Dapagliflozine can Induce and Maintain Type-2 Diabetes Remission

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ABSTRACT

Introduction: Type 2 diabetes mellitus, has gained a lot of attention in recent years as one of the most important chronic progressive diseases in the world, which slowly crawls towards longevity and which involves many chronic complications, which are dangerous to health and the economy. Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a category of newly discovered drugs that work by preventing glucose reabsorption in the proximal renal tubules. (SGLT2) inhibitors may induce type 2 diabetes remission.

Design: Randomized, -controlled trial, 6-month trial.

Materials and Methods: 100 type 2 diabetes patients were randomized into 2 groups.

Results: The results show a statistically significant decrease of A1C levels after 3 and 6 months treatment with dapagliflozin and significant change in A1C levels after 3 months treatment of glimepiride but a no significant change in the next 3 months. The results also show a statistically significant decrease in BMI in the dapagliflozin group after 6 months of treatment.

Conclusion: As type 2 diabetes is one of the most disabling diseases, it is necessary to find a drug that can lead to remission. Dapagliflozin can lead to type 2 diabetes remission.

Keywords: Type 2 diabetes; Remission; Dapagliflozin

INTRODUCTION

Type 2 diabetes mellitus, has gained a lot of attention in recent years as one of the most important chronic progressive diseases in the world [1], which slowly crawls towards longevity and which involves many chronic complications, which are dangerous to health and the economy [2], and which requires constant Long life treatment with hypoglycemic medications that control blood glucose level [3].

Many patients can control the level of blood glucose only by using a low-energy or low-carb diet and exercise [4]. It is surprising to know that the process of disease development of type 2 diabetes results from many causes and ways, and not one cause. It leads to many clinical forms in different patients [5]. It is known that the occurrence of type2 diabetes is closely related to the unremitting increase in weight [6], and the presence of fat cells ectopically in

the pancreas and the liver, which affects the work of beta cells in the pancreas and affects insulin processing and secretion and the sensitivity of the hepatic cells to insulin leading to inappropriate gluconeogenesis [7].

The end result of type2 diabetes precipitating factors is the occurrence of pancreatic beta cells weakness with resistance to insulin action in the liver, muscles, and fat cells [8]. Maintaining the function of the beta cells and the insulin signal in the beta cells and in the tissue processing glucose will maintain the glucose balance and is the target of type 2 diabetes therapy [9]. One of the distinguishing signs of the pathogenesis of type 2 diabetes is that exposure to a high level of glucose for long and chronic periods leads to the appearance of inflammatory markers, as well as a defect in the process of genes expressions [10], leading to beta cells failure and defect in the insulin secretion as a result of the destruction of cell organelles such as Mitochondria and endoplasmic reticulum [11].

Obesity is one of the causes of chronic inflammation of a low grade, and thus the fat cells are a source of inflammation in the body and an important source of inflammatory markers [12]. And so obesity is considered to be a cause of type 2 diabetes by reducing response to insulin in the peripheral tissues, which in turn leads to a burden on beta cells, which leads to their weakness and consequently a failure [13].

At the beginning of type 2 diabetes occurrence, the diet system may lead to controlling the level of blood glucose without the need to use hypoglycemic drugs, but as time passes, most patients with type 2 diabetes need to use hypoglycemic drugs to control the blood glucose level [14], but it is important to note that most patients cannot Continue on a specific diet system [15].

The process of diabetes remission was defined by American diabetes association as achieving a level of blood glucose below the distinct level of diabetes diagnosis without using hypoglycemic medications [16].

This is divided into 3 types

- The first is called partial remission;

In it, the level of glycated hemoglobin is below the distinct level of diabetes diagnosis which isA1C (5.7–6.4%), and the fasting blood glucose level is below the distinct level of diabetes diagnosis, which is100–125 mg/dl for a whole year.

- The second type is called complete remission

In it, the level of fasting blood glucose is below 100 mg/dl and glycated hemoglobin is below 5.7% for a year.

- The third type is permanent remission

In it, the level of glycated and fasting blood glucose is below the level of diabetes diagnosis, for 5 years, and here it is called cure of diabetes [17].

It has been observed that type 2 diabetes remission may occur after bariatric surgery and also by using a low-carb or low-energy diet system intensively [18]. This includes not only controlling blood glucose levels without the use of hypoglycemic medications but also includes reconstructing the functional pancreatic beta cells capacity and regaining insulin sensitivity in the liver [19].

And with this, it can be recognized that the process of type2 diabetes remission after bariatric surgery occurs through one of two ways or through both [20]. The first is to improve the number and functions of beta cells in the pancreas. This usually occurs in patients at a young age. The second way occurs through decreasing insulin resistance in the liver and peripheral cells in which, obesity is present before the surgery [21].

