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Research Article

Reducing Body Weight and Improving Lipid Profile with SGLT-2 Inhibitors in Type 2 Diabetes: Current Evidence and Clinical Implications

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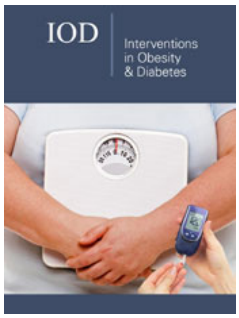

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Abstract

Background: Type 2 diabetes, a chronic condition with insulin resistance and impaired glucose metabolism, often leads to obesity and dyslipidaemia. Traditional antidiabetic medications struggle with weight reduction and lipid profile improvement. Sodium-Glucose Cotransporter 2 (SGLT-2) inhibitors offer a unique therapeutic approach.

Objective: The study investigates the impact of SGLT-2 inhibitors on weight reduction and lipid profile improvement in type 2 diabetes patients, evaluating evidence from various patients.

Methods: A study involving 103 Libyan patients with type 2 diabetes mellitus evaluated the effects of SGLT-2 inhibitors on body weight and lipid profiles. The study compared two types of SGLT-2 inhibitors, Dapagliflozin (DAPA, 5-10mg/kg, n=69) and Empagliflozin (EMPA, 12.5mg/kg, n=34). Patients were categorized based on weight and age.

Result: The study found that treatment with SGLT-2 inhibitors significantly reduced body weight compared to placebo or other antidiabetic drugs, particularly for patients receiving both DAPA and EMPA. EMPA data shows that patients under 50 years old and weighing less than 90kg experienced the largest weight decrease among the groups. SGLT-2 inhibitors showed a 13% loss in DAPA impact and a pooled effect size of 17.95%. They also showed positive effects on lipid profiles, decreasing triglycerides and increasing high-density cholesterol.

Conclusion: SGLT-2 inhibitors significantly impact weight loss and fat reduction in type 2 diabetics, promising potential for disease alleviation. However, further research is needed to ensure safety and tolerability.

Keywords: Diabetes; SGLT-2 inhibitors; Body weight reduction; Lipid profile improvement

Introduction

Type 2 Diabetes Mellitus (T2DM) is a global health issue affecting millions, with its prevalence expected to increase further by 2045 [1]. It primarily affects adults, with the highest number of cases occurring between 40 and 59 [1-3]. T2DM is characterized by B-cell dysfunction and insulin resistance, leading to macrovascular and microvascular complications [4,5]. It is associated with obesity and dyslipidaemia and is at risk of developing cardiovascular disease [6]. Treatment has evolved from blood sugar control to a comprehensive approach that considers kidney disease, atherosclerosis, heart failure, cardiovascular disease, and other complications [7]. Oral Antihyperglycemic Drugs (OADs) have been used as first-line therapies, with seven classes available [8]. SGLT-2 inhibitors, the latest class, provide an insulin-independent anti-hyperglycaemic effect by suppressing glucose reabsorption in renal tubules, leading to its excretion in urine [9]. These drugs lower blood glucose levels, improve glycaemic control, and have omnidirectional effects on body weight, blood pressure, hyperuricemia, dyslipidaemia, and fatty liver disease [10]. The FDA has approved three drugs-

canagliflozin, dapagliflozin, and empagliflozin-for treating T2DM since 2012, with others in the US, EU, and Japan in advanced clinical development stages [11-13].

Accordingly, SGLT-2 inhibitors are a type of antidiabetic drug used to treat type 2 diabetes. They are known for their efficacy, safety, and tolerability, with a low risk of hypoglycaemia. They improve glycaemic control, have multiple effects on Body Weight, Blood Pressure, Hyperuricemia, Dyslipidaemia, and Fatty Liver Disease. They are used as a second or third-line treatment for type 2 diabetes, or as monotherapy when metformin is contraindicated or inadequate [14]. The prescription rate for SGLT-2 inhibitors increased from 3.8% to 11.9% between 2015 and 2019 [15]. They have positive effects on cardiovascular outcomes, renal function outcomes, lipid improvement, and weight loss [16,17]. However, the extent of these effects may vary between different SGLT-2 inhibitors [18,19]. SGLT-2 inhibitors prevent sodium and glucose reabsorption in the kidneys, improving glycaemic levels in diabetic patients and reducing cardiovascular and renal risk factors [20]. The majority of glucose uptake in the tubules occurs in the early proximal tubule, facilitated by SGLT2 [21]. Mutations in the SGLT1 and SGLT-2 genes significantly contribute to renal glucose reabsorption. Mutations in SGLT-2 cause persistent renal glucosuria, often ranging from 60 to 120g/day [22,23]. Despite its rarity and limited study, these findings support the development of SGLT-2 inhibitors as antidiabetic drugs. The expression of the Na+-D-glucose cotransporter SGLT-2 in rodents is specific to the kidney and accounts for approximately 97% of renal glucose reabsorption under normoglycemic conditions [24]. This study was conducted to identify the effect of two sodium inhibitors on weight and fat gain in patients with type 2 diabetes, noting their effectiveness in enhancing their effect on the heart and kidneys.

