

## Original Article

# SGLT-2 inhibitor intervention in diabetes mellitus patients can reduce the incidence of renal injury and adverse events

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Received October 15, 2020; Accepted December 23, 2020; Epub April 15, 2021; Published April 30, 2021

**Abstract:** Objective: To explore the therapeutic value of sodium-dependent glucose transporters 2 (SGLT-2) inhibitor in type 2 diabetes mellitus (DM). Methods: A total of 131 patients with type 2 DM admitted to our hospital from October 2017 to November 2019 were recruited as research objects, including 58 patients treated with insulin + metformin + acarbose as the control group (CG), and 73 patients treated with SGLT-2 inhibitor on the basis of control group as the study group (SG). The levels of blood glucose, serum creatinine (Scr), 24-hour urinary protein quantity, serum uric acid, and the incidence of adverse events were compared between the two groups. Results: After treatment, fasting blood glucose (FPG), 2 hours postprandial blood glucose (2hPG), body mass index (BMI), hemoglobin A1c (HbA1c), type IV collagen (CIV), procollagen type III (PCIII), serum creatinine (Scr), 24-hour urinary protein quantity and blood uric acid (UA) decreased significantly ( $P > 0.05$ ), and they were lower in SG than in CG ( $P < 0.05$ ). Besides, the total effective rate of SG was 95.89%, which was notably higher than that of CG (84.48%,  $P < 0.05$ ). The adverse reaction rate (ADR) of patients in SG was notably lower than that in CG ( $P < 0.05$ ). Conclusion: SGLT-2 inhibitor can effectively control the blood glucose level of DM patients, and can reduce the incidence of renal injury and adverse events.

**Keywords:** SGLT-2 inhibitor, type 2 diabetes mellitus, renal injury, adverse events

## Introduction

Diabetes mellitus (DM) is a metabolic disease with the characteristics of hyperglycemia [1]. Its prevalence is increasing all over the world, especially type 2 DM, which is correlated with the change of people's lifestyle, obesity and population aging [2]. The prevalence of type 2 DM has quadrupled in the past four decades, which is comparable to the prevalence of obesity [3]. The International Diabetes Federation stated that the total number of adults with DM worldwide was approximately 425 million in 2017 and is expected to increase to 700 million in 2045 [4]. China is the country with the largest number of DM patients in the world, with a prevalence of 9.4%, up to 109.6 million, and the number of people suffering from DM is expected to reach 150.7 million by 2040. In China, type 2 DM accounts for 93.70% of all types of DM, and 1.3 million people died of DM in 2015 alone, with 40.8% of the deaths occur-

ring in people under the age of 60 [5]. People with DM have poor immune functions and are susceptible to various infections, especially pneumonia [6]. Besides, DM is also the main risk factor of cardiovascular disease [7].

Sodium-glucose linked transporter 2 (SGLT-2) inhibitor is a new type of oral hypoglycemic drug for type 2 DM [8]. It is the last anti-diabetic drug approved by FDA and EMA regulatory agencies, which can be used in any stage of type 2 DM [9]. SGLT-2 inhibitor can inhibit renal glucose reabsorption by lowering the threshold of renal glucose excretion in an insulin-independent mechanism, which is suitable for patients with long-term DM and impaired cell function [10]. In addition to controlling blood glucose, SGLT-2 inhibitor has the potential to reduce body weight because it can reduce calories through glycosuria and, due to its action as an osmotic diuretic, contributes to lowering blood pressure [11].

## Efficacy of SGLT2 inhibitors in type 2 DM

In this study, the therapeutic value of SGLT-2 inhibitor in type 2 DM was discussed by comparing the indexes of blood glucose, hemoglobin A1c (HbA1c) and adverse events between two groups of type 2 DM patients after treatment.

