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A Dynamic Approach in Type 2 Diabetes Management: Empagliflozin Plus Linagliptin

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Abstract

Scientific literature has shown that a significant number of diabetic patients have a poor glycemic control. Also, as the disease progresses, the glycemic control is lost leading to type 2 diabetes mellitus (T2D) related complications. Thus, one of the major unmet needs in T2D management is maintaining sustained glycemic control to prevent progression of complications. Patient adherence and compliance is notably poor with multiple drug regimens thereby making fixed drug combinations a viable option. Current literature has demonstrated the use of various combinations in T2D management. One of the combinations on empagliflozin, an SGLT2-inhibitor and linagliptin, a DPP4-inhibitor has gained researchers' interest. Published data suggests that this combination has demonstrated considerable reductions in HbA1c and other parameters like weight and BP reduction while exhibiting complimentary actions on DeFronzo's ominous octet. Scientific literature has shown reasonable safety with this combination while catering to the unmet needs in T2D. This review highlights and discusses the clinical rationale, complimentary mechanisms and clinical evidence for this combination.

Keywords: Type 2 diabetes mellitus; Glycemic control; Empagliflozin; Linagliptin

Introduction

Ensuring good glycemic control is undoubtedly the mainstay of diabetes management despite findings in the ACCORD, ADVANCE and VADT studies stating concerns regarding safety with tight glucose control. In spite of significant advantages on micro vascular outcomes with tight glucose control over a span of 3.5-5.6 years, these studies failed to demonstrate a significant reduction in macro vascular complications; whereas in the ACCORD trial, there was an increase in all-cause mortality, risk of hypoglycemia and weight gain in patients on tight glycemic control [1,2].

The above findings clearly suggest that intensive glucose therapy is not a benchmark for diabetes management. On the contrary, the glycemic targets should be individualized based on the patient characteristics determined by risk assessment [1]. Ideal treatment of T2D must consider the various comorbidities which are frequently observed in patients as the disease progresses [3]. Consequently, instead of a common approach, catering to individual patient needs is necessary, harmonizing the benefits of glycemic control with its impending risks, considering the adverse effects of glucose-lowering medications (mainly hypoglycemia), and the patient's age, lifestyle, and health status, among other factors [3]. The patient centered approach includes a combination of life style modification such as weight control, physical activity and healthy eating along with appropriate pharmacotherapy [2,3].

Scientific literature has shown that a significant number of diabetic patients have a poor glycemic control [4,5]. The reasons for inadequate glycemic control are multifarious ranging from the disease process itself to inadequacy of therapeutic regimens and attitudes of both patient and doctors [5]. Another significant cause of poor glycemic control is prolonged use of monotherapy and resistance to polypharmacy. Notably, the glycemic control from 50% at the end of 3 years post therapy declined progressively, and by the end of 9 years this number further declined to approximately 25%. These statistics clearly indicate that majority of patients need multiple therapies to achieve glycemic targets [4,5].

The use of multiple daily medications may fail to provide necessary patient adherence and compliance. Consequently, there is an emerging interest in the use of single-pill combinations that would aid in reducing the pill burden [6]. Talking of the single-pill combinations, an ideal combination would be the one which is effective, well-tolerated and would improve patient adherence [5,6]. So far, most single-pill formulations have combined metformin along with a second agent, but the use of such formulations may be restricted in some patients as metformin is not appropriate for all diabetics; eg: In patients with gastrointestinal intolerance. Thus, combinations of other agents may be a suitable alternative to traditional metformin combinations [6]. An ideal combination of anti-diabetic agents should have complementary mechanisms of action, exclusively target all stages of the disease, be well tolerated with less risk of hypoglycemia, cardiovascular events, or weight gain, and improve patient compliance [5,6]. Of the available classes of anti-diabetic drugs, sodium glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors have shown to fulfil these criteria [6].

One such combination is that of sodium glucose co-transporter 2 inhibitor empagliflozin with dipeptidyl peptidase-4 inhibitor linagliptin which offers a novel and attractive alternative, because of their complementary mechanisms of action. In this review, we discuss the rationale, scope and evidence for a single-pill combination of linagliptin and empagliflozin. In 2015, the US Food and Drug Administration (FDA) and in 2017, Drug Controller General of India (DCGI) under the gamut of Central Drugs Standard Control Organization (CDSCO) approved the use of this combination as an

adjunct to diet and exercise to improve glycemic control in adults with T2D when treatment with both empagliflozin and linagliptin is appropriate [7].

