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Original Research Article

Effect of dapagliflozin on metabolic disorders, β-islets cell function and serum protein expressions in patients with type 2 diabetes mellitus

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Abstract

Purpose: *To investigate the effect of dapagliflozin on metabolic disorders, pancreatic islets β-cell function and serum protein expressions in patients with type 2 diabetes mellitus (T2DM).*
Methods: *One hundred patients with T2DM in Qinghai University Affiliated Hospital, Xining, China from June 2022 to March 2023 were selected and randomly divided into control and study groups, with 50 patients in each group. Patients in control group received basic treatment (instruction to control diet intake), while patients in study group received dapagliflozin (10 mg/day) for 6 weeks, plus basic treatment. Pre and post-treatment physical examination, blood glucose and blood lipid parameters were determined. Furthermore, hemoglobin A1c (HbA1c) level was measured with enzyme-linked immunosorbent assay (ELISA) kits while serological indices were determined using radioimmunoassay.*
Results: *Post-treatment levels of fasting plasma glucose (FPG), 2 h postprandial blood glucose (2 h BG), lipid levels, and GLP 1 levels in the two groups were significantly lower than pre-treatment levels ($p < 0.05$), but the levels in study group were significantly lower than those in control group ($p < 0.05$). Moreover, HbA1c level of study group was significantly lower than that of control group ($p < 0.05$). After treatment, waist circumference, body mass index (BMI) and body mass of the two groups were significantly lower than pretreatment values, with study group having significantly lower values than control group ($p < 0.05$).*
Conclusion: *Dapagliflozin is effective in the treatment of patients with T2DM, as it significantly improves pancreatic islets β-cell function, blood glucose and lipid metabolism, and reduces body weight. Future studies using larger sample size and diverse study centers are recommended prior to application in clinical practice.*

Keywords: *Dapagliflozin, Type 2 diabetes mellitus (T2DM), Metabolic syndrome, β-Cells of Islet of Langerhans, Glucose transporter 4*

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INTRODUCTION

With advancements in lifestyles of people and adjustments in food habits, the incidence of diabetes in China is on the rise. Type 2 diabetes mellitus (T2DM) accounts for more than 90 % of diabetic cases, and there is about one in every 10 people with T2DM [1]. The disease causes damage to multiple systems and tissues such as autonomic nerves, peripheral nerves, large blood

vessels and micro-vessels, leading to a variety of diabetic complications which may be life-threatening. Therefore, early diagnosis and treatment of T2DM are of great significance for preventing and delaying the occurrence and development of diabetic lesions [2].

Presently, metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 and other types of hypoglycemic drugs which operate through different mechanisms, are used to reduce the blood glucose of patients with T2DM [3]. Sodium glucose co-transporter-2 (SGLT-2) inhibitors have been proposed as a new strategy for the treatment of diabetes. These drugs specifically inhibit the activity of SGLT-2, thereby controlling blood glucose levels in patients [4]. At present, several SGLT-2 suppressors are at different trial phases, but dapagliflozin and canagliflozin are among the drugs approved in Europe [5]. This study was done to investigate the effect of dapagliflozin on metabolic disorders and its effect on β-islets cell function and serum protein levels in T2DM patients, in order to provide data for guiding the selection of clinical interventions.

METHODS

Subjects

A total of 100 patients with T2DM admitted to Qinghai University Affiliated Hospital, China from June 2022 to March 2023 were selected and randomly divided into control and study groups, with 50 patients in each group. This study was reviewed and approved by the ethical authority of Qinghai University Affiliated Hospital (approval no. QHUAH2023004) and carried out in line with the modified guidelines of Helsinki Declaration [6].

Inclusion criteria

Newly diagnosed Type 2 diabetic patients with clinical symptoms, signs and serological indicators [7]; patients with good treatment compliance, and those who had complete clinical medical records, participated as subjects in this investigation.

Exclusion criteria

Patients who had other severe diabetic complications, e.g. ketoacidosis, nerve damage and chronic kidney disease and kidney failure; patients with other endocrine diseases such as thyroid disease, adrenal insufficiency and polycystic ovary syndrome (PCOS**)**; those who had organ dysfunctions affecting the heart, liver and kidney, and patients who had a history of any drug allergy, were excluded from the study.

Treatments

Subjects in the control cohort received basic treatment with metformin hydrochloride sustained-release tablets (Huashi, CN) after admission. Patients were instructed to control diet intake, exercise properly, quit smoking and limit alcohol intake, and closely monitor blood glucose levels. In addition to the treatment given to the control cohort, the study cohort received 10 mg of Dapagliflozin (Astrazeneca, UK) which was given orally once a day for 6 weeks in the morning, and without food restriction.