### Materials and methods

#### General data

A total of 131 patients with type 2 DM received treatment in The Second Affiliated Hospital of Anhui Medical University from October 2017 to November 2019 were recruited for the experiment. Among them, 58 patients treated with insulin + metformin + acarbose were enrolled in the control group (CG), including 31 males and 27 females, with a mean age of  $46.59 \pm 10.64$  years. Another 73 patients treated with SGLT-2 inhibitor on the basis of control group were enrolled in the study group (SG), including 42 males and 31 males, with a mean age of  $47.24 \pm 11.19$  years.

**Inclusion criteria:** The patient was admitted with complete clinicopathological data accompanied by his/her family, and was diagnosed as type 2 DM based on the diagnostic criteria of the World Health Organization (WHO) [12]. **Exclusion criteria:** Patient had previous history of mental illness or family history of mental illness, autoimmune deficiency, serious viscera disease, drug dependence, craniocerebral trauma, or patient who was unable to cooperate with the examiner due to aphasia, dysphoria, or unconsciousness. The study was conducted with the approval of the ethics committee of our hospital. All the patients and their families signed the informed consent after understanding the experimental process.

#### Methods

Patients in CG were treated with insulin + metformin + acarbose. Metformin was orally taken 0.5 g/time and 3 times/day, acarbose was chewed 50 mg/time and 3 times/day before meals, and insulin was injected subcutaneously once/day, with the initial dose of 8 IU, and increased or decreased 2 IU/time every 2 days according to blood glucose, so as to avoid adverse reactions (ADR). Patients in SG received treatment of SGLT-2 inhibitor Dapagliflozin (AstraZeneca, 10 mg) on the basis of

the control group, with the initial dose of 5 mg, once a day in the morning, and the dose was adjusted according to the recovery of patients in the later stage. The duration of treatment in both groups was 3 months.

#### Outcome measures

Fasting blood glucose (FPG) and 2 hours postprandial blood glucose (2hPG) were measured with glucometer. Body mass index (BMI) was calculated based on the height and weight of each patient before and after treatment. HbA1c was determined using high-performance liquid chromatography (HPLC) after venous blood collection in the morning. Blood uric acid (UA) and serum creatinine (Scr) were measured by an automatic biochemical analyzer. 24-hour urinary protein was quantified by Biuret method, and collagen type IV and procollagen type III were analyzed by radioimmunoassay. Treatment effects and the occurrence of adverse events of the two groups were counted. Therapeutic effects: Apparent response: symptoms such as emaciation, polydipsia and hyperphagia disappeared, and FPG decreased by more than 30%; efficient response: symptoms were alleviated, and FPG reduced by 10-29%; inefficient response: inadequate blood sugar control.

#### Statistical methods

All statistical analysis of the experimental results was carried out by SPSS20.0. All graph results were plotted by GraphPad Prism 7 (GraphPad, San Diego, USA). The counting data were represented by [n (%)], and the chi-square test was utilized for inter-group comparison. The measurement data were expressed by ( $\bar{x} \pm sd$ ), and the two groups were compared with t-test.  $P < 0.05$  indicated a statistically significant difference.

### Results

#### Comparison of general data

General data such as age, gender and BMI of patients in the two groups were collected (**Table 1**), showing no remarkable difference ( $P > 0.05$ ).

#### Comparison of blood glucose before and after treatment between the two groups

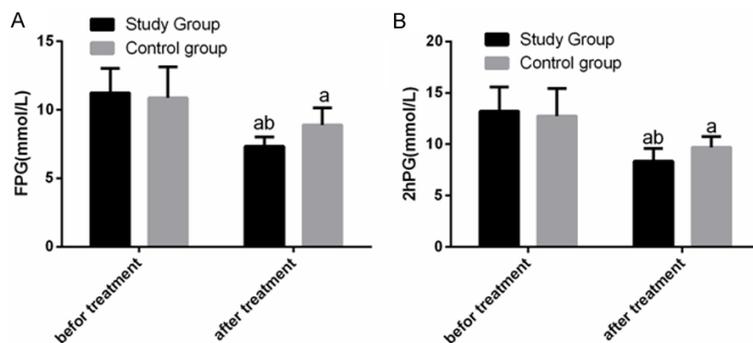
The blood glucose of the two groups was compared, as shown in **Figure 1**. There was no

