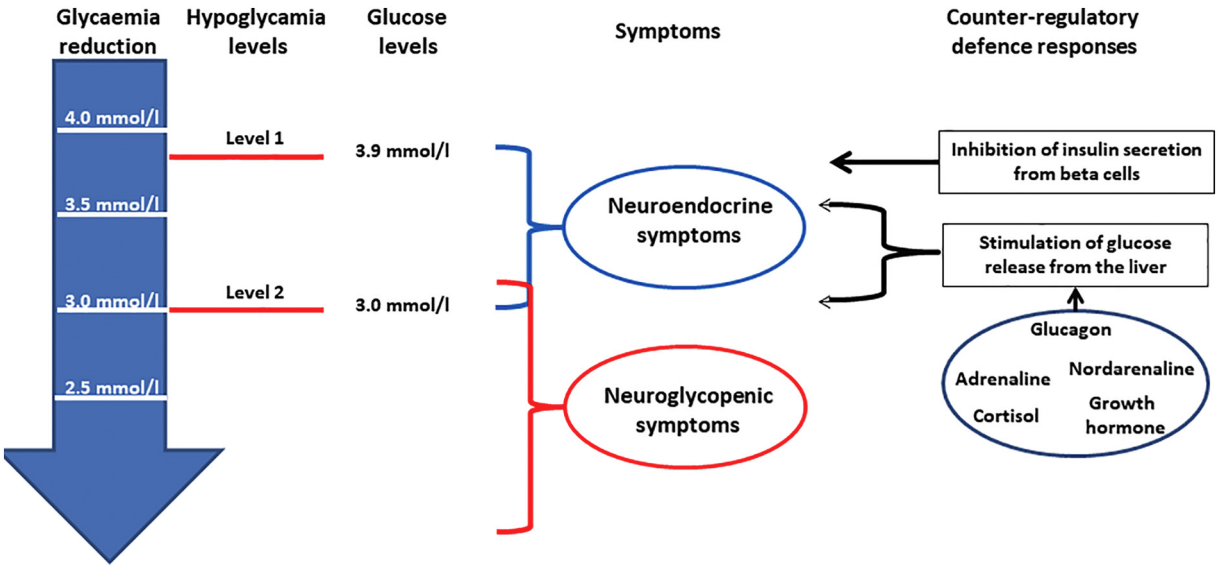

Fig. 1. Schematic view of definitions, symptoms and counter-regulatory defense responses to hypoglycaemia.

1.5. Initiation of hypoglycaemia

Several factors may initiate hypoglycaemia, particularly in high-risk populations. Most common initiators are missed meal or ingestion of a smaller meal than planned with preservation of glucose-lowering therapy. Also fasting, alcohol consumption, increased physical activity and increased insulin sensitivity may initiate hypoglycaemia [20,21]. Hypoglycaemia by itself also impairs physiological and behavioral defenses against subsequent hypoglycaemia [22]. However, the most important initiating factor for hypoglycaemia, either alone or in combination with the other initiating factors, is glucose-lowering therapy [1,2,7,20,23–25].

2. Risk for hypoglycaemia with glucose-lowering drugs

The glucose-lowering drugs of today have different risks of eliciting hypoglycaemia, because of their different modes of action. Drugs eliciting the highest risk are those that increase the circulating insulin levels independently from changes in glucose levels, in particular if insulin levels are elevated even when glucose levels decline. Therefore, highest risk is seen for exogenous insulin treatment and therapies which increase insulin secretion in a largely glucose-independent manner, mainly sulphonylureas [26]. Fig. 2 shows results of meta analysis regarding risk for hypoglycaemia with different therapies in monotherapy and as add-on to metformin [27,28]. It is seen that thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor agonists have largely a similar low risk of eliciting hypoglycaemia as placebo or metformin. In contrast, sulphonylureas raise the risk of hypoglycaemia three-fold as monotherapy and eightfold as add-on to metformin, whereas exogenous insulin is associated with an even higher risk for hypoglycaemia. The data reported in Fig. 2 are derived from a large number of individual trials and should therefore be regarded with caution, because the studies use different definitions of hypoglycaemia. It should also be emphasized that the risk for hypoglycaemia with sulphonylureas and exogenous insulin may vary between different individual drugs within these classes and, most importantly, depending on the doses used. Nevertheless, the data show the high risk for hypoglycaemia with insulin and sulphonylurea therapy whereas the risk for hypoglycaemia is lower for the other classes, which all have other modes of action than insulin and sulphonylureas. The low risk for hypoglycaemia with these other therapies is also underlined in current guidelines [26,29].