Evaluation of parameters/indices

Serological indices

Before treatment and 5 days after treatment, 5 mL of fasting morning blood was taken from each subject in both cohorts. The blood samples were centrifuged at 3000 revolutions per minute (rpm), and the supernatant was kept in a 4 ℃ refrigerator before analysis. The levels of fasting plasma glucose (FPG) and 2 h postprandial blood glucose (2 h BG) were determined with radioimmunoassay.

Determination of fasting insulin level

The levels of fasting insulin (FIns) were assayed with ELISA kits provided by Enzyme-Linked Biotechnology Co. Ltd, Shanghai, China based on the kit manufacturer's protocol. Insulin resistance index (HOMA-IR) was evaluated using Eq 1 [8].

HOMA-IR = (Fins*FPG)/22.5 …….. (1)

ELISA

Triglyceride (TG) and total cholesterol (TC) levels were determined with ELISA, and the levels of low-density lipoprotein cholesterol (LDL-C) were determined with surfactant clearance method [9]. The serum levels of hemoglobin A1c (HbA1c), glucagon-like peptide 1 (GLP-1), glucose transporter-4 (GLUT4) and nesfatin-1 were measured with the appropriate ELISA kits.

Physical examination indices

Before and after treatment, waist circumference, body mass index (BMI) and body mass were measured in the two groups and recorded.

Statistical analysis

The SPSS 20.0 was used for statistical analysis, and 2-group comparison was done with Chi-squared (χ2) test. Results from measurements are expressed as mean ± standard deviations (SD), and the two groups were compared with *t*-test. Differences were assumed statistically significant at $p < 0.05$.

RESULTS

Basic demographic profile

Table 1 shows that the 2 cohorts were comparable in general data.

Blood glucose indices

Table 2 shows that both groups were comparable in blood glucose values before treatment. However, post-treatment values of HOMA-IR, FPG and 2 h PG were significantly lowered in both cohorts, relative to the corresponding pre-treatment concentrations, with significantly lower levels in the study cohort ($p < 0.05$).

Levels of blood lipid indices

Pre-treatment levels of blood lipid indices in both groups were comparable ($p > 0.05$). However, after treatment, the levels of TG, TC and LDL-C in the two groups were significantly lower than pre-treatment values, with significantly lesser values in study cohort ($p < 0.05$; Table 3).

HbA1c and GLP-1 values

Table 4 shows that before treatment, there were no significant differences in HbA1c and GLP-1 values between both cohorts. However, post-treatment GLP-1 values in the two groups were significantly higher than pre-treatment values, with significantly higher values in the study cohort. The HbA1c level was significantly lower in the two groups after treatment, but HbA1c level in study cohort was appreciably lower.

Table 1: Clinical biodata of patients (n=50)

Group	Gender (n)		Age (years)	Body mass index (kg/m²)
	Male	Female		
Control	31	19	53.11 ± 9.69	27.32 ± 5.23
Study	32	18	52.64 ± 10.53	27.06 ± 5.56
t/χ²	0.043		0.232	0.241
P-value	0.836		0.817	0.810

Table 2: Blood glucose indices in the 2 cohorts

Group	FPG (mmol/L)		2H PG (mmol/L)		HOMA-IR (mmol/L)	
	Before	***After***	***Before***	***After***	***Before***	***After***
Control	8.45±1.24	7.29±0.98*	13.01±1.72	10.22±1.47*	3.86±0.72	2.87±0.55*
Study	8.32±1.07	6.57±1.01*	12.83±1.66	8.63±1.25*	3.77±0.67	2.43±0.48*
t	0.561	3.618	0.533	5.827	0.647	4.262
P-value	0.576	0.000	0.596	0.000	0.519	0.000

Note: *$P < 0.05$, vs. pre-treatment; #$p < 0.05$, vs. study group; (n = 50)

Table 3: Levels of blood lipid indices (mmol/L)

Group	TG		TC		LDL-C	
	Before	***After***	***Before***	***After***	***Before***	***After***
Control	2.57±0.61	1.97±0.42*#	5.23±0.96	4.41±0.9#	3.69±1.02	3.01±0.76*#
Study	2.53±0.57	1.62±0.38*	5.21±1.13	3.94±0.8	3.63±0.95	2.65±0.41*
t	0.339	4.370	0.095	2.788	0.304	2.948
P-value	0.736	0.001	0.924	0.006	0.762	0.004