The level of c-peptide levels before the surgery is considered an important factor in the occurrence of type 2 diabetes remission, meaning that if the level of c-peptide before the surgery is more than 2, then type 2 diabetes remissions is easier [22].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors represent a category of newly discovered drugs that work by preventing glucose reabsorption in the proximal renal tubules in the kidneys and several studies have proven their ability to reduce the level of glycated hemoglobin and weight [23].

Hence, this class of drugs leads to a decrease in the blood glucose in a way that is not dependent on insulin, but rather by increasing the excretion of glucose in the urine by preventing its absorption by the kidneys [24]. This leads to a decrease in the level of fasting blood glucose and the level of glucose in the blood after meals and also leads to decrease weight by increasing energy consumption [25].

Some studies have shown that SGLT2 inhibitors play an important role in reducing the risk of cardiovascular disease and reducing blood pressure [26].

MATERIALS AND METHODS

A total of 100 patients with Type 2 diabetes patients were randomized into 2 parallel groups, they have not been controlled on metformin 2 gm per day, had been monitored in a private clinic, number 50 each group, with 35 females and 15 males after the written consent of all patients.

All the patients Lied between 35-50 years old with 5-15 years of diabetes onset.

The first group recieved dapagliflozin 10mg orally per day for 6 months after stopping metformin therapy.

The second group recieved glimepiride 3 mg orally for 6 months after stopping metformin.

In the first group; the investigator measured A1C levels before and after 3 and 6 months of dapagliflozin 10mg daily and also measured BMI at the start and after 6 months.

In the second group, the investigator measured A1C levels at the beginning of the trial and after 3 and 6 months and also measured BMI at the start and after 6 months.

After the first 6 months, the investigator was still following dapagliflozine group who were still on treatment for another 6 months, at the end of the year the investigator measured A1C comparing with A1C measured at 6 months.

All chosen patients had c peptide levels above 2ng/mL.

All patients selected had a body mass index between 24 and 36.

RESULTS

For the analysis of data, the investigator used unpaired t-test using GraphPad Prism 8.0.2.

The results data exhibited a statistically significant decrease of A1C levels after 3 months of treatment with dapagliflozin as shown in Tables 1,2 and Figures 1,2 with p-value ＜0.0001 with A1C mean 6.755 after treatment with dapagliflozin compared to A1C mean 7.734 before treatment.

Group A			Group B		
A1(BASAL)	A1C(3M)	A1C(6M)	A1(BASAL)	A1C(3M)	A1C(6M)
7	6	5.6	7	6.3	6.3
7.2	6.5	5.5	7.2	6.4	6.5
7.3	6.7	5.6	7.3	6	6.2
7.5	6.8	5.7	7.6	6.5	6.4

7.6	6.7	5.4	7.6	6.7	6.6
7.7	6.6	5.4	7.7	6.8	6.7
7.4	6.5	5.6	7.4	6.7	6.8
7.9	6.6	5.7	7.9	66	6.9
8	6.8	5.7	8	6.5	6.4
8.1	7	5.5	8.2	6.9	6.8
8.2	7.2	5.6	8.2	6.8	6.9
8.3	6.8	6.7	8.3	7.3	7.4
8.4	7	6.3	8.4	7.2	7.3
8.5	7.1	6.3	8.5	6.8	6.9
7	6	5.5	7.2	7	7.1
7	6.2	5.6	7	7.1	7.1
7.1	6.2	5.7	7.1	6	61
7.2	6.4	5.8	7.2	6.2	63
7.3	6.4	5.9	7.4	6.2	6.1
7.4	6.5	5.7	7.4	6.5	6.4
7.5	6.7	5.8	7.6	6.3	6.2
7.6	6.9	5.9	7.6	6.7	6.7
7.7	6.8	5.8	7.7	6.7	6.7
7.7	6.9	5.9	7.8	6.9	6.9
7.9	6.5	5.7	7.8	6.8	6.8
7.9	6.6	5.9	7.9	6.9	6.9
8	7	5.7	8	6.5	6.4
8	6.9	5.7	8	6.6	6.7
8	7	6	8	7	7.2
8.1	7.1	5.8	8.1	6.9	7.8
8.2	7.3	6	8.2	7.3	7.2
8.2	7.1	5.9	8.2	7.6	7.5
8.5	7.3	6.1	8.5	7.3	7.3
8.4	7	6.2	8.4	7.4	6.2
8.4	7.4	6.3	8.4	7.3	6.3
7	6	5.7	7	6	6.6
7	6	5.6	7	6.4	6.1
7.1	6.2	5.5	7.1	6.7	6.3
7.1	6.3	5.7	7.1	6	6.1
7.4	6.8	5.6	7.4	6.2	6.3
7.4	6.3	5.7	7.4	6.3	6.3
7.5	6.5	5.5	7.5	6.8	6.9
7.5	6.8	5.9	7.5	6.3	6.2
7.7	6.9	6	7.7	6.7	6.3
7.8	6.9	5.9	7.8	6.8	6.9
8	7.1	5.6	8	6.9	6.8
8	7.3	6.3	8	6.9	6.7
8.2	7.46	6.4	8.2	7.6	7.5