Complementary Mechanism

Linagliptin and empagliflozin as a combination fill the gap of unmet need for pharmacological agents with complementary mechanisms of action which can be used to improve glycemic control in a wide gamut of diabetic patients, with a low risk of adverse events and good tolerability [8-10]. Linagliptin is known to augment postprandial insulin secretion and inhibit glucagon secretion by preventing the break-down of endogenously released incretin based hormones [glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)], whose concentrations physiologically increase following food intake [9,10]. Interestingly, linagliptin promotes insulin secretion and suppresses glucagon secretion in a glucose-dependent manner, thereby reducing hyperglycemia with minimal risk of hypoglycemia [9,10]. Additionally, current literature suggests that it does not cause weight gain (Figure 1) [9].

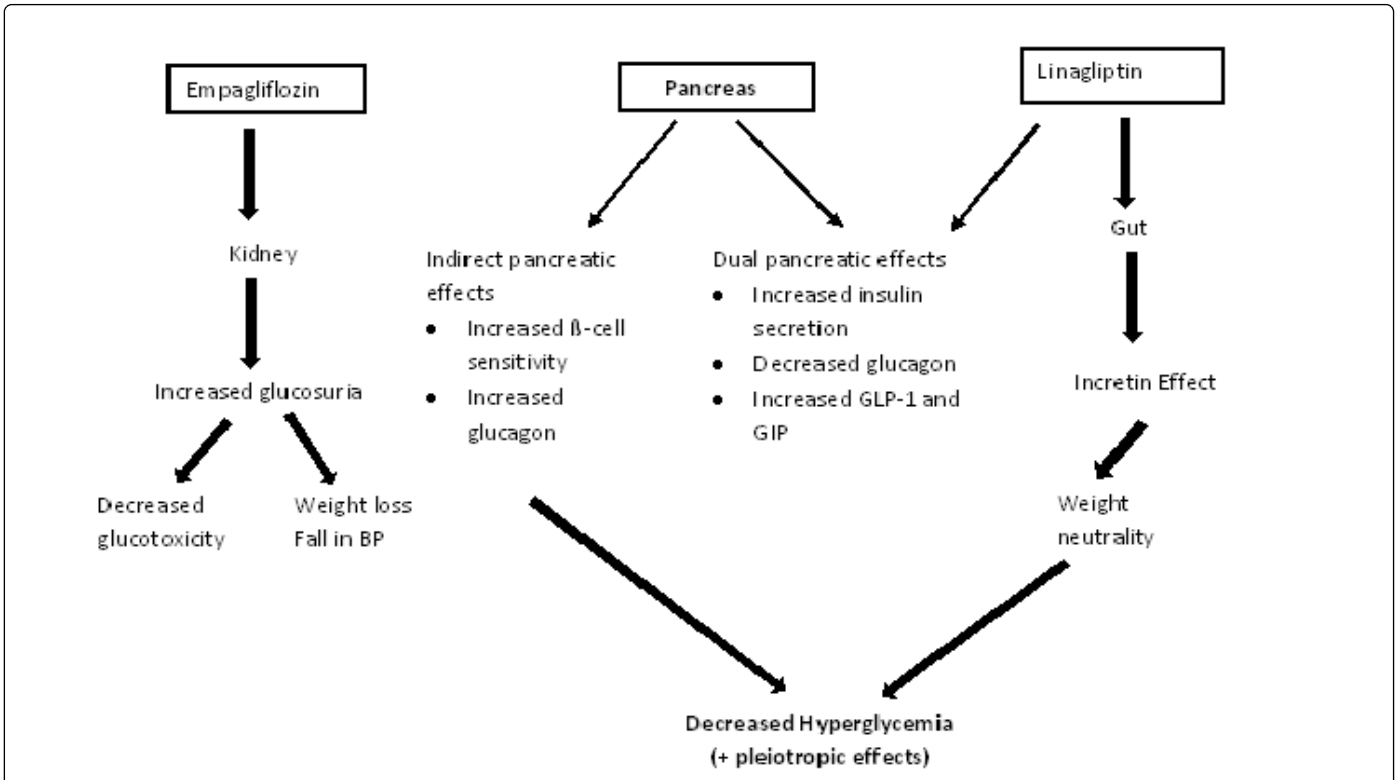

Figure 1: Complementary mechanisms of action of Empagliflozin and Linagliptin [9].

