Effects of Dapagliflozin on Serum and Urinary Uric Acid Levels in Type 2 Diabetic Patients: a Prospective Pilot Trial

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Research

Keywords: serum uric acid, fractional excretion of uric acid, dapagliflozin, type 2 diabetes mellitus, islet β-cell function, SGLT2 inhibitors

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Abstract

Background

We aimed to evaluate the effects of dapagliozin short-term therapy on serum uric acid (SUA) and urinary uric acid (UUA) levels in type 2 diabetic patients.

Methods

In this prospective pilot trial, 8 patients with type 2 diabetes mellitus were assigned to the treatment group with dapagliozin 10 mg once daily for one week, and 7 subjects with normal glucose tolerance were recruited in the control group. Data of anthropometric measurements, SUA, 24-hour UUA, the fractional excretion of UA (FEUA), serum lipid parameters and 3-hour oral glucose tolerance test (OGTT) were collected in both treatment and control groups, also repeated after treatment. Area under curve of glucose (AUC\text{Glu}) was calculated to reflect the general glucose levels, insulin resistance and islet $\beta$-cell secretion function were reflected by indices calculated according to the data obtained from OGTT.

Results

The weight and serum lipid parameters showed no differences before and after dapagliozin treatment for one week. We found SUA levels reduced from $347.75 \pm 7.75 \mu\text{mol/L}$ before treatment to $273.25 \pm 43.18 \mu\text{mol/L}$ after treatment with a significant difference ($p = 0.001$), accompanying with a significant increase in FEUA from 0.009 to 0.029 ($p = 0.035$), and there was a linear correlation between SUA and FEUA levels. The glucose control, insulin sensitivity and islet $\beta$-cell secretion function were improved to a certain extent. We also found the decrease in glucose levels were positively correlated with the improvement of islet $\beta$-cell secretion function.

Conclusions

Dapagliozin can present the effect on reducing SUA by increasing UA excretion within one-week treatment, a certain degree of improvement in glucose levels and islet $\beta$-cell function were observed.

Trial registration:

Type 2 diabetes mellitus (T2DM) is a complex metabolic disease, which is characterized by insulin resistance of different insulin target tissues (including liver, adipose tissue, skeletal muscle) and insufficient insulin secretion of pancreatic β-cell, as well as associated with other metabolic diseases, including obesity, dyslipidemia, hyperuricemia and non-alcoholic fatty liver disease\(^1\). Therefore, ideal hypoglycemic drugs were considered to not only improve glycemic control but also benefit to combined metabolic disorders. Under these circumstances, there are many new hypoglycemic drugs emerging in recent years, including sodium-glucose cotransporter-2 (SGLT2) inhibitors. SGLT2 is an active glucose transporter located in the early proximal renal tubule which account for up to 90% of renal glucose reabsorption, the expression of which is increased in both animal models of diabetes and diabetic patients. SGLT2 inhibitors exert hypoglycemic effect by increase urine glucose excretion in an insulin-independent way\(^2\). Nowadays, a variety of SGLT2 inhibitors have been marketed around the world with gradually increasing clinical application.

Studies on beneficial effects other than the hypoglycemic effect of SGLT2 inhibitors have attracted more and more attention, including decreasing the risks of cardiovascular diseases, heart failure, and kidney diseases, also reducing serum uric acid (SUA) levels and events related to gout flare among T2DM patients\(^3\),\(^4\),\(^5\). In addition, a few studies found that SGLT2 inhibitors can play a beneficial role in improving insulin resistance and islet β-cell secretion function\(^6\)--\(^8\), also help to reduce weight, increase lipolysis of adipose tissue and reduce fat production after a long-term treatment. Therefore, the long-term treatment period adopted by most previous studies, make it difficult to distinguish whether the beneficial effects on islet β-cell function resulted from the improvement of glucotoxicity, or changes of weight and lipid metabolism.

In this study, we aimed to set a one-week study, to evaluate effects of dapagliflozin on levels of serum and urinary uric acid, and explore whether the improvement of glucotoxicity alone can benefit insulin resistance and islet β-cell secretion function.