## Efficacy of SGLT2 inhibitors in type 2 DM

**Table 1.** Comparison of general data of patients in the two groups ( $\bar{x} \pm sd$ )/n [%]

	Study group (n=73)	Control group (n=58)	t/X <sup>2</sup>	P
Average age (years)	47.24±11.19	46.59±10.64	0.34	0.74
BMI (kg/m <sup>2</sup> )	26.61±2.37	27.34±2.29	1.78	0.08
Gender			0.22	0.64
Male	42 (57.53)	31 (53.45)		
Female	31 (42.47)	27 (46.55)		
Average course of disease	4.26±2.14	4.19±2.17	0.18	0.85
Smoking history			0.19	0.66
Present	48 (65.75)	36 (62.07)		
Absent	25 (34.25)	22 (37.93)		
Drinking history			0.44	0.51
Present	37 (50.68)	26 (44.83)		
Absent	36 (49.32)	32 (55.17)		
SBP (mmHg)	149.62±15.14	150.27±15.63	0.24	0.81
DBP (mmHg)	92.35±7.68	90.51±10.27	1.17	0.24
TG (mmol/L)	2.95±1.19	2.86±1.27	0.42	0.68
TC (mmol/L)	6.54±1.62	6.71±1.54	0.61	0.54
HDL-C (mmol/L)	0.95±0.16	0.89±0.24	1.71	0.09
LDL-C (mmol/L)	4.35±1.06	4.30±1.14	0.26	0.80

Notes: SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = triglyceride, TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.



**Figure 1.** Comparison of blood glucose between the two groups. A: There is no significant difference in FPG between the two groups before treatment. After treatment, FPG decreases in both groups, and FPG of the study group is significantly lower than that of the control group. B: There is no significant difference in 2hPG between the two groups before treatment. After treatment, 2hPG decreases significantly in both groups, and 2hPG of the study group is significantly lower than that of the control group. Notes: a means comparison with the same group before treatment,  $P < 0.05$ . b means comparison with the control group after treatment,  $P < 0.05$ .

remarkable difference in FPG and 2hPG of the two groups before treatment ( $P > 0.05$ ). However, the two indexes decreased significantly in both groups after treatment ( $P > 0.05$ ), and were notably lower in SG than CG ( $P < 0.05$ ).

### Curative effects in the two groups

After treatment, the total effective rate of SG was 95.89%, which was remarkably higher than that of CG (84.48%,  $P < 0.05$ ), as shown in **Figure 5**.

### Comparison of BMI and HbA1c before and after treatment between the two groups

BMI and HbA1c of patients in the two groups were compared, as shown in **Figure 2**. There was no remarkable difference in BMI and HbA1c between the two groups before treatment ( $P > 0.05$ ). While the two indexes decreased significantly in both groups after treatment ( $P > 0.05$ ), and were notably lower in SG than CG ( $P < 0.05$ ).

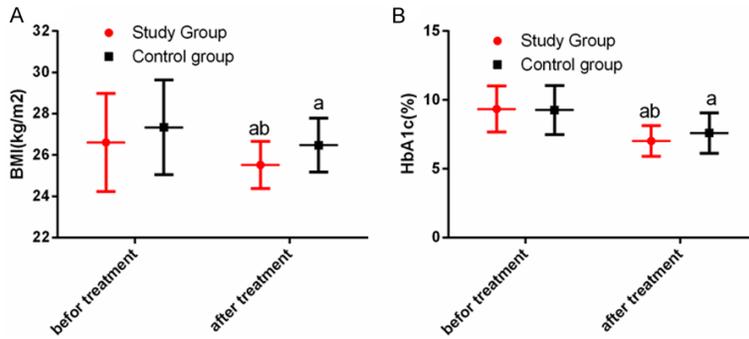
### Comparison of CIV and PCIII before and after treatment between the two groups

CIV and PCIII of patients were compared in the two groups, as shown in **Figure 3**, and no remarkable difference could be found before treatment ( $P > 0.05$ ). After treatment, the two indexes decreased significantly in both groups ( $P > 0.05$ ), and were notably lower in SG than CG ( $P < 0.05$ ).