Empagliflozin inhibits glucose reabsorption at the renal proximal tubule thereby promoting glucosuria, an effect independent of insulin. The main feature of T2D is progressive deterioration of beta-cell function; thus, a glucose-lowering agent that does not depend on pancreatic beta-cell function for its action makes empagliflozin a suitable choice for patients with advanced T2D, especially if targeted glycemic control is not achieved with other oral glucose-lowering agents. It reduces glucotoxicity by promoting glucosuria and dampening hyperglycemia thereby indirectly improving beta-cell function and peripheral insulin sensitivity [9,11-13]. But, treatment with empagliflozin causes an increase in plasma glucagon concentrations, which was associated with a significant increase in endogenous (hepatic) glucose production (Figure 1) [9,11,12]. This explains that addition of linagliptin, a DPP-4 inhibitor which has an inhibitory effect on glucagon and augmenting effect on insulin secretion may have the potential to prevent the increase in endogenous glucose production and enhance the glucose-lowering ability of empagliflozin. Thus, combination treatment with linagliptin and empagliflozin appears to be a promising option for patients with T2D initiating pharmacological therapy, or for patients with a pre-existing background of a glucose-lowering agent, especially metformin, but require additional medications to achieve target glycemic level. Current findings suggest that both these agents act in combination with a range of other oral antidiabetics agents to achieve glycemic control and at the same time are complementary by themselves [9-12].

Pharmacokinetics

Sixteen healthy male subjects in an open-label, randomized, multiple-dose, crossover study received empagliflozin 50 mg once daily for 5 days, both empagliflozin 50 mg once daily and linagliptin 5 mg once daily for 7 days, and linagliptin 5 mg once daily for 7 days [9,14]. Co-administration of empagliflozin did not change linagliptin total exposure and peak concentration (Table 1). Similarly, co-administration of linagliptin did not affect empagliflozin total exposure. However, a small reduction in empagliflozin peak exposure was observed when linagliptin was co-administered, which was clinically insignificant (Table 1). Thus, results from this study support that no dose adjustment is required while co-administering linagliptin and empagliflozin [9,14].

Reference	Multiple Dose (5-7 days)	(n)	Empagliflozin		Linagliptin	
			C max, ss	AUC tau, ss	C max, ss	AUC tau, ss
Friedrich et al. [14]	Empagliflozin 50 mg/ Linagliptin 5 mg *vs* Linagliptin 5 mg	16	NA	NA	1.01 (0.87-1.19)	1.03 (0.96-1.11)
	Empagliflozin 50 mg/ Linagliptin 5 mg *vs* Empagliflozin 50 mg	16	0.88 (0.79-0.99)	1.02 (0.97-1.07)	NA	NA

Table 1: Pharmacokinetic interactions in studies combining empagliflozin and linagliptin. Data are adjusted geometric mean ratios (90% confidence interval).

Pharmacodynamics

In patients with T2D, following empagliflozin administration, urinary glucose excretion was found to be increased. [7]. However, glucagon response increased contributing to a significant rise in endogenous glucose production. [9,12] After a meal tolerance test, linagliptin 5 mg substantially increased the two incretin hormones GLP-1 and GIP; and thereby significantly decreased glucagon [15]. These complementary pharmacodynamic changes noted with empagliflozin and linagliptin contributed to reduction in postprandial hyperglycemia in patients with T2D [9,12,16].

Clinical data on empagliflozin/linagliptin combination

A double-blind, randomized study assessed the efficacy and safety of the empagliflozin/linagliptin fixed dose combination T2DM patients who were either treatment naïve i.e there was no previous history of treatment with any anti-diabetic agent [17] or who did not achieve target glycemic control with metformin [18]. The baseline characteristics are furnished in Table 2. The duration of this trial was 54 weeks, and the primary efficacy endpoint was the change in HbA1c from baseline at the end of 24 weeks. Results showed that in treatment-naïve patients, HbA1c reduction was significantly greater at the end of 24 weeks for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P<0.001$), but not when compared with empagliflozin 25 mg ($P=0.179$). It was also noted that drop in HbA1c was significantly greater for empagliflozin 10 mg/linagliptin 5 mg when compared with both empagliflozin 10 mg and linagliptin 5 mg ($P<0.001$ for both). A sustained reduction in HbA1c was noted till week 52 (Table 3) [17]. Additionally, the percentage of patients reaching a goal of HbA1c <7.0% at Week 24 in both the combination-dose groups were significantly higher than with either monotherapy ($P<0.005$) [17].