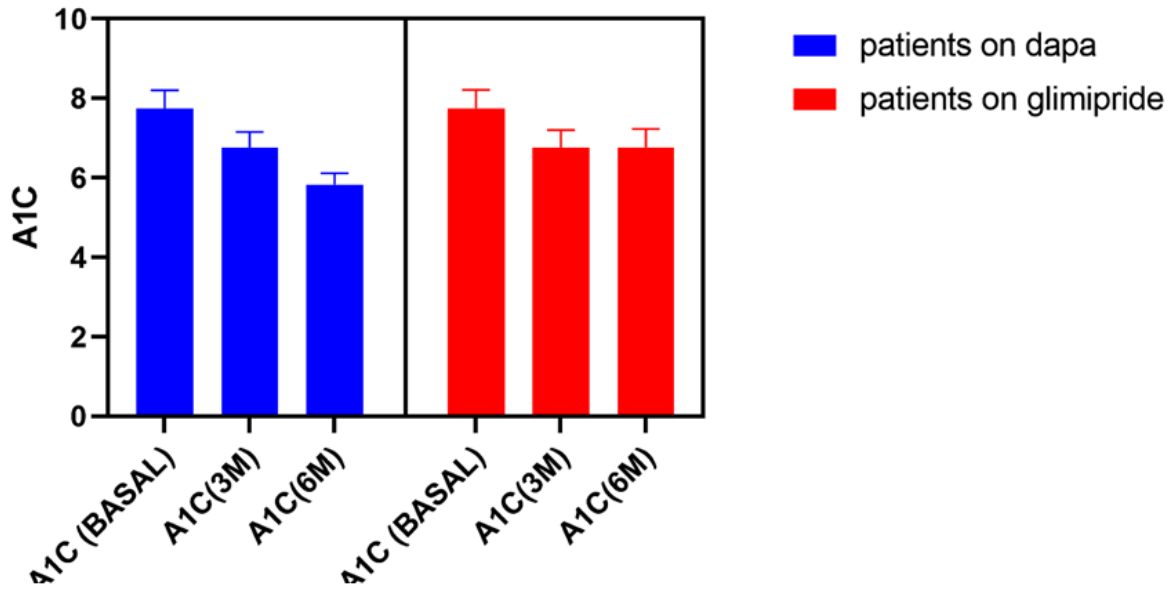| 8.3	7.4	6.3	8.3	7.7	7.8

Table1: All Patients data

Figure 1: All Patients data.

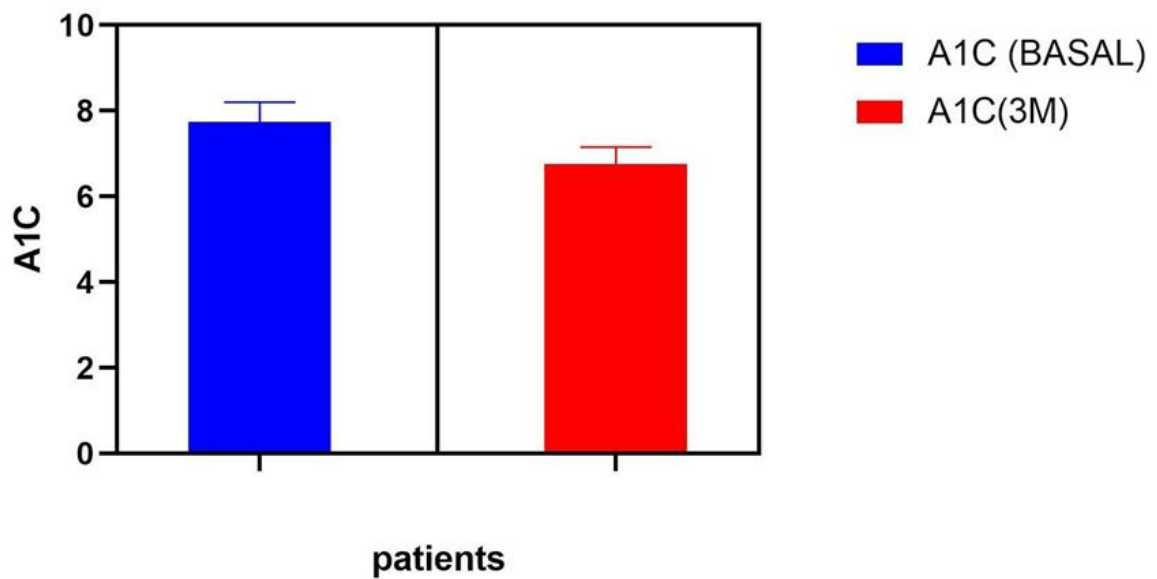**Figure 2:** Showing significantly decreased A1C levels in the dapagliflozin group after 3months of treatment.