3. Low risk for hypoglycaemia with incretin therapy

3.1. Risk for hypoglycaemia with incretin therapy in monotherapy or in combination with metformin

Fig. 2 shows that incretin therapy is characterized by a low risk for hypoglycaemia as evident from meta analysis when used as monotherapy and in combination with metformin. This low risk for hypoglycaemia with DPP-4 inhibitors or GLP-1 receptor agonists is also evident from the results of the long-term and large cardiovascular outcomes trials of incretin therapy [30–38] (Table 1). Also studies directly comparing incretin therapy with other therapies have arrived at the same conclusion. For example, one study compared the DPP-4 inhibitor vildagliptin versus the sulphonylurea glimepiride as add-on to metformin for 52 weeks in patients with type 2 diabetes. It was found that although glycaemic control was improved similarly by vildagliptin and glimepiride, the sulphonylurea was associated with a 10-fold higher incidence of hypoglycaemia than vildagliptin [39]. A subanalysis of this study showed that the DPP-4 inhibitor had significantly lower risk of hypoglycaemia than glimepiride at any HbA1c level and regardless dose of glimepiride [40]. Similar differences between DPP-4 inhibitors and sulphonylureas have been documented in a large number of studies, as recently reviewed [41]. Furthermore, a two-year placebo-controlled study comparing the GLP-1 receptor albiglutide, the DPP-4 inhibitor sitagliptin and the sulphonylurea glimepiride as add-on to metformin in type 2 diabetes showed that HbA1c was reduced by all active therapies but with a significant difference in incidences of documented hypoglycaemia: 3.0% for albiglutide, 1.7% for sitagliptin, 4.0% for placebo and 17.9% for glimepiride [42]. Similarly, a study comparing addition of the GLP-1 receptor agonist liraglutide with glimepiride showed a risk of hypoglycaemia of 3% for liraglutide versus 17% for glimepiride, again therefore confirming the huge difference in risk of hypoglycaemia between these classes of treatment [43].

Moreover, the different risk of hypoglycaemia between incretin therapies and exogenous insulin when added to metformin has also been documented in several studies with GLP-1 receptor agonists. A