Methods

A study examining the effects of Dapagliflozin (DAPA) and Empagliflozin (EMPA) on type 2 diabetes patients in Libya was conducted from March to August 2022. The study involved 103 obese patients, with 69 receiving DAPA and 34 receiving EMPA treatments at DHI-Al HILAL Primary Health Care Center, Alzawia, Libya. The participants were categorized into four groups based on age and weight, with each group being followed over a three-month period. The participants were enrolled, with 69 receiving treatments with DAPA and 34 with EMPA. Each group of patients were followed over a three-month period. The distribution of participants was analyzed based on age and weight, creating four distinct groups.

Subgroup and sensitivity analysis

Subgroup and sensitivity analyses were performed to verify the stability of the results and to identify potential causes of heterogeneity, such as SGLT-2 inhibitors, treatment durations, and baseline characteristics.

Safety considerations

Adverse events associated with SGLT-2 inhibitors, such as genitourinary infections and diabetic ketoacidosis, were evaluated. The overall safety profile of SGLT-2 inhibitors was consistent with previous literature, and the observed benefits in weight reduction and lipid profile improvement outweighed the potential risks.

Data collection

Data were collected from the medical records database, including demographic data such as age, sex, and body weight. A cross-sectional, randomized, open-labelled trial, surveyed 103 obese Type 2 diabetes patients at DHI-Al HILAL Primary Health Care Centre in Libya, over a 3-month period.

Data analysis

Data was analyzed using the Analysis of Variance Technique and Duncan's Multiple Range Test, with significant differences determined by P≤0.05, using SPSS Version 22.

Result

Table 1: Showing the division of patient numbers into different categories for conducting the study before and after treatment with DAPA and EMPA.

Groups	Subgroups	No. of Patients	
Before DAPA	≥90Kg ≤50 Year	13	69
	≥90Kg >50	21	
	<90Kg ≤50	13	
	<90Kg >50	22	
After DAPA	≥90Kg ≤50 Year	12	69
	≥90Kg >50	12	
	<90Kg ≤50	14	
	<90Kg >50	31	
Before EMPA	≥90Kg ≤50 Year	6	34
	≥90Kg >50	9	
	<90Kg ≤50	4	
	<90Kg >50	15	
After EMPA	≥90Kg ≤50 Year	4	34
	≥90Kg >50	7	
	<90Kg ≤50	6	
	<90Kg >50	17	
Total		103	

This study involved 103 type 2 diabetes patients treated with DAPA and EMPA, two different SGLT-2 inhibitors, from March to August 2022. Table 1 shows that out of 103 participants, 69 were treated with DAPA and 34 used EMPAA for three months. Participants were categorized based on age (under and over 50) and weight (under and over 90kg). The study revealed that the use of SGLT-2 inhibitors DAPA and EMPA lead to slight weight loss in all groups (Table 2), particularly EMPA in patients initially weighing less than 90kg and under 50 years old (Figure 1 & 2). Whose reach 17% and more of weight reduction (Figure 3). Furthermore, SGLT-2 inhibitors demonstrated favourable effects on lipid profiles, including reductions in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, along with increases in high-density lipoprotein cholesterol levels ($p<0.05$ for all outcomes,

Table 3). SGLT-2 inhibitors decrease the total cholesterol levels in type 2 diabetes patients, typically within a 2-5% increase from baseline. They also increase High-Density Lipoprotein Cholesterol (HDL-C) levels, with an average increase of 2-5% from baseline. However, these inhibitors have a reducing effect on triglyceride levels, with an average increase of 3-6% from baseline (Table 4).