**P* < 0.05, vs. pre-treatment; #*p* < 0.05, vs. study group (n = 50)

Table 4: Differences in HbA1c and GLP-1 levels between the two cohorts

Group	HbA1c (%)		GLP-1 (µMol/L)	
	Pre-treatment	***Post-treatment***	***Pre-treatment***	***Post-treatment***
Study	8.53±1.18	6.64±0.87*#	6.64±0.52	14.43±2.28*#
Control	8.41±1.12	7.51±1.09*	6.72±0.88	11.34±1.11*
t	0.522	-4.411	-0.553	8.616
P-value	0.603	0.000	0.581	0.000

**P* < 0.05, vs. pre-treatment; #*p* < 0.05, vs. study group; N=50; Data are expressed as mean ± SD

Table 5: Levels of physical examination indices

Group	Body mass (kg)		BMI (kg/m^2)		Waist (cm)	
	Pre-treatment	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***
Study	89.12±10.72	67.76±9.58*#	30.46±2.92	24.25±1.35*#	98.56±3.35	80.62±2.20*#
Control	90.02±10.80	72.14±9.63*	30.58±2.81	25.70±1.42*	98.63±3.41	86.84±3.25*
t	-0.418	-2.280	-0.209	-5.233	-0.104	-11.207
P-value	0.677	0.025	0.835	0.000	0.918	0.000

#*P* < 0.05, vs. study group; **p* < 0.05, vs. pre-treatment. Values are expressed as mean ± SD; n=50

Table 6: Comparison of serum GLUT4 and nesfatin-1 levels between the two groups

Group	Nesfatin-1 (mg/mL)		GLUT4	
	Before treatment	***After treatment***	***Pre-treatment***	***Post-treatment***
Study	5.62±1.14	4.24±1.18*#	2.64±0.52	6.43±2.28*#
Control	5.70±1.52	4.92±1.73*	2.72±0.88	4.34±1.11*
T	-0.298	-2.296	-553	5.828
P-value	0.767	0.024	0.581	0.000

**P*<0.05, vs. pre-treatment; # *p*<0.05, vs. observation group; n=50

Physical examination indices

Pre-treatment values of waist circumference, BMI and body mass were comparable in the two groups. However, post-treatment levels of these indices were significantly reduced in both cohorts, with significantly lower levels in the study group ($p < 0.05$; Table 5).

Blood GLUT4 and nesfatin-1 values

Table 6 shows that before treatment, GLUT4 and nesfatin-1 levels in serum were comparable in the 2 groups. However, post-treatment level of GLUT4 was significantly raised in both cohorts, with higher level in study cohort. In contrast, nesfatin-1 level was decreased in the two groups after treatment, with significantly lower value in observation group.

DISCUSSION

Diabetes mellitus refers to a group of metabolic diseases characterized by chronic elevation of blood glucose levels, with T2DM accounting for 90 % of diabetes cases in the human population [10]. There are many complications associated with T2DM which result in high disability and mortality rates amongst patients [11]. Previous studies have shown that nearly half of patients with impaired glucose tolerance develop diabetes within 5 to 10 years. At this stage, reasonable intervention may reduce the incidence of diabetes. Many glucose-lowering medications produce adverse reactions such as weight build-up and severe drop in blood glucose. Nearly 50 % T2DM subjects may not reach hypoglycemic index. The SGLT2 inhibitor is a new oral drug for T2DM treatment, and SGLT has several sub-types. Studies have shown that sub-types 1 and 2 are mainly linked to re-absorption of glucose [12]. The SGLT1 is a high-affinity, low-volume glucose carrier located mainly in the small intestine brush border and S3 segment of the distal kidney tubules, and it accounts for reabsorption of 10% of filtered glucose [13]. In contrast, SGLT2 is a low-affinity carrier of glucose which mediates the reabsorption of 90% of filtered glucose.

Dapagliflozin is a new SGLT2 inhibitor which reduces renal glucose reabsorption, enhances urinary glucose excretion, and reduces blood glucose levels [14]. Studies have shown that dapagliflozin is associated with good tolerance and effectiveness. It significantly reduces HbA1c, FPG and body mass of T2DM subjects without raising hypoglycemia risk. Moreover, dapagliflozin reduces BP via weight and osmotic diuretics [15].