Reference	Background therapy	Characteristic	Empagliflozin 25 mg/linagliptin 5 mg	Empagliflozin 10 mg/ linagliptin 5 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Linagliptin 5 mg
Lewin et al. [17]	Diet + Exercise	n	134	135	133	132	133
		Age (years)	54.2	55.2	56.0	53.9	53.8
		HbA1c (%)	7.99	8.04	7.99	8.05	8.05
		Time since diagnosis T2DM (n) ≤ 1 years >1 to 5 years >5 to 10 years >10 years	41 53 28 12	46 48 30 11	48 48 25 12	43 60 15 14	50 57 22 4
DeFronzo et al. [18]	Metformin	n	134	135	140	137	128
		Age (years)	57.1	56.2	55.5	56.1	56.2
		HbA1c (%)	7.90	7.95	8.02	8.00	8.02
		Time since diagnosis T2DM (n) ≤ 1 years >1 to 5 years >5 to 10 years >10 years	10 46 46 32	19 49 41 26	10 50 50 30	13 51 39 34	10 44 42 32

Table 2: Baseline characteristics.

Another study with patients on metformin background was conducted. Baseline and demographic data is furnished in Table 2. In these patients, there was a significantly greater reduction in HbA1c at the end of 24 weeks for empagliflozin 25 mg/linagliptin 5 mg compared with empagliflozin 25 mg and linagliptin 5 mg and for empagliflozin 10 mg/linagliptin 5 mg compared with empagliflozin 10 mg and linagliptin 5 mg (all P<0.001). A sustained reduction in HbA1c was noted till week 52 [18].

Furthermore, the percentage of patients reaching a goal of HbA1c <7.0% at Week 24 in both the combination-dose groups were significantly higher than with either monotherapy (P<0.001).

In both the studies, therapy with both combination doses led to reductions from baseline in weight and systolic BP (SBP); differences were significant as compared to linagliptin monotherapy and varied as compared to empagliflozin monotherapy (Table 3) advocating that these benefits were primarily due to the action of empagliflozin [17,18].

A phase III, randomized, double-blind, double-dummy, parallel group studies were conducted to assess the efficacy and safety of empagliflozin as compared to placebo as add-on therapy in T2D patients and inadequate glycemic control with a combination of linagliptin and metformin [19]; and efficacy and safety of linagliptin as compared to placebo as add-on to empagliflozin and metformin in patients with T2D [20].

The duration of this trial was 24 weeks and the primary efficacy end-point was change from baseline in HbA1c at week 24. The baseline and demographic data is listed in Table 4.

Reference	Back-ground therapy	Duration (weeks)	Treatment	Patients (n)	ΔBW kg	ΔFPG mg/dl	Baseline HbA1c %	ΔHbA1c%	% Patients reaching HbA1c <7%
Lewin et al. [17]	Diet + exercise	24	Empagliflozin 25 mg +Linagliptin 5 mg	134	-2 p=0.801[a] p=0.018[b]	-29.6 p=0.161[a] p<0.001[b]	7.99 ± 0.95	-1.08 ± 0.06 p=0.179[a] p<0.001[b]	55.4 p=0.022[a] p<0.001[b]
			Empagliflozin 10 mg +Linagliptin 5 mg	135	-2.7 p=0.362[a] p<0.001[b]	-28.2 p=0.125[a] p<0.001[b]	8.04 ± 0.96	-1.24 ± 0.06 p<0.001[a] p<0.001[b]	62.3 p<0.001[a] p<0.001[b]
			Empagliflozin 25 mg	133	-2.1	-24.2	7.99 ± 0.97	-0.95 ± 0.06	41.5
			Empagliflozin 10 mg	132	-2.3	-22.4	8.05 ± 1.03	-0.83 ± 0.06	38.8
			Linagliptin 5 mg	133	-0.8	-5.9	8.05 ± 0.89	-0.67 ± 0.06	32.3
DeFronzo et al. [18]	Metformin	24	Empagliflozin 25 mg +Linagliptin 5 mg	134	-3.0 p=0.66[a] p<0.001[b]	-35.3 p<0.001[a] p<0.001[b]	7.9 ± 0.79	-1.19 ± 0.06 p<0.001[a] p<0.001[b]	61.8 p<0.001[a] p<0.001[b]
			Empagliflozin 10 mg +Linagliptin 5 mg	135	-2.6 p=0.876[a] p<0.001[b]	-32.2 p<0.002[a] p<0.001[b]	7.95 ± 0.80	-1.08 ± 0.06 p<0.001[a] p<0.001[b]	57.8 p<0.001[a] p<0.001[b]
			Empagliflozin 25 mg	140	-3.2	-18.8	8.02 ± 0.83	-0.62 ± 0.06	32.6
			Empagliflozin 10 mg	137	-2.5	-20.8	8.00 ± 0.93	-0.66 ± 0.06	28
			Linagliptin 5 mg	128	-0.7	-13.1	8.02 ± 0.90 -	-0.70 ± 0.06	36.1