Table 2: Shows the effects of diabetic medication with SGLT-2 inhibitors, DAPA on patients of varying weight and ages before and after treatment. The data is presented as means of three replicates ±standard deviation, with significant differences observed within columns with different letters a, b, c and d (P<0.05, P<0.01 and P<0.001). Abbreviations: LDL: Low Density Lipoproteins, HDL: High Density Lipoproteins, TGs: Triglycerides, Total Ch: Total Cholesterol, FBS: Fasting Blood Sugar, HbA1c: Cumulative Sugar Test.

Groups	Weight	LDL	HDL	TGs	Total Ch	FBS	HbA1c
Before DAPA Treatment							
≥90Kg ≤50 Year	107.46^{b}	139.59^{cd}	44.69^{abcd}	161.77^{abc}	183.15^{abcd}	230.88^{bcd}	9.62^{cde}
	±9.83	±71.33	±26.47	±55.47	±57.66	±73.71	±2.22
≥90Kg >50	102.67^{b}	115.66^{abc}	47.26^{abcd}	179.49^{abc}	197.32^{bcd}	237.43^{cd}	9.44^{cde}
	±15.81	±55.45	±36.03	±74.90	±81.69	±73.27	±2.18
<90Kg ≤50	77.00^{a}	122.30^{abc}	41.56^{abcd}	211.30^{c}	220.54^{d}	334.23^{e}	11.19^{e}
	±7.56	±49.80	±26.36	±101.21	±79.06	±87.02	±2.54
<90Kg >50	73.27^{a}	116.95^{abc}	48.13^{abcd}	186.31^{abc}	198.38^{bcd}	236.05^{cd}	10.08^{de}
	±8.49	±63.57	±36.19	±85.90	±55.50	±74.23	±2.10
After DAPA Treatment							
≥90Kg ≤50 Year	97.50^{b}	99.60^{abc}	55.58^{abcd}	151.36^{abc}	138.92^{abc}	147.27^{a}	7.20^{a}
	±7.98	±34.29	±17.03	±72.03	±41.75	±17.53	±1.26
≥90Kg >50	102.58^{b}	83.12^{ab}	64.38^{cd}	122.44^{a}	138.08^{abc}	148.50^{a}	7.96^{abc}
	±15.11	±27.61	±23.72	±55.75	±53.49	±28.83	±1.71
<90Kg ≤50	77.57^{a}	87.09^{ab}	68.57^{d}	133.21^{ab}	143.50^{abc}	121.43^{a}	7.88^{abc}
	±8.86	±32.87	±26.60	±48.09	±32.24	±27.07	±1.74
<90Kg >50	74.32^{a}	86.94^{ab}	63.81^{cd}	121.92^{a}	136.70^{ab}	132.86^{a}	7.02^{a}
	±10.77	±42.22	±21.66	±45.88	±47.12	±32.87	±0.89

Table 3: Shows the effects of diabetic medication with SGLT-2 inhibitors, EMPA on patients of varying weight and ages before and after treatment: The data is presented as means of three replicates ±standard deviation, with significant differences observed within columns with different letters a, b, c and d (P<0.05, P<0.01 and P<0.001). Abbreviations: LDL: Low Density Lipoproteins, HDL: High Density Lipoproteins, TGs: Triglycerides, Total Ch: Total Cholesterol, FBS: Fasting Blood Sugar, HbA1c: Cumulative Sugar Test.