**Methods**

**Participants**

Eight subjects were recruited from T2DM patients (the treatment group) in the clinic of endocrinology department in Peking Union Medical College Hospital (PUMCH) from January 2019 to December 2019. These subjects were selected from individuals aged 18 to 70 (including 18 and 70 years), whose glycosylated hemoglobin A1c (HbA1c) ≥ 7%, estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m\(^2\) without contraindications to SGLT2 Inhibitors, there were no limitations to the duration of T2DM, genders and basic antidiabetic therapy.

Exclusion criteria included: (1) a diagnosis of other types of diabetes mellitus (DM); (2) unstable control of blood glucose (fasting blood glucose (FBG) > 11.1 mmol/L); (3) acute complications of T2DM within 6 months; (4) history of myocardial infarction or stroke within 6 months, or existing severe cardiovascular
disease and risk; (5) abnormal liver function [i.e. serum alanine aminotransferase or aspartate aminotransferase is 1.5 times higher than the normal upper limit]; (6) severe hypertension that defined as systolic blood pressure $\geq 160$ mmHg, diastolic blood pressure $\geq 90$ mmHg with drug therapy, or hypotension (resting seat blood pressure $< 90/50$ mmHg); (7) psychosis, alcohol dependence or history of drug abuse, lactation women, participation in other studies three months before the trial, allergic constitution or allergic to a variety of drugs and a judgment of ineligibility to participate by researchers for any other reasons.

Other seven healthy volunteers with normal glucose tolerance (NGT) and FBG were recruited as the control group.

This study was approved by the PUMCH Ethics Committee and followed the ethical standards of the responsible committee on human experimentation (institution and national) and with the Helsinki Declaration of 1964, as revised in 2013. All participants signed written informed consent voluntarily. The clinical trial number for this study is NCT04014192.

**Study Design**

Subjects in the treatment group were treated with dapagliflozin 10 mg once daily by oral in the morning for one week. All measurements of physical examinations, blood and urine samples were collected at baseline for all subjects in two groups and repeated for subjects in the treatment group after one-week treatment.

Clinical trial flow chart was showed in Fig. 1.

**Anthropometric Measurements**

Medical records were accessed for baseline information including age, sex, weight, height, and waist circumference. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height in meters ($m^2$).

**Laboratory Measurements**

Laboratory parameters were collected after fasting for 8 to 12 hours, such as FBG, HbA1c, SUA, blood urea nitrogen, serum creatinine, serum total cholesterol (TC), high- and low-density lipoprotein cholesterols (HDL-c and LDL-c), and triglyceride (TG) levels.

The blood samples were collected from the forearm to assay serum blood glucose, insulin and C-peptide at fasting time (0 minute), and 30 minute, 60 minute, 120 minute and 180 minute after 75 g anhydrous glucose load by oral. Area under curve of glucose ($AUC_{Glu}$) was calculated to reflect the glucose levels.
Quantitative Insulin Sensitivity Check Index (QUICKI)\textsuperscript{9}, insulin sensitivity index proposed by Matsuda et al. (ISI\textsubscript{Matsuda}) \textsuperscript{10}, insulin sensitivity index proposed by Stumvoll et al. (ISI\textsubscript{Stumvoll}) \textsuperscript{11}, the ratio of area under curve of glucose and insulin (AUC\textsubscript{Glu}/AUC\textsubscript{Ins}) \textsuperscript{12} and homeostasis model assessment of insulin resistance (HOMA-IR) \textsuperscript{13} were calculated to reflect insulin resistance. Homeostasis model assessment of β-cell function (HOMA-β)\textsuperscript{13}, area under curve of insulin (AUC\textsubscript{Ins}), Stumvoll first (1st) phase index and Stumvoll second (2nd) phase index were calculated to reflect islet β-cell secretion function\textsuperscript{14}.

The samples of 24-hour urinary were collected to assay the urinary uric acid (UUA), urinary sodium (UNa), urinary chlorine (UCl), and urinary creatinine, the fractional excretion of UA (FEUA), sodium (FENa) and chlorine (FECI) were calculated respectively.