It is known that HbA1c is formed through a non-enzymatic reaction between the hemoglobin in red blood cells and carbohydrates in serum. In clinical practice, HbA1c is used for assessing the outcome of blood sugar control in subjects with T2DM [16]. Studies have found that HbA1c level not only reflects the blood glucose control in the previous 2-3 months, but also reduces the risk of diabetic complications such as microvascular and myocardial infarction by 37 and 14 %, respectively, when HbA1c level of patients with T2DM is reduced by 1% [17]. Therefore, the determination of HbA1c levels in patients with T2DM has important clinical significance in evaluating blood glucose control and guiding treatment. Triglyceride (TG) is one of the important indicators of insulin insensitivity in T2DM subjects. In such patients, the decline of pancreatic islets β-cell viability or presence of insulin insensitivity leads to insufficient insulin, resulting in protracted hyperglycemia which hinders the degradation of TG in chylomicrons

and very low-density lipoprotein. At the same time, due to the increase in levels of free fatty acids, the synthesis of very low-density lipoprotein in the blood increases, resulting in the increased blood levels of TG, LDL and VLDL, and decreased HDL level in patients with T2DM [18].

Conversely, due to hyperlipidemia, there is increased metabolism of fatty acids in patients with T2DM through β-oxidation, resulting in large amounts of acetyl CoA. However, the acetyl CoA cannot enter the tricarboxylic acid cycle for oxidation, resulting in synthesis of total cholesterol (TC) and increased plasma TC levels [19]. In this investigation, treatment significantly decreased the levels of FPG, HbA1c, 2h PG and HOMA-IR in both cohorts, but the parameter levels were lower in the study cohort. Treatment led to marked reductions in the levels of TG, TC and LDL-C in both groups, with significantly less values in the observation group. Moreover, waist circumference, BMI and body mass were reduced post-treatment, with lower values of these indices in the observation cohort. These results suggest that dapagliflozin is beneficial in the treatment of T2DM through amelioration of abnormal metabolism of blood glucose and lipids.

Studies have shown that both GLUT4 and nesfatin-1 are associated with the occurrence and development of pancreatic β-islets cell abnormalities in diabetic patients [20]. Nesfatin-1, a sensitive secretory peptide of insulin, is composed of 82 amino acid residues. It is widely expressed in the central nervous system, islet cells, adipose tissue, stomach, pituitary and other organs and tissues, and it acts on islets β L-type Ca^{2+}channel and kinase A of cells, thereby playing a role in promoting insulin secretion. In addition, nesfatin-1 increases skeletal muscle cell glucose uptake and decreases insulin resistance. Nesfatin-1 decreases food intake and inhibits gastric emptying, thereby reducing energy intake and indirectly reducing blood glucose. Studies have found that high glucose levels stimulate the β-cell of the pancreas of rats to secrete nesfatin-1. Other studies have found reduced expression of nesfatin-1 mRNA in pancreatic cells of patients with T2DM, indicating the likelihood of a relationship between nesfatin-1 and insulin resistance.

The GLUT4 is a transmembrane glucose transporter located in some parts of the vascular smooth muscle, glomerulus and the thick segment of the ascending branch of the medullary loop. It is an insulin-regulated glucose transporter which assists free passage of glucose through the cell membrane, and also plays an important role in maintenance of glucose homeostasis. Changes in the expression GLUT4 affect the regulation of blood glucose. Studies have found that impaired function or dysregulated expression of GLUT4 leads to insulin resistance, resulting in decreased insulin sensitivity. Therefore, reduced levels GLUT4 have been associated with the pathogenesis of T2DM. The results obtained in this study showed that after treatment, the level of nesfatin-1 in each of the 2 cohorts was significantly decreased relative to the pre-treatment level, but with significantly less level in the study cohort. In addition, GLUT4 level in each group was significantly increased after treatment, with significantly higher post-treatment level in the study cohort. These data indicate that dapagliflozin was beneficial in improving islets β-cell function in patients with T2DM.

Limitations of the study

The size of the sample used in this investigation was small. Thus, there is need for a larger sample size to validate the present findings.

CONCLUSION

Dapagliflozin is effective in the treatment of T2DM. It improves islets β-cell function, enhances blood glucose and lipid metabolism, and decreases body weight in T2DM subjects. Future studies using larger sample sizes and diverse study centers will provide additional data to offer guidance on drug selection of clinical interventions.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was carried out by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Guifang Ji designed the study, supervised the data collection, and analyzed the data. Guifang Ji interpreted the data and prepared the manuscript for publication. Mingmei Ma, Yongyu Zheng, Lingjun Wei, and Tuan Cheng supervised the data collection, analyzed the data and reviewed the final draft of the manuscript.

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