Groups	Weight	LDL	HDL	TGs	Total Ch	FBS	HBA1C
Before EMPA Treatment							
Patients ≥90Kg ≤50 Year	103.33^{b}	98.67^{abc}	30.83^{ab}	187.83^{abc}	178.83^{abcd}	258.95^{d}	10.38^{de}
	±6.56	±52.47	±12.95	±16.76	±43.47	±86.02	±2.63
≥90KG>50	106.89^{b}	175.00^{d}	27.44^{a}	288.56^{d}	291.89^{e}	330.33^{e}	10.87^{de}
	±9.25	±29.85	±7.60	±116.47	±97.44	±99.93	±2.48
<90KG ≤50	80.25^{a}	131.25^{bcd}	43.25^{abcd}	207.00^{bc}	201.75^{cd}	258.25^{d}	9.20^{bcd}
	±3.59	±52.11	±33.63	±74.17	±74.55	±114.10	±1.86
<90kg >50	78.33^{a}	128.31^{bc}	36.83^{abc}	174.88^{abc}	200.27^{bcd}	260.07^{d}	9.95^{de}
	±9.48	±43.18	±12.61	±67.58	±65.79	±99.18	±1.84
After EMPA Treatment							
Patients ≥90Kg ≤50 Year	98.75^{b}	98.78^{abc}	63.50^{cd}	134.00^{ab}	147.00^{abc}	124.75^{a}	6.23^{a}
	±9.57	±42.73	±18.70	±48.83	±51.56	±32.88	±0.21
≥90Kg >50	102.86^{b}	99.57^{abc}	58.00^{bcd}	130.10^{a}	155.14^{abc}	185.14^{abc}	7.11^{a}
	±11.45	±36.72	±13.04	±50.55	±38.76	±79.21	±1.27
<90Kg ≤50	71.33^{a}	76.37^{a}	60.83^{cd}	149.17^{abc}	128.25^{a}	163.32^{ab}	7.98^{abc}
	±9.91	±28.38	±24.76	±45.51	±25.31	±61.02	±1.42
<90Kg >50	74.82^{a}	92.58^{abc}	70.12^{d}	151.04^{abc}	142.92^{abc}	171.70^{abc}	7.41^{ab}
	±9.49	±28.76	±34.39	±57.59	±38.05	±97.65	±1.68

Table 4: Displays the percentage of inhibition by DAPA and EMPA post-treatment in patients of varying weight and ages.

Groups	HDL improvement	HDL improvement %	TGs inhibition	TGs
DAPA Treatment				
≥90Kg≤50 Year	19.68	94.53	-28.73	-11.42
	±18.08	±113.56	±59.39	±20.55
≥90Kg >50 Year	12.33	73.8	-74.08	-32.93
	±34.90	±87.42	±64.51	±24.20
<90Kg ≤50	19.26	96.01	-58.85	-29.64
	±33.92	±172.98	±31.88	±12.09
<90 Kg> 50	17.78	83.95	-55.81	-25.85
	±24.18	±120.82	±64.03	±22.35
EMPA Treatment				
≥90Kg ≤50	31.25	166.57	-58.5	-29.08
	±25.93	±206.46	±51.54	±24.53
≥90Kg >50	31.29	124.17	-169.9	-52.74
	±6.58	±34.87	±131.55	±17.55
<90Kg ≤50	22.67	97.92	-48.33	-24.59
	±9.64	±81.90	±29.13	±12.11
<90Kg >50	34.09	95.54	-32.51	-11.79
	±26.22	±55.80	±41.08	±44.55

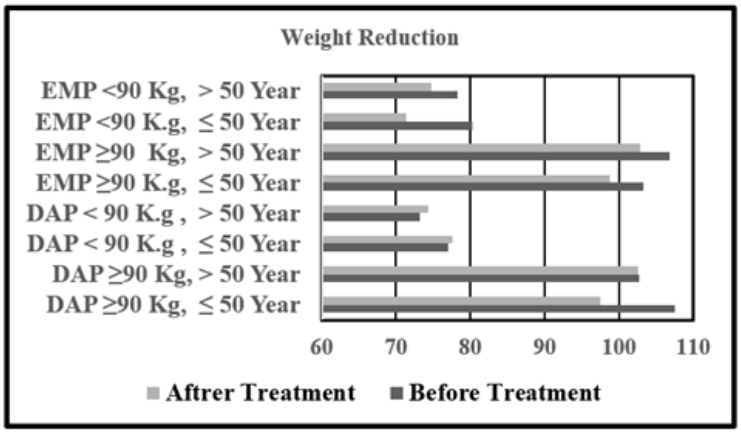

Figure 1: Shows the weight-lowering effect of both SGLT-2 inhibitors DAPA and EMPA in diabetic patients of different weight and ages.