Unpaired t test	
Column B	patient on dapa after 3month
vs	vs
Column A	patient on dapa at start
Unpaired t test	
P Value	<0.0001
P Value Summary	****
Significantly different	yes

(P<0.05)?	
one or two tailed P value ?	two tailed
t,df	t=11.7,df=98
How big is the difference ?	
Mean of column A	7.734
Mean of column B	6.755
Difference between means (B-A)± SEM	-0.9788±0.08764
95% Confidence interval	-1.153 to -0.8049
R squared (eta squared)	0.56
F test to compare variances	
F,DFn,Dfd	1.386,49,49
P value	0.2563
P value Summary	ns

Table 2: showing significantly decreased A1C levels in the dapagliflozin group after 3months of treatment

When comparing A1C at 3 months and at 6 months of dapagliflozin, the results data exhibited a statistically significant decrease of A1C levels at 6 months of dapagliflozine compared to at 3 months of treatment as exhibited in Tables 1, 3 and Figures 1,3 with p-value ＜0.0001 with A1C mean 5.826 after 6 months treatment with dapagliflozin compared to A1C mean 6.755 at 3 months treatment.

Unpaired t test	
Column B	dapa 6m
vs	vs
Column A	dapa 3m
Unpaired t test	
P Value	<0.0001
P Value Summary	****
Significantly different (P<0.05)?	yes
one or two tailed P value ?	two tailed
t,df	t=13.28,df=98
How big is the difference ?	
Mean of column A	6.755
Mean of column B	5.826
Difference between means (B-A)± SEM	-0.9292±0.06999
95% Confidence interval	-1.068 to -0.7903
R squared (eta squared)	0.6427
F test to compare variances	
F,DFn,Dfd	1.916,49,49
P value	0.0248
P value Summary	*

Table 3: showing significant improvement in A1C levels from3 to 6 months of dapagliflozine treatment
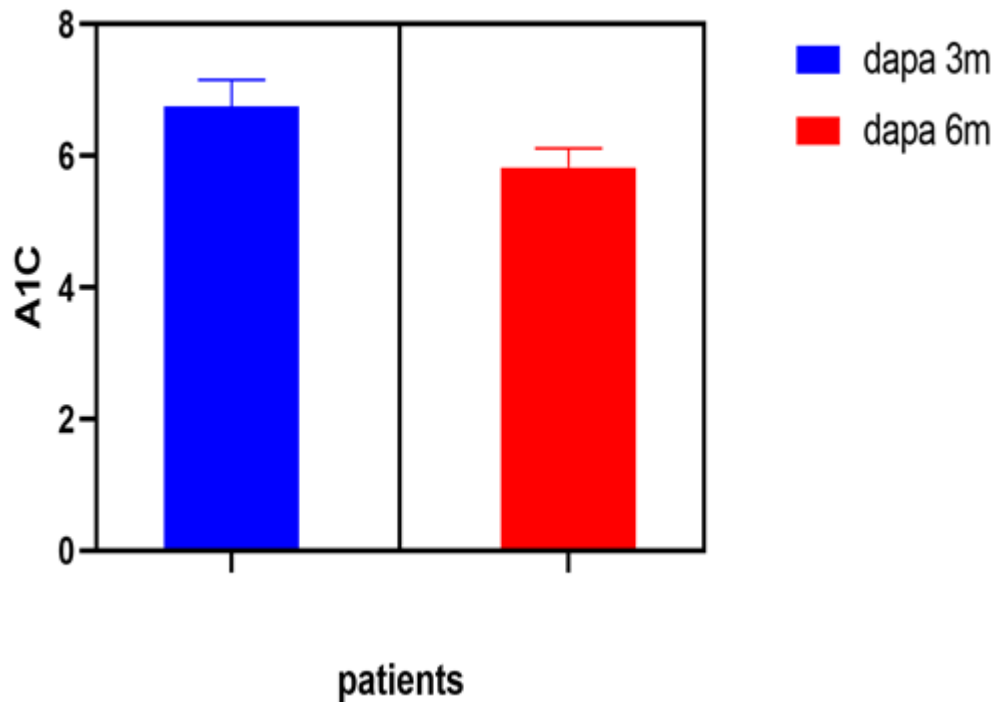

Figure 3: Showing significant improvement in A1C in dapagliflozine group from 3 to 6 months.