**Outcome Measures**

The primary endpoint was changes from baseline to post-treatment in SUA levels. Additional outcomes included changes in 24-hour UUA, FEUA, parameters of glucose, insulin resistance and islet β-cell secretion function, weight, lipid parameters and urinary parameters of sodium and chlorine.

**Statistical analysis**

Continuous variables were expressed as mean ± standard deviation. Students' t test was used to compare differences between continuous variables of each group, and the continuous variables that failed the normality test were tested by non-parametric test. P-value less than 0.05 was considered statistical significant. Associations between variables were assessed using Pearson's correlation coefficient. All statistical analyses were carried out using the statistical program SPSS (version 25, SPSS, Chicago, IL).

**Results**

**Clinical characteristics of participants**

Between the treatment group and the control group, there were no significant differences in genders, waist circumstances, weight and BMI. FBG (p = 0.005), AUC\textsubscript{Glu} (p < 0.001) in 3-hour oral glucose tolerance test (OGTT) and HbA1c (p = 0.002) were significantly higher in the treatment group which accorded with the characteristics of glucose metabolism in these two groups. SUA levels were higher in the treatment group than in the control group.

In the treatment group, a significant lower SUA levels (p = 0.001) could be observed after taking dapagliflozin. The levels of AUC\textsubscript{Glu} (p = 0.066) decreased after treatment but without significant difference which might be due to the short term period of treatment. Weight and lipid parameters also showed no significant differences before and after treatment.
The baseline clinical characteristics between two groups, and before and after treatment of dapagliflozin were summarized in Table 1.

**Table 1**
Demographic and general laboratory blood parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Dapagliflozin 10 mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Con vs Bef</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.71 ± 6.96</td>
<td>54.00 ± 9.61</td>
<td>—</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>4 (57.14)</td>
<td>5 (62.5)</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.57 ± 16.15</td>
<td>83 ± 9.46</td>
<td>66.76 ± 9.79</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.16 ± 3.56</td>
<td>27.10 ± 2.49</td>
<td>—</td>
</tr>
<tr>
<td>Waist circumstance (cm)</td>
<td>87.86 ± 12.14</td>
<td>100.00 ± 7.33</td>
<td>—</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;Glu&lt;/sub&gt; (mmol/L·h)</td>
<td>20.02 ± 4.15</td>
<td>46.73 ± 7.49</td>
<td>42.66 ± 7.45</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.43 ± 0.23</td>
<td>7.54 ± 1.42</td>
<td>—</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>5.03 ± 0.55</td>
<td>7.43 ± 1.58</td>
<td>7.43 ± 0.97</td>
</tr>
<tr>
<td>FINS (µIU/ml)</td>
<td>9.75 ± 5.05</td>
<td>11.10 ± 4.26</td>
<td>11.49 ± 4.10</td>
</tr>
<tr>
<td>SUA (µmol/L)</td>
<td>283.57 ± 99.93</td>
<td>347.75 ± 32.53</td>
<td>273.25 ± 43.18</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.98 ± 0.57</td>
<td>5.35 ± 0.83</td>
<td>5.34 ± 0.90</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.69 ± 0.87</td>
<td>2.10 ± 0.98</td>
<td>1.71 ± 0.74</td>
</tr>
<tr>
<td>HDL-c (mmol/L)</td>
<td>1.36 ± 0.44</td>
<td>1.05 ± 0.13</td>
<td>1.09 ± 0.16</td>
</tr>
<tr>
<td>LDL-c (mmol/L)</td>
<td>3.04 ± 0.51</td>
<td>3.57 ± 0.79</td>
<td>3.72 ± 1.01</td>
</tr>
</tbody>
</table>

Con, control; Bef, before; Aft, after; BMI, body mass index; AUC, area under curve; Glu, glucose; HbA1c, glycated hemoglobin A1c; FBG, fasting blood glucose; FINS, fasting serum insulin; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol.

**Characteristics Of Urinary Parameters**

At baseline, the concentration of 24-hour UUA and FEUA were both higher in the treatment group than the control group, which indicated the higher excretion of uric acid (UA) in T2DM subjects.
After treatment, the FENa (p = 0.022) and FECl (p = 0.015) were significantly increased which were in line with the action mechanism of this class of drugs. Notably, the FEUA (p = 0.035) was significantly increased after one-week treatment of dapagliflozin, and the SUA levels inversely correlated with the FEUA levels (r = -0.775, P < 0.001; Fig. 2). The concentrations of 24-hour UNa, 24-hour UCl and 24-hour UUA were increased but showing no significant differences.