a: Versus Empagliflozin alone at corresponding dosage, b: Versus Linagliptin 5 mg, Delta (Δ) : Change from baseline, BW : Body weight, FPG : Fasting plasma glucose, HbA1c : Glycated haemoglobin.

Table 3: Results of clinical trials with the combination empagliflozin-linagliptin in patients with T2D

At week 24, HbA1c was significantly reduced in the empaglflozin 10 mg and 25 mg (as add-on to linagliptin) groups as compared to placebo (both P<0.001) [19].

Additionally, significant reduction in fasting plasma glucose and weight were observed in both empagliflozin groups versus placebo (P<0.001 for all comparisons) [19].

Reference	Linagliptin 5 mg+Metformin				
Søfteland et al. [19]	Characteristics		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
	n		108	109	110
	Age (years)		55.9	54.3	55.4
	HbA1c (%)		7.97	7.97	7.97
	Time since diagnosis T2DM (n)				
	≤ 1 years		9	6	7
	>1 to 5 years		31	30	41
	>5 to 10 years		38	42	35
	>10 years		30	31	27
Tinahones et al. [20]	Characteristics	Empagliflozin 10 mg+Metformin		Empagliflozin 25 mg+Metformin	
		Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
	n	125	122	110	110
	Age (years)	56.8	56.6	56.1	56.6
	HbA1c (%)	8.03	8.04	7.88	7.81
	Time since diagnosis T2DM (n)				
	≤ 1 years	16	7	9	8
	>1 to 5 years	40	42	33	31
	>5 to 10 years	37	40	39	40
	>10 years	32	33	29	31

Table 4: Demographics and baseline characteristics

Results showed significant reductions in HbA1c at week 24 with linagliptin *vs* placebo (P=0.001) and in patients both on empagliflozin 10 mg and metformin and on empagliflozin 25 mg and metformin (Table 5) [20].

Reference	Back-ground therapy	Duration (weeks)	Treatment	Patients (n)	ΔBW Kg	ΔFPG mg/dl	ΔHbA1c%	% Patients reaching HbA1c <7%
Søfteland et al. [19]	Linagliptin+Metformin	24	Empagliflozin (10 mg)	109	-3.06 kg	-26.3	-0.65	37
					p<0.0001	p<0.0001	p<0.0001	
	Linagliptin+Metformin	24	Empagliflozin (25 mg)	110	-2.52	-31.6	-0.56	32.7
					p<0.0001	p<0.0001	p<0.0001	
	Linagliptin+Metformin	24	Placebo	108	-0.3	6.1	0.14	17
Tinahones et al. [20]	Empagliflozin (10 mg) +Metformin	24	Linagliptin (5 mg)	126	-0.2	-8	-0.53	25.9
					p=0.095	p=0.013	p=0.0013	
	Empagliflozin (10 mg) +Metformin	24	Placebo	130	-0.79	3.7	-0.21	10.9
	Empagliflozin (25 mg) +Metformin	24	Linagliptin (5 mg)	112	-0.17	-12.3	-0.58	36
					p=0.801	p=0.0452	p<0.0001	

	Empagliflozin (25 mg) +Metformin	24	Placebo	112	-0.26	-4.4	-0.1	15
Delta (Δ): Change from baseline, BW: Body weight, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin								

Table 5: Results of clinical trials when both empagliflozin and linagliptin were added sequentially on metformin background in patients with T2D

Safety of This Combination

There was no difference in the general safety profile of empagliflozin/linagliptin as compared to the already known safety profiles of the individual agents. In drug-naïve T2D patients, there was no significant difference in the proportion of subjects with adverse events over 52 weeks in the three interventional groups namely empagliflozin monotherapy, linagliptin monotherapy or the combination [17]. On a general basis, the three treatments were well tolerated. A low risk of hypoglycemia was noted when both the agents were given as monotherapy; however, no established episodes of hypoglycemia were observed with the combination therapy [17].