The results data exhibited a statistically significant decrease in A1C levels after 3 months treatment of glimepiride as shown in Tables 1,4 and Figures 1,4 with p-value ＜0.0001 with A1C mean 6.754 after glimepride compared to A1C mean 7.746 before treatment.

Unpaired t test	
Column B	Patients on glimipride 3m
vs	vs
Column A	Patients on glimipride basal
Unpaired t test	
P Value	<0.0001
P Value Summary	****
Significantly different (P<0.05)?	yes
one or two tailed P value ?	two tailed
t,df	t=10.82,df=98
How big is the difference ?	
Mean of column A	7.746
Mean of column B	6.754
Difference between means (B-A)± SEM	-0.9920±0.09167

95% Confidence interval	-1.174 to -0.8101
R squared (eta squared)	0.5444
F test to compare variances	
F,DFn,Dfd	1.058,49,49
P value	0.8444
P value Summary	ns
Significantly different (P<0.05)	No

Table 4: showing significant improvement in A1C after 3 months of glimepiride
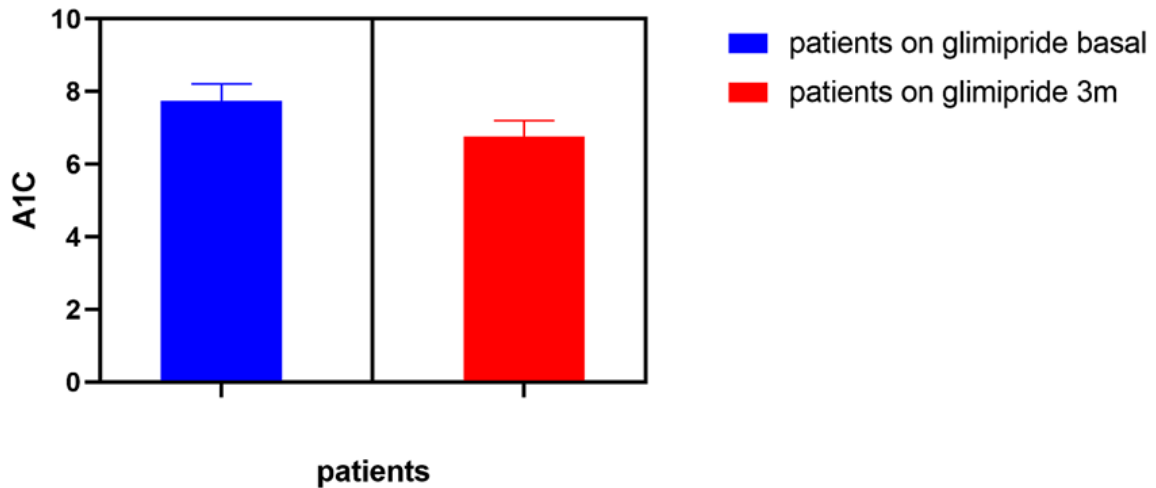
The results data exhibited no significant change in the next 3 months of glimepride treatment with p-value 0.9134 as shown in Tables 1,5 and Figures 1,5 with A1C mean 6.764 after 6 months of glimepride treatment compared to A1C mean 6.754 after 3 months of treatment.

Un paired test	
Column B	pats on glimipride 6m
vs	vs
Column A	pts on glimipride 3 m
Unpaired test	
P value	0.9143
P value summary	ns
Significantly different (P<0.050?	No
One-or two-tailed P value	Two tailed
t,df	t=0.1091,df=98
How big is the difference	
Mean of Column A	6.754
Mean of Column B	6.764
Difference between means (B-A)+0.09169	0.01000±0.09169
95% Confidence Interval	-0.1720 to 0.1920

R squared (eta squared)	0.000121
F test to compare variances	
F,DFn,Dfd	1.059,49,49
P value	0.8416
P value summary	ns