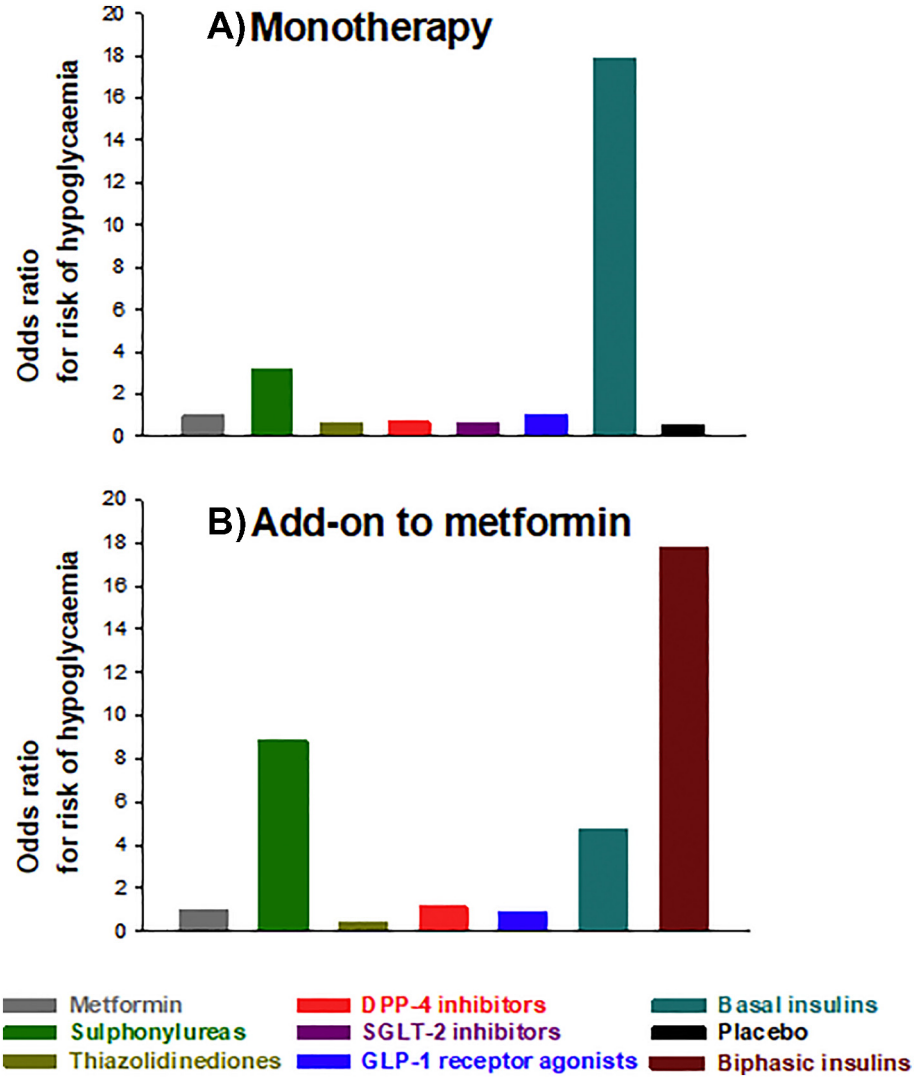

Fig. 2. 2A Relative risk for hypoglycaemia with different glucose-lowering therapies when added in monotherapy in subjects with type 2 diabetes as evident from a meta-analysis of 26 randomized placebo-controlled clinical trials with duration of ≥24 weeks involving 14,477 subjects [28]. Columns show mean odd ratios for the various add-on therapies versus the risk for hypoglycaemia with metformin. 95% confidence intervals for the odd ratios were 2.39 to 4.12 (sulphonylurea), 0.50 to 0.88 (thiazolidinediones), 0.50 to 0.92 (DPP-4 inhibitors), 0.30 to 1.32 (SGLT-2 inhibitors), 0.74 to 1.52 (GLP-1 receptor agonists), 1.97 to 162 (basal insulin) and 0.40 to 0.83 (placebo). 2B Relative risk for hypoglycaemia with different glucose-lowering therapies when added as the second drug to on-going metformin treatment in subjects with type 2 diabetes as evident from a meta-analysis of 39 randomized placebo-controlled clinical trials with duration of 12–52 weeks involving 17,860 subjects [27]. Columns show mean odd ratios for the various add-on therapies versus the risk for hypoglycaemia in the placebo group, i.e., metformin alone. 95% confidence intervals for the odd ratios were 4.63 to 17.83 (sulphonylurea), 0.15 to 1.34 (thiazolidinediones), 0.62 to 2.17 (DPP-4 inhibitors), 0.42 to 2.07 (GLP-1 receptor agonists), 1.35 to 18.3 (basal insulin) and 4.84 to 68.98 (biphasic insulins), respectively.

meta-analysis of 19 clinical trials comparing GLP-1 receptor agonists with exogenous insulin treatment as add-on to oral agents in subjects with type 2 diabetes showed a 35% lower risk for hypoglycaemia with GLP-1 receptor agonists than with insulin [44]. This lower risk for hypoglycaemia, together with the different effect on body weight (reduction by GLP-1 receptor agonists and increase by insulin), has led to

Table 1
Risk of hypoglycaemia in the large cardiovascular outcomes trials with DPP-4 inhibitors and GLP-1 receptor agonists. Observe that hypoglycemia was differently defined in the different studies and therefore comparison cannot be performed between the studies, but only between study medication and placebo within each study. OW = once weekly.