The changes of urinary parameters of the control group, before and after taking dapagliflozin in the treatment group were presented in Table 2. It revealed changes in levels of FENa (3A), FECl (3B) and FEUA (3C) in Fig. 3.

### Table 2
Comparison of urinary parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>Dapagliflozin 10 mg</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Con vs Bef</td>
</tr>
<tr>
<td>24-hour UUA (mmol)</td>
<td>3.26±</td>
<td>3.53±</td>
<td>3.79±</td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>0.61</td>
<td>1.05</td>
</tr>
<tr>
<td>24-hour UNa (mmol)</td>
<td>174.57±</td>
<td>126.18±</td>
<td>129.61±</td>
</tr>
<tr>
<td></td>
<td>46.13</td>
<td>18.89</td>
<td>27.34</td>
</tr>
<tr>
<td>24-hour UCl (mmol)</td>
<td>167.71±</td>
<td>129.61±</td>
<td>177.00±</td>
</tr>
<tr>
<td></td>
<td>53.83</td>
<td>27.34</td>
<td>36.43</td>
</tr>
<tr>
<td>FEUA</td>
<td>0.047±</td>
<td>0.062±</td>
<td>0.093±</td>
</tr>
<tr>
<td></td>
<td>0.044</td>
<td>0.009</td>
<td>0.029</td>
</tr>
<tr>
<td>FENa</td>
<td>4.75 ± 4.46</td>
<td>5.58 ± 1.19</td>
<td>8.35 ± 2.63</td>
</tr>
<tr>
<td>FECI</td>
<td>6.63 ± 6.39</td>
<td>7.84 ± 2.27</td>
<td>11.71 ± 3.74</td>
</tr>
</tbody>
</table>

Con, control; Bef, before; Aft, after; UUA, urinary uric acid; UNa, urinary sodium; UCl, urinary chlorine; FEUA, fractional excretion of uric acid; FENa, fractional excretion of sodium; FECI, fractional excretion of chlorine.

### Comparison Of Glycemic Metabolism And Islet β-cell Function

The comparison of insulin resistance parameters, including HOMA-IR, QUICKI, ISIMatsuda, ISIstumvoll and AUC\(_{\text{Glu/Ins}}\) revealed improvement in insulin sensitivity. Also, the islet β-cell secretion function identified by HOMA-β, Stumvoll 1st phase index and Stumvoll 2nd phase index were increased. The level of AUC\(_{\text{Ins}}\) decreased after taking dapagliflozin.
The comparison of islet β-cell function between control and treatment groups, and changes before and after taking dapagliflozin were showed in Table 3. The curve of serum blood glucose (4A), insulin (4B) and C-peptide (4C) in 3-hour OGTT were showed in Fig. 4.

### Table 3
Comparison of insulin sensitivity and islet β-cell secretion function

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dapagliflozin 10 mg</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Con vs Bef</td>
</tr>
<tr>
<td>Stumvoll 1st phase index</td>
<td>1342.43±585.89</td>
<td>-1032.85±1017.65</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>585.89</td>
<td>928.78</td>
<td></td>
</tr>
<tr>
<td>Stumvoll 2nd phase index</td>
<td>367.02±164.83</td>
<td>-150.13±223.52</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>164.83</td>
<td>271.71</td>
<td></td>
</tr>
<tr>
<td>HOMA-β</td>
<td>115.06±50.61</td>
<td>56.02±26.08</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>50.61</td>
<td>32.77</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.27±1.24</td>
<td>4.52±2.27</td>
<td>0.044</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.35±0.023</td>
<td>0.31±0.02</td>
<td>0.019</td>
</tr>
<tr>
<td>ISIstumvoll</td>
<td>0.078±0.038</td>
<td>0.009±0.017</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>0.017</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>ISIMatsuda</td>
<td>119.35±79.74</td>
<td>54.45±25.11</td>
<td>0.097</td>
</tr>
<tr>
<td></td>
<td>79.74</td>
<td>54.69</td>
<td></td>
</tr>
<tr>
<td>AUC_{Glu/Ins}</td>
<td>0.20±0.17</td>
<td>0.55±0.49</td>
<td>0.446</td>
</tr>
<tr>
<td></td>
<td>0.17</td>
<td>1.00±1.53</td>
<td></td>
</tr>
<tr>
<td>AUC_{INS}</td>
<td>212.26±175.00</td>
<td>145.76±94.78</td>
<td>0.402</td>
</tr>
<tr>
<td></td>
<td>175.00</td>
<td>66.60</td>
<td></td>
</tr>
</tbody>
</table>