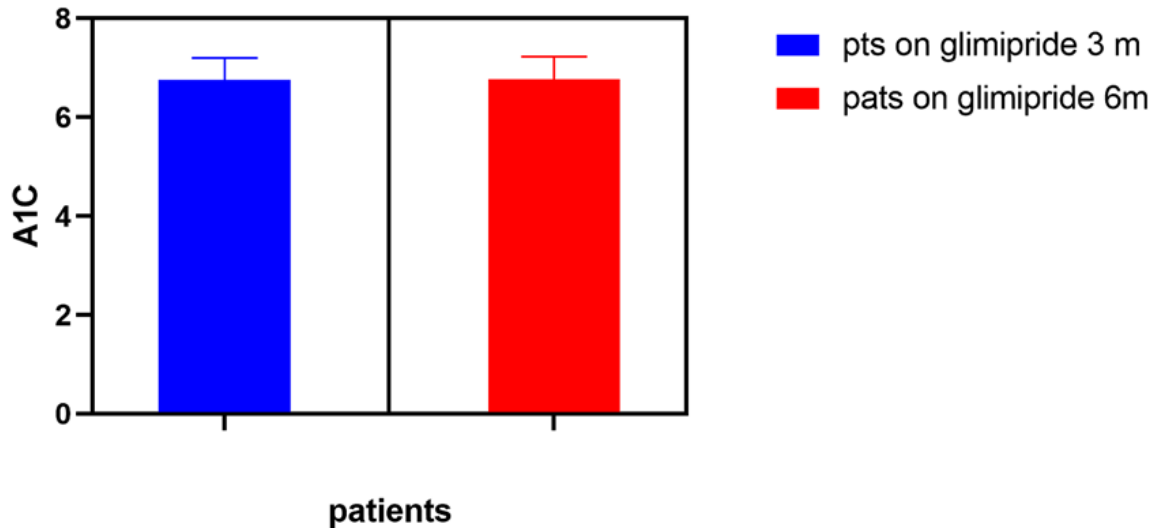Table 5: Showing non-significant change of A1C in the last 3 months

Figure 5: Showing non-significant change of A1C in the last 3 months.

The results data also exhibited a statistically significant decrease in BMI in the dapagliflozin group after 6 months of treatment with a p-value $<$ 0.0001 as shown in Table 6 and Figure 6, with BMI mean 27.2 after 6 months of dapagliflozin treatment compared to mean BMI 34.6 before treatment.

Un paired test	
Column B	pats on glimipride 6m
vs	vs
Column A	pts on glimipride 3 m
Unpaired test	
P value	0.9143
P value summary	ns
Significantly different (P<0.050?	No
One-or two-tailed P value	Two tailed
t,df	t=0.1091,df=98
How big is the difference	
Mean of Column A	6.754
Mean of Column B	6.764
Difference between means (B-A)+0.09169	0.01000±0.09169
95% Confidence Interval	-0.1720 to 0.1920

R squared (eta squared)	0.000121
F test to compare variances	
F,DFn,Dfd	1.059,49,49
P value	0.8416
P value summary	ns

Table 6: showing a significant decrease of BMI after 6 months of dapa
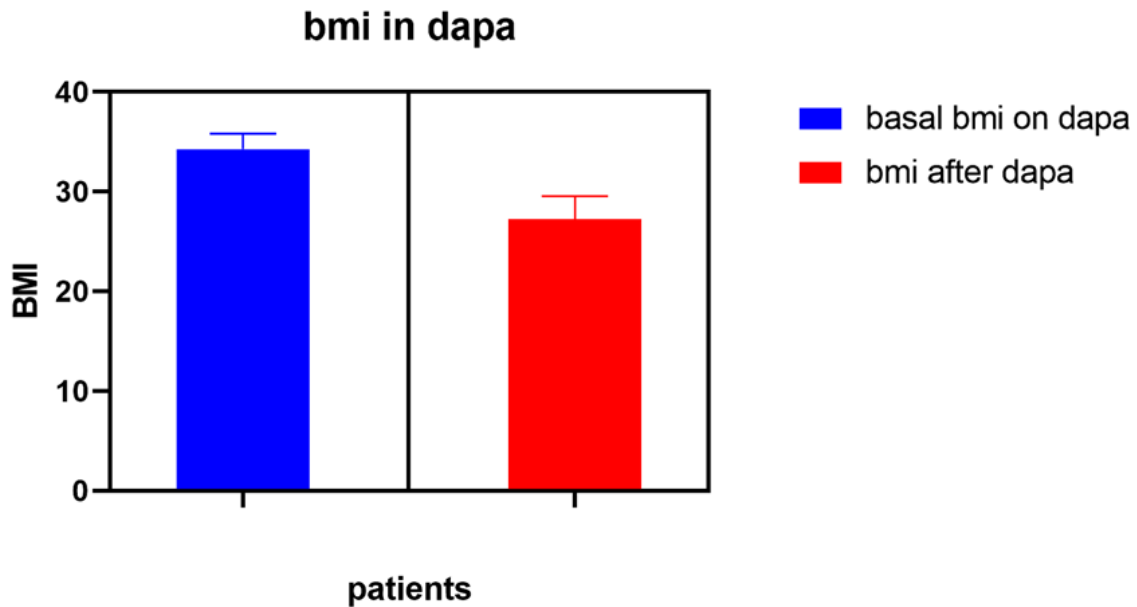

Figure 6: showing a significant decrease of BMI after 6 months of dapa.