Therapy class	Drug	Name of trial	Number of patients	Mean duration of therapy	Hypoglycemia (%)		Ref.
					Study drug	Placebo	
DPP-4 inhibitors	Saxagliptin	SAVOR-TIMI	16,492	2.1 years	0.5%	0.6%	[30]
	Sitagliptin	TECOS	14,671	3 years	2,2%	1.9%	[31]
	Alogliptin	EXAMINE	5380	1.5 years	6.7%	6.5%	[32]
	Linagliptin	CARMELINA	6979	2.2 years	15.9%	16.4%	[33]
GLP-1 receptor agonists	Lixisenatide	ELIXA	6068	1.0 year	0.2%	0.3%	[34]
	Liraglutide	LEADER	9340	3.8 years	16.6%	15.2%	[35]
	Semaglutide	SUSTAIN 6	3297	2.0 years	21.7%	21.0%	[36]
	Exenatide OW	EXSCEL	14,752	3.2 years	3.4%	3.0%	[37]
	Albiglutide	HARMONY OUTCOMES	9463	1.5 years	0.7%	1.2%	[38]

the present proposal in guidelines that GLP-1 receptor agonists are the preferred first injection therapy in the treatment paradigm of type 2 diabetes [26].

3.2. Risk for hypoglycaemia with incretin therapy in combination with other therapies than metformin

3.2.1. Combination with insulin

Incretin therapy is an option in combination with insulin therapy [45,46]. A recent review compiled data from 16 studies in which a DPP-4 inhibitor was added to insulin therapy in type 2 diabetes. The conclusion was that in combination with insulin and compared to a group with up-titration of insulin, DPP-4 inhibitors had lower risk of hypoglycaemia than exogenous insulin [47]. A similar review and meta-analysis of 11 studies when GLP-1 receptor agonists were added to insulin in comparison with up-titration of insulin in type 2 diabetes showed a significantly better effect on HbA1c with the combination with yet no increase in risk for hypoglycaemia [48]. Hence, incretin therapy is favorable to add to exogenous insulin rather than up-titrating the insulin dose from the view of risk of hypoglycaemia. Also, a subsequent further up-titration of the insulin dose is possible with a lesser risk of hypoglycaemia if also an incretin therapy is used. These findings form the clinical background to the fixed dose combinations of GLP-1 receptor agonists and insulin which now exist on the market [49,50].

3.2.2. Combination with SGT-2 inhibitors

The combination of incretin therapy with SGLT-2 inhibitors does not result in an increased risk for hypoglycaemia, neither for DPP-4 inhibitors [51] nor for GLP-1 receptor agonists [52]. Therefore, these combinations, in particular the oral combination of DPP-4 inhibitors and SGLT-2 inhibitors, have been suggested to be used early in the treatment paradigm [53].

3.2.3. Combination with sulphonylureas

Combination of incretin therapy with sulphonylureas increases the risk for hypoglycaemia compared to sulphonylureas alone, as also is the case for other combinations with sulphonylureas. Fig. 3 shows a meta analysis of risk for hypoglycaemia in studies in which different glucose-lowering drugs have been added to sulphonylureas plus metformin, compared to placebo, i.e., sulphonylurea plus metformin alone

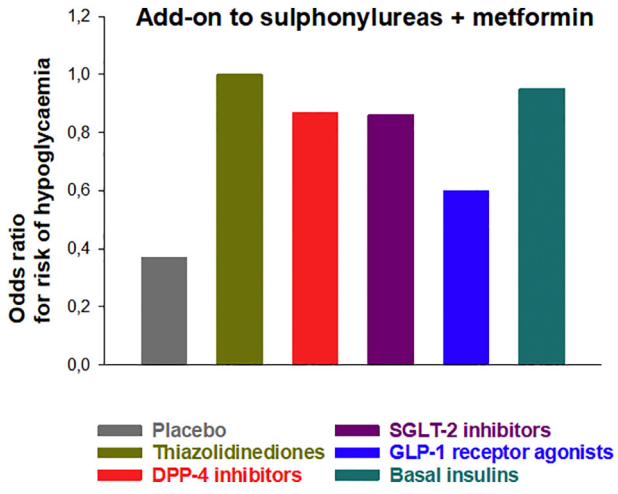

Fig. 3. Relative risk for hypoglycaemia with different glucose-lowering therapies when added as a third therapy to sulphonylurea plus metformin in subjects with type 2 diabetes as evident from a meta-analysis of 5 randomized clinical trials of placebo-controlled studies with duration of ≥24 weeks involving 3267 subjects [28]. Columns show mean odd ratios for the various add-on therapies versus the risk for hypoglycaemia when a thiazolidinedione was added. 95% confidence intervals for the odd ratios were 0.24 to 0.57 (placebo), 0.50 to 1.51 (DPP-4 inhibitors), 0.48 to 1.54 (SGLT-2 inhibitors), 0.39 to 0.94 (GLP-1 receptor agonists) and 0.60 to 1.52 (basal insulin).