In patients with metformin background, no significant difference was found across the treatment groups in the incidence of one or more adverse events [18]. Confirmed hypoglycemic episodes which did not require any assistance were reported in 3.6% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 2.2% on empagliflozin 10 mg/linagliptin 5 mg, 3.5% on empagliflozin 25 mg, 1.4% on empagliflozin 10 mg, and 2.3% on linagliptin 5 mg which was not clinically meaningful [18]. At the end of 52 weeks, no episodes of ketoacidosis were noted in these two trials; only one case of pancreatitis was observed in the drug-naïve patients on empagliflozin 25 mg/linagliptin 5 mg [17,18].

Furthermore, relatively lower rates of genital infections and urinary tract infections were noted on adding linagliptin to empagliflozin compared with empagliflozin monotherapy [17,18]. This finding is consistent with a meta-analysis conducted by Fadini et al. [21]. A possible explanation for this could be that there was a greater reduction in glycemia and glucosuria with DPP-4 inhibitor/SGLT2-inhibitor combination therapy than SGLT2- inhibitors alone, thereby lowering the rate of genito-urinary tract infections [21]. However, there is no data supporting this hypothesis. Another probable explanation could be both SGLT2 and DPP4 are membrane proteins which are expressed at high levels in the kidney and they may probably interact as proteins at the membrane level. Additionally, DPP4 activity is observed within some bacteria, yeasts and moulds and inhibition of DPP-4 enzyme may directly alter their functioning [21]. However, further investigation is needed to validate this theory.

While prescribing this combination, it is advisable to monitor for the symptoms of acute pancreatitis as there have been post-marketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. However, it is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using this combination. Symptomatic hypotension may occur after initiating empagliflozin due to intravascular volume depletion particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Thus, before initiating this combination, one must assess for volume depletion and correct volume status if required. Regular monitoring for signs and symptoms of hypotension is advisable. Also, patients should be evaluated for signs and symptoms of diabetic ketoacidosis (DKA) and acute kidney injury (AKI) as there have been post-marketing surveillance reports of DKA and AKI with SGLT2-inhibitors including empagliflozin.

This combination is not recommended in second and third trimesters of pregnancy and lactating mothers. It should be used with caution in elderly patients and in patients with renal impairment as higher incidence of adverse reactions related to volume depletion and reduced renal function may occur. This combination is well tolerated in patients with hepatic impairment whereas safety and efficacy in pediatric population is not established [7].

Clinical Perspective

Current research shows that empagliflozin/linagliptin combination therapy is a dynamic option for T2D management, offering about 1.1% to 1.5% reductions in HbA1c; and about 2 kg of weight reduction when used as an add-on to metformin [18]. For patients who are intolerant to metformin, this combination could be a feasible option to monotherapy with individual agents, however, it is important to note that there is a paucity of exclusive clinical trials on metformin intolerant patients; and so far, there is only 1 study in treatment-naïve patients that has been documented [9,10,17].

The mechanisms of action of empagliflozin and linagliptin complement each other thereby addressing the complex pathophysiological abnormalities present in T2DM. Additionally, the triple drug combination with metformin addresses most of the underlying pathophysiological pathways leading to T2D [10].

To sum up the clinical benefits, we can say that this dynamic combination is suitable for early treatment intensification due to its good tolerability, relatively low risk of hypoglycemia, observed weight loss, and minimum treatment burden [9,10]. Lastly, the empagliflozin/linagliptin combination can be administered in combination with other hypoglycemic agents from different classes, including insulin, although further studies to support this implication are needed [8-10].

Conclusion

In conclusion, the combination of empagliflozin and linagliptin is a promising treatment option for a wide range of patient pool with T2D, including those who are inadequately controlled on metformin, metformin intolerant or in patients where metformin is an absolute contraindication, and those who are at a higher risk of hypoglycemia and weight gain. Furthermore, this combination therapy is apt for patients having a higher baseline HbA1c (>7.5%), and can be co-administered with other classes of oral anti-diabetic agents including insulin. Currently, there is limited safety and efficacy data available for this combination therapy (up to 1 year post treatment). Thus, further real-world evidence and long-term post marketing studies are needed to substantiate the benefits of this combination both in terms of efficacy and safety.

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