Non-significant change in BMI in the glimepiride group with p-value 0.1333 as shown in Table 7 and Figure 7 with BMI mean 34 after 6 months of glimepride treatment compared to BMI 33.22 before treatment.

Un paired test	
Column B	bmi after dapa
vs	vs
Column A	basal bmi on dapa
Unpaired test	
P value	<0.0001
P value summary	****
Significantly different (P<0.050?	yes
One-or two-tailed P value	Two tailed
t,df	t=17.66,df=98
How big is the difference	
Mean of Column A	34.26
Mean of Column B	27.2
Difference between means (B-A)	-7.060±0.3998
95% Confidence Interval	-7.853 to -6.267
R squared (eta squared)	0.7609

F test to compare variances	
F,DFn,Dfd	2.330,49,49
P value	0.0037
P value summary	**

Table 7: showing a non-significant change in BMI after 6months treatment of glimepiride
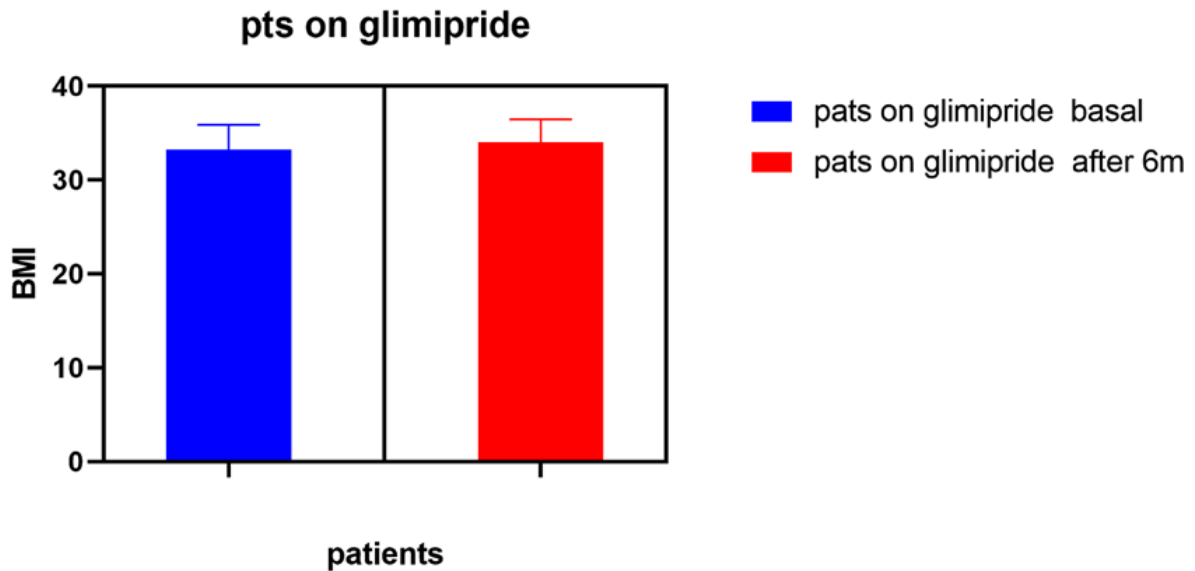

Figure 7: Showing a non-significant change in BMI after 6 months of treatment of glimepiride.

Results data also exhibited that A1C levels were still decreasing after another 6 months (at the end of the year) with a p-value< 0.0001 as shown in Table 8 and Figure 8 with A1C mean 5.310 after 1 year of dapagliflozin treatment compared to A1C mean 5.826 after 6 months of treatment .