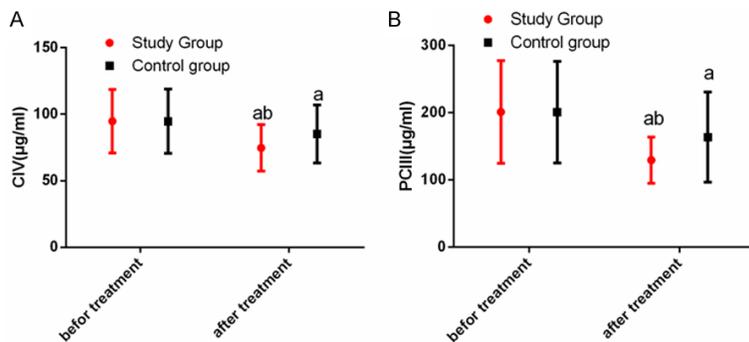
### Comparison of Scr, UA and 24-hour urinary protein quantity between the two groups before and after treatment

Scr, UA and 24-hour urinary protein quantity of patients in the two groups was compared, as shown in **Figure 4**. Before treatment, there was no remarkable difference in the three indexes between the two groups ( $P > 0.05$ ), while they decreased significantly in both groups after treatment ( $P > 0.05$ ), and were notably lower in SG than CG ( $P < 0.05$ ).

## Efficacy of SGLT2 inhibitors in type 2 DM



**Figure 2.** Comparison of BMI and HbA1c before and after treatment between the two groups. A: There is no significant difference in BMI between the two groups before treatment. After treatment, BMI decreases in both groups, and BMI of the study group is significantly lower than that of the control group. B: There is no significant difference in HbA1c between the two groups before treatment. After treatment, HbA1c decreases significantly in both groups, and HbA1c of the study group is significantly lower than that of the control group. Notes: a means comparison with the same group before treatment,  $P < 0.05$ . b means comparison with the control group after treatment,  $P < 0.05$ .



**Figure 3.** Comparison of CIV and PCIII before and after treatment between the two groups. A: There is no significant difference in CIV between the two groups before treatment. After treatment, CIV decreases in both groups, and CIV of the study group is significantly lower than that of the control group. B: There is no significant difference in PCIII between the two groups before treatment. After treatment, PCIII decreases significantly in both groups, and PCIII of the study group is significantly lower than that of the control group. Notes: a means comparison with the same group before treatment,  $P < 0.05$ . b means comparison with the control group after treatment,  $P < 0.05$ .

### ADR in the two groups

During the treatment, no serious ADR occurred in both groups, and all the ADR were quickly alleviated after symptomatic treatment. The ADR rate in SG was evidently lower than that in CG ( $P < 0.05$ ), as shown in **Table 2**.