[28]. It is seen that all therapies increased the risk for hypoglycaemia when added to sulphonylurea and metformin. Another meta analysis of 10 studies with DPP-4 inhibitors showed a 52% increased risk for hypoglycaemia with the combination compared to sulphonylureas alone [54]. Similarly, when the GLP-1 receptor agonist liraglutide was tested as add-on to glimepiride, there was an increased risk for hypoglycaemia from 2.6% with glimepiride alone to 5.2–9.1% for liraglutide (depending on the dose) [55]. The reason for this increased hypoglycaemia risk is that sulphonylureas continue to stimulate insulin secretion also after the reduction in glycaemia achieved by the combination with incretin therapy. A clinical consequence is that when this combination is used, the dose of sulphonylurea needs to be reduced.

3.3. Risk for hypoglycaemia with incretin therapy in high-risk populations

3.3.1. Kidney failure

The low risk of hypoglycaemia with incretin therapy has also been demonstrated in several studies in high-risk populations. A high risk population of major clinical interest is those with impaired renal function, particularly with an estimated glomerular filtration rate below 60 ml/min/1,73 m^2. As recently reviewed, addition of DPP-4 inhibitors to therapy in patients with kidney impairment does not increase the risk of hypoglycaemia [47].

3.3.2. Elderly subjects

In elderly subjects (>75 years of age) there is an increased risk of hypoglycemia during glucose-lowering therapy and symptoms of hypoglyceamia are sometimes atypical in old age [56]. However, incretin therapy has been shown to be associated with low risk of hypoglycaemia also in the elderly [57].

3.3.3. Liver failure

Another high-risk population is those with liver failure. Studies on glucose-lowering therapy in liver failure are lacking. However, experiences that exist suggest a low risk of hypoglycaemia with incretin therapy also in this patient group [58,59].

3.4. Mechanism of low risk of hypoglycaemia in incretin therapy

3.4.1. Glucose dependency

An explanation for the low risk of hypoglycaemia with incretin therapy is the glucose-dependency of the action of GLP-1 [60]. This is explained by the signaling mechanisms of GLP-1 in the islets such that a certain glucose level is required for GLP-1 to stimulate insulin secretion and inhibit glucagon secretion. This in turn results in lesser stimulation of insulin secretion and lesser inhibition of glucagon secretion when glucose levels drop, which together assure that further reduction in glucose is prevented. The reduction of insulin secretion when glucose is lowered has been demonstrated in a multistep hypoglycaemia clamp study with native GLP-1 in healthy subjects [61].

3.4.2. Sustained glucagon counter-regulation

Another explanation for the low risk of hypoglycaemia with incretin therapy is that the glucose counter-regulatory response, in particular the increase in glucagon, is sustained during incretin therapy. It is known that hypoglycaemia elicits a series of counter-regulatory combat mechanisms, the purpose of which is to restore glycaemia [1,20,62,63] (Fig. 1). This combat is usually triggered when glucose levels fall below 3.9 mmol/l in healthy subjects and involves a reduction in insulin secretion together with a stimulated release of counter-regulatory hormones. The reduction in insulin secretion is usually the initial consequence of reduction in glucose and is initiated already at 3.9 mmol/l. A further reduction in glucose, to approximately 3.3–3.6 mmol/l results in stimulation of hepatic glucose release, which aims at restoring the circulating glucose. Triggers for this stimulation involve glucagon, adrenaline, noradrenaline, cortisol and growth hormone.

In the immediate acute situation, the increase in glucagon is a critical mechanism for defending hypoglycaemia [62]. A series of mechanisms assure the stimulation of glucagon secretion during hypoglycaemia: the low glucose itself, the reduction of insulin secretion from the beta cells, adrenaline released from the adrenals and activation of the autonomic nervous system [20,62,63]. For incretin therapy, the glucagon response may be particularly critical, since glucagon secretion is inhibited by GLP-1 above a certain glucose level [61]. Therefore, protection from hypoglycaemia requires that the inhibition of glucagon secretion by incretin therapy should have vanished at a certain hypoglycaemic level to assure a sustained glucagon response.