Un paired test	
Column B	pats on glimpse after 6m
vs	vs
Column A	pats on glimipride basal
Unpaired test	
P value	0.13333
P value summary	ns
Significantly different (P<0.050?	No
One-or two-tailed P value	Two tailed
t,df	t=1.514,df=98
How big is the difference	
Mean of Column A	33.22
Mean of Column B	34.00
Difference between means (B-A)	0.7800± 0.5153
95% Confidence Interval	-0.2426 to 1.803

R squared (eta squared)	0.02285
F test to compare variances	
F,DFn,Dfd	1.126,49,49
P value	0.6793
P value summary	ns

Table 8: showing significant decrease in a1c after 1 year of dapagliflozine compared to a1c measured at 6 months
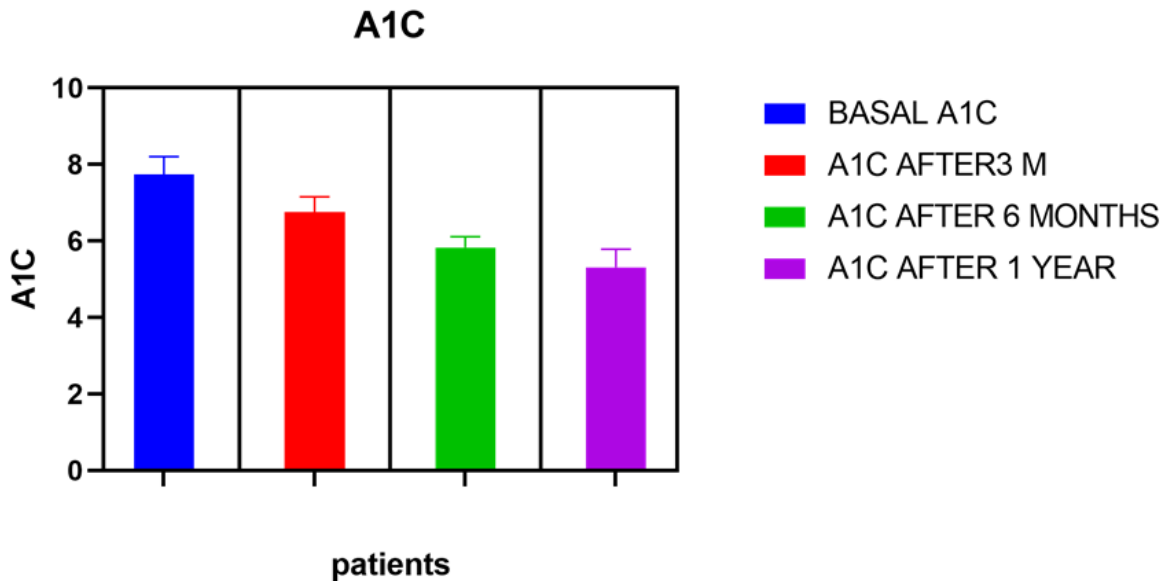

Figure 8: Showing significant decrease in a1c after 1 year of dapagliflozine compared toA1C measured at 6 months.

Dapagliflozin decreases A1C to the level below 6.4% in 6 months (with a mean A1C of 5.826) which is considered as the limit of partial diabetes remission. And below 5.7% at the end of one year (with mean A1C of 5.310) which is considered as the limit of complete diabetes remission.

DISCUSSION

Type 2 diabetes is one of the most common chronic diseases that irritate humans as patients and physicians because of its complications, which affect patients greatly, as it affects the eyes, kidneys, and nerves, as well as the cardiovascular system [27].

The main target of treating type 2 diabetes is to stop it, which is called diabetes remission which can happen through weight loss by using a diet of low carbohydrates or low energy, and it can also happen through the use of medications [28].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are considered one of the most promising drugs in the treatment of type 2 diabetes which doesn't depend on insulin in its action. Many studies have confirmed its effectiveness in treating type 2 diabetes but it is important to know when and how to use it [29].

Dapagliflozin is considered as one of the SGLT2 inhibitors which are approved by the FDA [30]. The role of dapagliflozin in type 2 diabetes remission is still in need of clarifications [31].

In this study, we used dapagliflozin, 10mg orally once daily for 6 months comparing them with the group of patients on glimepiride 3mg daily. As regards A1C and BMI and if it can decrease A1C below type 2 diabetes remission levels. And in fact, dapagliflozin decreases A1C to below 6.4 which is considered the distinct remission level. This type of remission which is induced and maintained by dapagliflozin, we give it the name conditional remission, as remission is connected to dapagliflozin use.

There are 2 limitations of this study; the first the small number of patients but we can explore the results to the general population, the second limitation is whether the results are transient or persistent. As type 2 diabetes is a chronic disabling disease and there are many stresses on patients and their relatives, we hope to find a new decisive therapy. The results of our study show that dapagliflozin may be a good choice for type 2 diabetes remission. Further large-scale studies and clinical trials are required to verify our results.

CONCLUSION

As type 2 diabetes is one of the most disabling diseases, it is necessary to find a drug that can lead to remission. Dapagliflozin can lead to type 2 diabetes remission.

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