Con, control; Bef, before; Aft, after; AUC_{Glu}, area under curve of glucose; AUC_{Ins}, area under curve of insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; QUICK, quantitative insulin sensitivity check index; ISIstumvoll, insulin sensitivity index proposed by Stumvoll et al.; ISIMatsuda, insulin sensitivity index proposed by Matsuda et al.; 1st, first; 2nd, second.

**Correlations between changes in glucose levels and islet β-cell function**

The changes in glucose levels inversely correlated with the changes in Stumvoll 1st phase index ($r = -0.985$, $P < 0.01$; Fig. 5A) and Stumvoll 2nd phase index ($r = -0.832$, $P = 0.01$; Fig. 5B). However, there were no significant associations between the reduction of glucose levels and lipid parameters and insulin sensitivity parameters.
Discussion

In this study, we explored the changes of SUA, 24-hour UUA and FEUA levels before and after taking dagligliozin 10 mg once daily for one week, also comparing the changes of parameters of insulin resistance and islet β-cell secretion function before and after treatment. We found decreased SUA levels and increased FEUA levels after taking dagligliozin, both showing significant differences. Also, there were improvement in glycemic control, insulin resistance and islet β-cell secretion function but without significant differences. We also found the positive correlation between the improvement of glycemic control and Stumvoll 1st phase index and Stumvoll 2nd phase index, which suggested the alleviation of glucotoxicity solely benefits the islet β-cell secretion function.

UA is the final metabolic product of purine compounds. Disorders in UA metabolism may cause hyperuricemia and gout. In recent years, a large body of studies have proved the clinical significance of UA in development of various metabolic disorders including T2DM. One the one hand, the prevalence of hyperuricemia in T2DM subjects is higher than in NGT subjects, on the other hand, hyperuricemia has been linked to both micro- and macrovascular complications in DM patients. Hyperuricemia can result from elevated UA production and reduced renal excretion. As for the main cause of hyperuricemia in DM patients, it was thought dominated by reduced UA excretion because of decreased UA clearance and increased reabsorption caused by hyperinsulinemia and decreased GFR resulted from diabetic nephropathy.

Traditionally, parameters to evaluate the renal ability to excrete UA include 24-hour UUA, clearance rate of UA, FEUA, excretion of UA per volume of glomerular filtration and UA to urinary creatinine ratio, among which FEUA and 24-hour UUA are subject to less impact of eGFR. Whereas, the level of 24-hour UUA is affected by many factors including dietary purine intake, the amount of drinking water, urine output, renal function, and SUA. Some scholars recommend a more accurate and reliable index, FEUA, instead of 24-hour UUA quantification method to evaluate the level of uric acid excretion. In our study, we found the levels of 24-hour UUA and FEUA were both increased in T2DM subjects at baseline, while the SUA levels were still higher than that of NGT subjects, we speculate that increased renal excretion of UA in urine might reflect an already compensatory mechanism of high SUA levels, or increased UA production might be the major cause of hyperuricemia in those T2DM patients because increased oxidative stress resulted from T2DM and lipid peroxidation could lead to increased SUA levels which acted as an endogenous antioxidants to protect the body. Similar to our results, it was also reported in a previous research that the mechanism of hyperuricemia is most probably due to overproduction of UA in certain DM patients.