The question whether counter-regulation to hypoglycaemia, in particular glucagon counter-regulation, is affected during incretin therapy has been the topic of several studies in different study populations and with different incretin drugs in both type 1 and type 2 diabetes [61,64–75]. The studies have used the hyperinsulinaemic, hypoglycaemic clamp technique to induce hypoglycaemia and to analyze the counter-regulation. These studies have been undertaken in healthy subjects as well as in subjects with type 1 or type 2 diabetes under various conditions. Table 2 shows the characteristics of these studies in terms of study population, study medication, number and mean age of study subjects, the glucose level achieved during the clamp and the duration of the incretin therapy. Furthermore, Table 2 shows also the main results in terms of counter-regulatory responses to hypoglycaemia for glucagon, adrenaline, noradrenaline and cortisol. As seen in the Table, almost all these studies show that at hypoglycaemic levels <3.1 mmol/l, the responses in glucagon, adrenaline, noradrenaline and cortisol are sustained and not different when compared to placebo. Therefore, the counter-regulation to hypoglycaemia is well documented to be sustained during incretin therapy. The sustained glucagon counter-regulation to hypoglycaemia is mainly explained by a reversal of the effect of GLP-1. However, for DPP-4 inhibition, a stimulatory action of GIP may contribute. GIP is, like GLP-1, inactivated by DPP-4 and the active levels of GIP are therefore raised during DPP-4 inhibition. This is of interest in the context of glucagon counter-regulation to hypoglycaemia, because GIP stimulates glucagon secretion during hypoglycaemia [76]. In fact, an experimental study in GIP receptor knockout mice has shown a defect in counter-regulation due to absence of an appropriate glucagon response [77].

Studies using multi-step hypoglycaemia clamp allow also estimation of the glucose levels when the counter-regulation is initiated during hypoglycaemia. Such studies have been performed on the effect of the DPP-4 inhibitor vildagliptin [71] and the GLP-1 receptor agonist lixisenatide [73]. The results suggest that the glucose threshold for the responses seems to be between 3.1 and3.5 mmol/l.

4. Summary and clinical outlook

4.1. Summary

An advantage of incretin therapy is the low risk of hypoglycaemia, and the mechanistic studies have underlined that incretin therapy does not compromise the counter-regulation if hypoglycaemia evolves. The clinical consequence of this knowledge is that incretin therapy can be used to prevent hypoglycaemia and to reduce the burden and fear of hypoglycaemia. This aspect of incretin therapy is often included in position documents and guidelines, where incretin therapy is suggested as a glucose-lowering option in patients in whom it is important to avoid hypoglycaemia [26,29].

Indeed, incretin therapy has a low risk for hypoglycaemia in all therapeutic combinations; as monotherapy and as add-on to metformin, thiazolidinediones and SGLT-2 inhibitors. Therefore, incretin therapy can be combined with these therapies. The lower risk for hypoglycaemia for GLP-1 receptor agonists in comparison with exogenous insulin is also a rationale for the recent positioning of GLP-1 receptor agonists as the first line injectable therapy in type 2 diabetes [26]. Incretin therapy is also an option in combination with sulphonylureas

Table 2
Studies in which the effects of native GLP-1 or incretin therapy have been examined on counter-regulatory responses to hypoglycaemia.