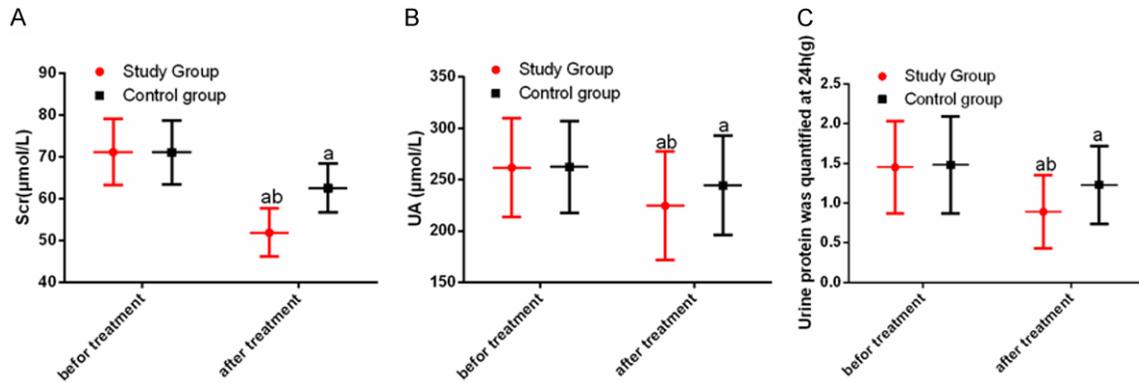
### Discussion

Type 2 DM is a complex disease characterized by high blood sugar due to insulin resistance

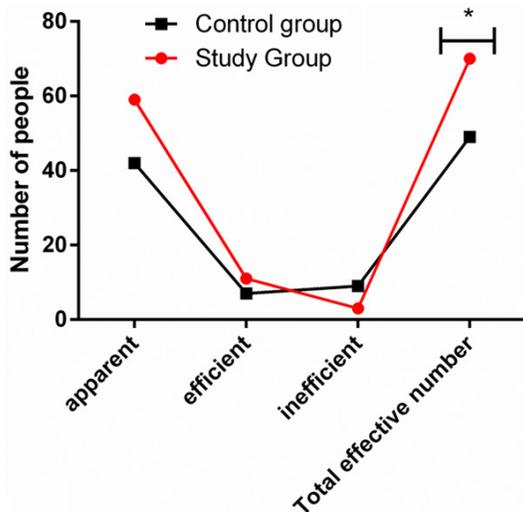
[13]. In addition to the problems associated with poor glycemic control, type 2 DM patients also have a higher risk of high blood pressure and its related complications, for example, renal injury and cardiovascular disease [14]. The main causes of DM-related renal injury and other complications are excessive production of reactive oxygen species and activation of inflammatory reaction in patients with hyperglycemia [15]. By gluconeogenesis, transport and utilization of circulating glucose, the kidney reabsorbs glucose from glomerular filtrate and regulates hormones related to glucose metabolism, which therefore plays a crucial part in regulating blood glucose homeostasis [16]. The increase of glucose reabsorption in renal tubules is one of the most significant pathophysiological mechanisms of type 2 DM [17]. SGLT-2 inhibitor can reduce blood glucose level by blocking the reabsorption of glucose in proximal renal tubules and increasing the excretion of glucose in kidney, which ameliorates renal injury and hypertension in type 2 DM patients, and has the advantages of losing weight and improving insulin resistance [18].

A previous study suggested that GLP-1RAs and SGLT-2 can significantly reduce FPG in type 2 DM patients [19], which is basically consistent with the results obtained in this study. Here, there was no remarkable difference between FPG and 2hPG in the two groups before treatment, but FPG and 2hPG reduced notably in both groups after treatment, indicating that both treatment methods can effectively control the blood glucose of type 2 DM patients. Combined with the fact that FPG and 2hPG in SG were evidently lower than those in CG after

## Efficacy of SGLT2 inhibitors in type 2 DM



**Figure 4.** Comparison of Scr, UA and 24-hour urinary protein quantity before and after treatment between the two groups. A: There is no significant difference in Scr between the two groups before treatment. After treatment, Scr decreases notably in both groups, and Scr of the study group is significantly lower than that of the control group. B: There is no significant difference in UA between the two groups before treatment. After treatment, UA decreases notably in both groups, and UA of the study group is significantly lower than that of the control group. C: There is no significant difference in 24-hour urinary protein quantity between the two groups before treatment. After treatment, 24-hour urinary protein quantity decreases notably in both groups, and 24-hour urinary protein quantity of the study group is significantly lower than that of the control group. Notes: a means comparison with the same group before treatment,  $P < 0.05$ . b means comparison with the control group after treatment,  $P < 0.05$ .