There have been a variety of researches confirmed the reduced SUA levels after taking SGLT2 inhibitors. A posthoc analysis of prospectively collected data within the CANVAS Program reported canagliozin reduced serum urate concentration and also reduced events related to gout among patients with T2DM. A meta-analysis of 62 randomized controlled trials involving 34 941 patients quantified the effect of any of the SGLT2 inhibitors (Enpagliozin, Canagliozin, Dapagliozin, Tofogliozin, Lucigliozin, or Ipragliozin) on reducing SUA levels in T2DM patients. However, in most previous studies, the reduced
SUA levels were observed in 12–26 weeks after treatment\(^2^5\), a few reported the excretion of UA could result in reduction of SUA in the first couple weeks\(^2^6\). Our study found the UA-lowering effect of dapagliozin can act within one-week, and the level of SUA decreased significantly to nearly the same level of healthy subjects, accompanying with the significant increase in FEUA, and the changes of SUA and FEUA levels were linear correlation. The exact mechanism of the UA-lowering effect of SGLT2 inhibitors is still unclear, the most widely accepted hypothesis is that the possible involvement of the renal SLC2A9 (GLUT9) transporter. The increase in glucose excretion in the urine could eventually result in an increased exchange of UA in the apical membrane of tubular cells causing an increased transporting of UA from blood to the urine, thus increasing urine UA levels and decreasing SUA levels\(^2^7\).

Reductions in insulin sensitivity and insulin secretion are the hallmark characteristics of T2DM, and a large number of studies have revealed that hyperglycemia and hyperlipidemia are critical risks for islet β-cell dysfunction, which are known as β-cell glucotoxicity and lipotoxicity\(^6\). Currently, the beneficial effects of SGLT2 inhibitors on islet β-cell function have been reported. For example, canagliflozin\(^2^8\) and dapagliozin\(^2^9\) were proved to improve hepatic and muscle insulin resistance, respectively. Enpagliflozin-induced glycosuria improved islet β-cell function and insulin sensitivity were also observed\(^3^0\). Whereas, a recent study using [18F]-fluorodeoxyglucose and positron emission tomography (PET) to measure tissue insulin sensitivity during hyperinsulinemic euglycemic clamp technique, reported no effect on tissue-level insulin sensitivity was observed\(^3^1\). However, considering most those studies used a relatively long period treatment, and the improvement of islet β-cell function accompanied with the improvement of lipotoxicity that achieved by loss of weight and amelioration in lipid metabolism, it was difficult to evaluate the individual effect of the alleviation of glucotoxicity on islet β-cell function. Thus, Shimo et al.\(^3^2\) analyzed C57BL/KsJ db/db mice treated for one week with 10 mg/kg/day enpagliflozin, they found expression levels of β-cell-related factors improved, such as MafA, Insulin 1 and PDX1, from gene levels to protein levels, and the enhancement of β-cell proliferation was observed. However, glucose-stimulated insulin secretion of isolated islets was not observed in enpagliflozin treated group. They concluded that, although alleviation of glucotoxicity for one week could alleviate the expression levels of genes associated with islet β-cell function but was insufficient to achieve substantial improvement in islet β-cell function. In our study, a short period treatment of dapagliozin reduced glucose levels represented by AUC\(_{\text{Glu}}\) according to 3-hour OGTT, but without significant difference, which indicated the emergence of obvious hypoglycemic effects requires more than one-week treatment. A certain degree of improvement in insulin sensitivity and β-cell function could be observed, but without statistical differences. As for the reasons, on the one hand, we thought it was because the glucose toxicity had not been completely relieved, there was no obvious difference in the improvement of islet β-cell function; on the other hand, it might be due to the improvement of glucose toxicity in one-week was not enough in humans to achieve obvious improvement in islet β-cell function, which accorded with the findings in the animal experiment\(^3^2\). Furthermore, the linear correlation found between changes of AUC\(_{\text{Glu}}\) and parameters representing islet β-cell secretion function, but not between glucose levels and insulin sensitivity parameters, showed improvement in islet β-cell secretion function was more related to improvement in glucose control after a
short period treatment. However, whether SGLT2 inhibitors can improve the islet β-cell function by alleviation of glucotoxicity alone, requiring further researches in larger sample populations, and longer treatment period.