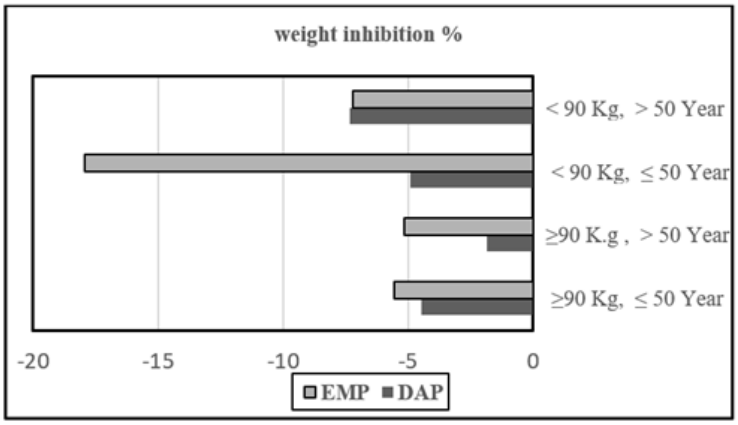

Figure 2: Shows the weight inhibition percentages following treatment with DAPA and EMPA in patients of varying weight and ages.

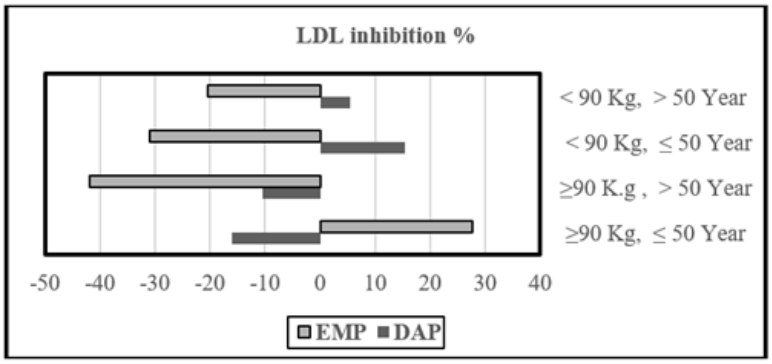

Figure 3: The percentage of LDL inhibition in patients of varying weight and ages after treatment with DAPA and EMPA.

Discussion

Sodium Glucose Cotransporter 2 (SGLT2) inhibitors are medications used to treat hyperglycaemia in type 2 diabetes. SGLT2 is expressed in the renal proximal tubules. Inhibition of SGLT2 reduces the reabsorption of filtered glucose, decreases the Renal Threshold for Glucose (RTG), and increases urinary glucose excretion. These effects improve blood glucose control and are independent of insulin [25,26]. The US Food and Drug Administration (FDA) has approved four types of SGLT2 inhibitors to treat type 2 diabetes in adults [27]. Invokana improves blood sugar management and reduces the risk of serious cardiovascular complications, kidney disease, cardiovascular death, and hospitalization for heart failure [16]. Farxiga improves blood sugar management, reduces the risk of hospitalization for heart failure, and slows the progression of kidney disease. Jardiance improves blood sugar management and reduces the risk of cardiovascular death in adults with diabetes and cardiovascular disease [28,29]. Steglatro improves blood sugar management in adults with type 2 diabetes. These medications are indicated for both type 2 diabetes and heart failure [30]. SGLT2 inhibitors improve insulin sensitivity and glucose utilization resulting in additional benefits to cardiovascular health through blood pressure monitoring and heart-healthy practices. Weight loss can enhance the effectiveness of SGLT2 inhibitors on the heart and kidneys, as SGLT2 inhibitors increase the excretion of glucose in the urine [31].

Clinically, SGLT2 inhibitors are not usually the initial treatment for most patients with type 2 diabetes. Initial treatment usually includes diet, weight reduction, exercise, and metformin (unless contraindicated). SGLT2 inhibitors are considered when other methods are insufficient [32]. Therefore, losing weight can enhance the effectiveness of SGLT2 inhibitors and can help better manage blood glucose levels. In this study, two types of inhibitors were chosen, DAPA (Farxiga) and EMPA (Jardiance), a three-month follow-up was conducted on a number of type 2 diabetes patients of different ages and weights for the purpose of comprehensiveness of the research and its impact on weight and fat. The results of this research indicated that the use of SGLT-2 inhibitors led to a significant reduction in body weight and improvement of lipid levels in patients with type 2 diabetes in varying proportions for different ages and weights. Noting the highest decrease in weights less than 90-100 kilograms of body weight. The rate of weight loss was equal to or greater than 17%. These notable benefits are believed to contribute to an overall reduction in cardiovascular risk. Associated with the use of SGLT-2 inhibitors. The underlying mechanisms of these effects include an increase in urinary glucose excretion, a decrease in energy expenditure, and regulation of adipokine and lipoprotein metabolism. Recent studies have suggested that an SGLT2 inhibitor could be an effective weight loss treatment in patients with obesity without diabetes [33], but they have not clarified its exact mechanism of action. The existing meta-analyses or systematic reviews that have pooled data from multiple studies examining the effects of SGLT-2 inhibitors on weight loss and lipid profiles in type 2 diabetes provide a strong overview of the overall evidence [34]. While DAPA is not directly related to weight reduction, it provides insight into the effects on various metabolic parameters. Consistency, previous study discussed the effect of canagliflozin, another medication in the same class as DAPA, on serum uric acid levels in patients with type 2 diabetes mellitus [35].