**Figure 5.** Comparison of curative effects between the two groups. After treatment, the total effective number of patients in the study group is significantly more than that in the control group. Notes: \* denotes comparison with the study group after treatment,  $*P < 0.05$ .

treatment, we concluded that SGLT-2 inhibitor could be more effective. In one study, type 2 DM patients were treated with SGLT-2 inhibitor for one and a half years, and their FPG and HbA1c were significantly reduced [20]. Here, the level of HbA1c was also notably reduced after treatment. HbA1c is a measure of chronic blood glucose that reflects the average blood

sugar level in the first two or three months, which is usually used for diabetes management to determine blood sugar control [21]. Therefore, SGLT-2 inhibitor can effectively control the blood glucose level of type 2 DM patients. All-cause mortality of type 2 DM patients is related to BMI [22], so this study calculated BMI by measuring the height and weight of two groups of patients. After treatment, the BMI of two groups of patients decreased considerably, and was lower in SG than CG, indicating that SGLT-2 inhibitor not only has the function of controlling blood sugar, but also has the potential of losing weight.

Collagen III glomerulopathy is a rare non-immune-mediated glomerular disease characterized by a large amount of organized collagen type III fibers deposited in mesangial and subcutaneous glomerular areas, which is related to the increased level of PCIII [23]. The increase of extracellular matrix in diabetic nephropathy is closely related to mitochondrial dysfunction. There was a study showing that the expression of CIV decreased and glomerular mesangial lesions improved in streptozotocin-induced DM rats [24]. Combined with the results of this study, CIV and PCIII of patients decreased significantly in both groups after treatment, and the two in SG were notably lower than those in CG, indicating that SGLT-2 inhibitor can effectively reduce renal injury in patients with type 2

## Efficacy of SGLT2 inhibitors in type 2 DM

**Table 2.** Comparison of adverse reactions between the two groups [n (%)]

	Gastrointestinal reaction	Hypoglycemia	Infection of genitourinary system	Adverse reaction rate
Study group (n=73)	1 (1.37)	2 (2.74)	1 (1.37)	4 (5.48)
Control group (n=58)	4 (6.90)	3 (5.17)	4 (6.90)	11 (18.97)
$\chi^2$	-	-	-	5.80
p	-	-	-	0.02

DM. One study demonstrated that high UA level can increase mortality in type 2 DM patients, and UA is a risk factor in all-cause mortality [25]. Combined with this study, Scr, UA and 24-hour urinary protein quantity of patients decreased obviously in both groups after treatment, and we concluded that the treatment plays a certain part in protecting the kidneys of type 2 DM patients. Given the fact that the Scr, UA and 24-hour urinary protein quantity of patients in SG were evidently lower than those in CG, we believed that SGLT-2 inhibitor can better protect the kidneys of type 2 DM patients. The total effective rate of SG was remarkably higher than that of CG, and the ADR rate of patients in SG was remarkably lower than that in CG, indicating the therapeutic value of SGLT-2 inhibitor in type 2 DM.

In this paper, the therapeutic value of SGLT-2 inhibitor in type 2 DM was discussed in a relatively comprehensive way. However, due to many factors affecting the prognosis of type 2 DM patients, this study still has certain limitations. In future studies, the effects of different doses in different environments on the prognosis of patients and various indicators should be specifically analyzed, so as to provide a basis for better treatment of type 2 DM in the future.

To sum up, SGLT-2 inhibitor can effectively control the blood glucose level of DM patients, and reduce the incidence of renal injury and adverse events.

### Acknowledgements

This study is financially supported by Efficacy and safety of SGLT2 inhibitor combined with metformin in the treatment of obese type 2 diabetes mellitus (2018xkj030).

### Disclosure of conflict of interest

None.

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## Efficacy of SGLT2 inhibitors in type 2 DM

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