This is a prospective, pilot and exploratory study, we found the effect of dapagliflozin on reducing SUA levels in addition to hypoglycemic treatment within one week. However, the sample size is small, and further studies containing different treatment period groups (including one-week, two-week, and four-week) can be conducted to observe the indicators of UA levels and islet β-cell function.

Conclusions

In this study, within one-week treatment of dapagliflozin 10 mg once daily, we found dapagliflozin can reduce SUA levels by increasing UA excretion by kidneys. Furthermore, a certain degree of improvement in islet β-cell function, and the positive correlation between changes in glucose levels and islet β-cell secretion function were also observed without the interferences with changes of weight and lipid metabolism.

Abbreviations

T2DM, type 2 diabetes mellitus; SGLT2, sodium-glucose cotransporter-2; SUA, serum uric acid; PUMCH, Peking Union Medical College Hospital; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; FBG, fasting blood glucose; NGT, normal glucose tolerance; BMI, Body mass index; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterols; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; AUCGlu, Area under curve of glucose; QUICKI, Quantitative Insulin Sensitivity Check Index; ISI Matsuda, insulin sensitivity index proposed by Matsuda et al.; ISI Stumvoll, insulin sensitivity index proposed by Stumvoll et al.; AUCGlu/AUCIns, the ratio of area under curve of glucose and insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function; AUCIns, area under curve of insulin; 1st, first; 2nd, second; UUA, urinary uric acid; UNa, urinary sodium; UCl, urinary chlorine; FEUA, the fractional excretion of UA; FENa, the fractional excretion of sodium; FECl, the fractional excretion of chlorine; OGTT, oral glucose tolerance test; PET, positron emission tomography.

Declarations

Ethics approval and Consent to participate

This study was approved by the Peking Union Medical College Hospital (PUMCH) Ethics Committee and followed the ethical standards of the responsible committee on human experimentation (reference number: JS-1945) and with the Helsinki Declaration of 1964, as revised in 2013. All participants signed written informed consent and provided consent for publication if any identifying information is included in the manuscript.
Consent to publication

The authors affirm that all individual participants provided informed consent for publication of the data. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Availability of data and materials

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

Competing interests

The authors declared no conflict of interest.

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Authors’ contributions

Conceptualization: Tao Yuan and Shixuan Liu; Investigation: Yingyue Dong and Yong Fu; Methodology: Yingyue Dong, Yan Tang and Tao Yuan; Writing - original draft: Tao Yuan and Shixuan Liu; Writing - review editing: Tao Yuan and Weigang Zhao; Supervision: Weigang Zhao.

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References


Figures
Figure 1

Clinical trial flow chart. T2DM, type 2 diabetes mellitus; NGT, normal glucose tolerance; BMI, body mass index; HbA1c, glycated hemoglobin A1c; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; UUA, urinary uric acid; UNa, urinary sodium; UCl, urinary chlorine; FEUA, fractional excretion of uric acid; FENA, fractional excretion of sodium; FECI, fractional excretion of chlorine; OGTT, oral glucose tolerance test; AUCGlu, area under curve of glucose; AUCIns, area under curve of insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; QUICK, quantitative insulin sensitivity check index; ISIStumvoll, insulin sensitivity index proposed by Stumvoll et al.; ISIMatsuda, insulin sensitivity index proposed by Matsuda et al.; 1st, first; 2nd, second.
Figure 2
Correlation between SUA levels and FEUA levels before and after treatment. The relationship between the two variables was assessed using Pearson's correlation coefficient. SUA, serum uric acid; FEUA, fractional excretion of uric acid.

Figure 3
The comparison of fractional excretion of Na (3A), Cl (3B) and UA (3C) in three groups. * represents statistical significance. FENa, fractional excretion of sodium; FECl, fractional excretion of chlorine; FEUA, fractional excretion of uric acid.
Figure 4

The curve of serum glucose (4A), insulin (4B) and C-peptide (4C) in 3-hour OGTT in three groups. OGTT, oral glucose tolerance test.

Figure 5

Correlation between changes in bloodglucose and Stumvoll 1st (5A) and 2nd (5B) phase indexes. The relationship between the changes was assessed using Pearson's correlation coefficient. 1st, first; 2nd, second.