Ref.	Study population	Study medication	N	Mean age (years)	Glucose clamp (mmol/l)	Duration of therapy	Glucagon response in incretin group versus placebo	Adrenaline, noradrenaline and cortisol responses in incretin group versus placebo
[61]	Healthy volunteers	Native GLP-1	9	28	3.7, 3.0 and 2.3	Acute	Sustained	Sustained
[64]	Healthy volunteers	Exenatide[a]	12	28	3.2 and 2.7	Acute	Sustained at 3.2 Enhanced at 2.7	Sustained
[65]	Drug-naïve T2D	Vildagliptin[b]	25	66	2.5	4 weeks	Enhanced	Sustained
[66]	T2D with OHA	Albiglutide[a]	41	51	3.3 and 2.8	3 days	Sustained	Sustained
[67]	T2D with metformin	Semaglutide[a]	37	54	2.5	12 weeks	Sustained	Sustained (adrenaline) Attenuated (noradrenaline, cortisol)
[68]	T2D with or without OHA	Liraglutide[a] and Linagliptin[b]	29	58	2.5	2 weeks	Sustained[c]	Attenuated[c]
[69]	Elderly T2D with metformin	Sitagliptin[b]	28	74	3.5 and 3.1	4 weeks	Attenuated at 3.5 Sustained at 3.1	Attenuated at 3.5, Sustained at 3.1
[70]	T2D with insulin treatment with or without OHA	Vildagliptin[b]	29	59	2.6	4 weeks	Sustained	Sustained
[71]	T2D with insulin and metformin treatment	Lixisenatide[a]	18	55	3.5 and 2.8	6 weeks	Attenuated at 3.5 Sustained at 2.8	Adrenaline attenuated at 3.5 and sustained at 2.8 Noradrenaline and cortisol sustained at both 3.5 and 2.8
[72]	T1D	Vildagliptin[b]	28	30	2.5	4 weeks	Sustained	Sustained
[73]	T1D	Sitagliptin[b]	16	32	2.0	6 weeks	Sustained	Sustained
[74]	T1D	Liraglutide[a]	45	35	2.5	4 weeks	Sustained	Sustained
[75]	T1D	Liraglutide[a]	17	37	2.5	12 weeks	Sustained	Sustained

T1D = type 1 diabetes, T2D = type 2 diabetes, OHA = oral hypoglycaemic agent, the glucose level indicates the glucose level achieved during the hypoglycaemia clamp at which the counter-regulatory responses were estimated, N = number of completers, OHA = oral anti-hyperglycaemic agents.

[a] Indicates GLP-1 receptor agonist.

[b] Indicates DPP-4 inhibitor.

[c] Indicates comparison with before treatment.

and insulin. However, in these combinations there is still an increased risk of hypoglycaemia and, therefore, when incretin therapy is used with these therapies, it is suggested that the dose of sulphonylureas and insulin should be reduced. The low risk for hypoglycaemia with incretin therapy is also seen in the special risk groups for hypoglycaemia, such as in kidney disease or in high age, and therefore incretin therapy is also an option in these subgroups.

4.2. Meeting the challenge

There are several aspects to consider when selecting glucose-lowering therapy for a subject with type 2 diabetes. Besides the efficacy of the therapies in reducing glucose, their risk for hypoglycaemia and other adverse events, their potential benefit for cardiovascular outcomes, and their compliance and cost are all important factors [29]. DPP-4 inhibitors have been regarded as a particularly important choice when avoiding hypoglycaemia is considered important, whereas GLP-1 receptor agonists and SGLT2-inhibitors have advantages in subjects with increased cardiovascular risk, GLP-1 receptor agonists in obese subjects and SGLT2 in subjects with kidney failure [29]. The consideration of risk for hypoglycaemia is important since for many years it has been regarded as a major limitation for glycaemia control and that a key for success in diabetes therapy is to avoid hypoglycaemia [1,2,20]. Therefore, along with efficacy and effects on long-term complications, including cardiovascular disease, adverse events and compliance, avoidance of hypoglycaemia is an important factor when choosing an agent for glucose-lowering therapy. Both GLP-1 receptor agonists and DPP-4 inhibitors offer a solution for the challenge of avoiding hypoglycaemia. This therapy therefore may help in advancing the glycemic control towards lower thresholds without this complication or the fear of it. This is of value in all subjects but of particular value in subjects with a daily life when hypoglycaemia needs to be avoided as well as in subjects at increased risk for hypoglycaemia, such as insulin-treated subjects, subjects with kidney disease and elderly subjects. Incretin therapy is therefore an option when minimizing the risk for hypoglycaemia is important, together with thiazolidinediones and SGLT2-inhibitors, which also have a low risk of hypoglycaemia [29].

Author contribution

BA and JF have both designed and written the manuscript.

Declaration of Competing Interest

Bo Ahrén has throughout the years been consulting for and/or lecturing for Boehringer Ingelheim, GSK, Lilly, MSD, Novartis, Novo Nordisk, Sanofi and Takeda, which all are companies producing DPP-4 inhibitors or GLP-1 receptor agonists.

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