But what all previous and recent research has found so far is that SGLT2 inhibitors help manage glucose levels in blood in general through the following mechanisms: Increased urinary glucose excretion by reducing glucose reabsorption in the kidney, leading to increased urinary glucose excretion. This lowers blood glucose levels. SGLT2 inhibitors promote weight loss by increasing urinary excretion of glucose and calories. This weight loss can enhance their effectiveness in improving cardiovascular health, reducing strain on the heart, and improving insulin sensitivity [36-38]. Unlike some other diabetes medications, SGLT2 inhibitors work independently of insulin. They enhance glucose control without relying on insulin production or sensitivity [38].

SGLT2 inhibitors have also shown additional benefits for heart health, reducing the risk of cardiovascular disease in people with diabetes [39]. The mechanism of action of these inhibitors is still not sufficiently known in terms of weight loss and improving blood lipids, which in turn leads to increasing the efficiency of these inhibitors and the extent to which diabetics and heart patients benefit from them. Overall, weight loss associated with SGLT2 inhibitors can positively impact cardiovascular risk factors in several ways [40]:

a. Reduced insulin resistance: Weight loss improves insulin sensitivity, making it easier for cells to utilize glucose effectively. This can lead to better blood sugar control [41].

b. Lower blood pressure: Excess weight is often linked to hypertension. By shedding pounds, blood pressure tends to decrease, reducing strain on the heart and blood vessels [42,43].

c. Improved lipid profile: Weight loss can positively affect lipid levels (such as cholesterol and triglycerides), which are crucial for heart health [44].

d. Decreased inflammation: Adipose tissue (fat) produces inflammatory molecules. Losing weight reduces overall inflammation, benefiting the cardiovascular system. These are consistent with previous studies that noted the role of treatment in weight loss [44,45]. The long-term effects of SGLT-2 inhibitor therapy in type 2 diabetes may depend on Sirtuin 1 activation versus inhibition [46]. SGLT-2 is a Sirtuin 1 activator critical to obesity, diabetes, and cardiovascular disease treatment [46,47]. SGLT2 inhibitors induce a fasting-like model, leading to nutrient deprivation pathways that promote cellular homeostasis, alleviating oxidative stress and promoting autophagy. Understanding Sirtuin 1 activation mechanisms could improve metabolic health and combat related disorders [48-50].

Conclusion

SGLT-2 inhibitors demonstrate efficacy in reducing body weight and improving lipid profiles in patients with type 2 diabetes. These findings highlight the potential role of SGLT-2 inhibitors as an innovative therapeutic option for managing type 2 diabetes, particularly in patients with obesity and dyslipidaemia. The role of Sirtuin 1 inhibitors is important to the use of SGLT-2 inhibitor therapy. Research is ongoing to explore how these pathways intersect and whether co-administration could enhance therapeutic outcomes. Thus, further research is warranted to elucidate the long-term effects, optimal treatment duration, and potential cardiovascular benefits associated with SGLT-2 inhibitor therapy.

Implications of the Result

These findings suggest that both DAPA and EMPA contribute to weight reduction in patients with type 2 diabetes, particularly those weighing less than 90kg. However, the nuanced differences observed may warrant further investigation into the underlying mechanisms of weight management associated with each SGLT2 inhibitor.

Suggestions for Future Research

Future research could explore the long-term impact of DAPA and EMPA on weight management, potentially extending the duration of treatment and monitoring patients over an extended period. A larger sample size for EMPA users would provide more robust insights into the effects of this particular SGLT2 inhibitor.

Limitations

The relatively short duration of the intervention (three months) may limit our ability to assess the long-term effects of DAPA and EMPA. Additionally, the small sample size for EMPA users necessitates cautious interpretation of the results specific to this group.

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