

# Effect of sodium-glucose co-transporter-2 inhibitors on the levels of serum asprosin in patients with newly diagnosed type 2 diabetes mellitus

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## Research

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# Abstract

## Background

Asprosin, a novel adipokine which raises glucose levels and stimulates appetite, has been proved to be pathologically increased in populations predisposed to type 2 diabetes mellitus (T2DM), obesity and cardiovascular diseases. The mechanisms of sodium-glucose co-transporter-2 (SGLT2) inhibitors for hypoglycemic effect and cardiovascular protection have not been fully clarified. Therefore, we conducted this study to assess change in the levels of serum asprosin after treatment with SGLT2 inhibitors in patients with newly diagnosed T2DM.

## Methods

This study was a randomized, double-blind, placebo-controlled trial. A total of 29 participants with newly diagnosed T2DM with body mass index (BMI)  $\geq 23.0 \text{ kg/m}^2$  and haemoglobin A1c (HbA1c) levels of 58 ~ 85 mmol/mol (7.5%~10%) were randomized to SGLT2 inhibitors dapagliflozin 10 mg/d ( $n = 19$ ) or placebo ( $n = 10$ ) treatment for 24 weeks. We analyzed asprosin concentrations by an enzyme-linked immunosorbent assay. In addition, body weight, BMI, HbA1c, fasting plasma glucose (FPG), and lipid levels were measured at baseline and at 24 weeks.

## Results

At 24 weeks, participants with SGLT2 inhibitors treatment exhibited lower the levels of serum asprosin (22.87 vs 45.06 ng/ml in the placebo group;  $P < 0.001$ ) after adjusting for baseline values. The levels of body weight, BMI, HbA1c, FPG and triglyceride (TG) were decreased, while high density lipoprotein-cholesterol (HDL-C) was increased after SGLT2 inhibitors dapagliflozin treatment compared with placebo ( $P < 0.05$  for all). Low density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) levels were unchanged in SGLT2 inhibitors group and placebo group. No statistical correlation was found between the levels of serum asprosin and body weight, BMI, HbA1c, FPG, and lipid levels during the SGLT2 inhibitor dapagliflozin treatment.

## Conclusions

This study shows that SGLT2 inhibitors can decrease the levels of serum asprosin in patients with newly diagnosed T2DM, which may be involved in SGLT2 inhibitors mechanisms of improving glucose levels and reducing cardiovascular diseases risk factors.

## Trial registration

ISRCTN, ISRCTN2013L01573. Registered 29 august 2013. <http://www.icmje.org/search/?q=ISRCTN+2013L01573>

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## Background

Cardiovascular diseases are the major diabetic complications and increase mortality of patients with type 2 diabetes mellitus (T2DM)[1]. Hyperglycaemia, obesity and dyslipidemia are independent high-risk factors for cardiovascular diseases[2].

Asprosin, a novel adipokine, has been proved to be pathologically increased in patients with T2DM and obesity[3]. The available evidence on the association of asprosin and cardiovascular diseases has also been discovered[4]. Asprosin is secreted by white adipose tissue, which acts on the liver, promotes hepatic glucose production, and raises glucose levels via activating G protein cyclic-AMP (cAMP)-protein kinase A( PKA) pathway[5], and asprosin crosses the blood-brain barrier and activates orexigenic agouti-related peptide (AgRP) neurons and inhibits anorexigenic proopiomelanocortin (POMC) neurons to stimulate appetite and accumulate adiposity and body weight[6]. Elevated serum asprosin concentrations also cause insulin resistance and glucose dysregulation in humans and mice[7]. And asprosin may be used as a biomarker to predict unstable angina pectoris and is shown that positively correlated with the degree of coronary stenosis[4]. Furthermore, its molecular mechanisms and function have been explored in other cardiovascular diseases, such as dilated cardiomyopathy[8] and myocardial infarction[9]. Thus, we hypothesize that asprosin is expected to be a therapeutic target for various metabolic diseases, particularly obesity, T2DM and cardiovascular diseases.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, new type of hypoglycemic agents, selectively act on proximal renal tubules SGLT2 to inhibit glucose reabsorption and promote the excretion of glucose from the urine, which is independent of insulin secretion, insulin resistance and islet function[10]. Several SGLT2 inhibitors are effective in controlling plasma glucose, including the improvement of haemoglobin (HbA1c) and fasting plasma glucose(FPG)[11–13]. Importantly, SGLT2 inhibitors have been confirmed that its effects of weight loss[14] <sup>14</sup>and cardiovascular protection[15]. These effects not completely depend on the hypoglycemic effect, which has some unique mechanisms that may affect the levels of adipokines such as leptin and adiponectin involved in cardiovascular disease[16, 17]. Therefore, we evaluated the change in the levels of serum asprosin after SGLT2 inhibitors treatment in patients with diagnosed newly T2DM, which may beneficial to explain its mechanisms for improving glucose and lowering cardiovascular diseases risks.

## Methods

### Participants

This study was a randomized, double-blind, placebo-controlled trial and was performed in the department of endocrinology, Nanjing First Hospital, Nanjing Medical University, between 2014 and 2015. Participants with newly diagnosed T2DM in accordance with the WHO diagnostic criteria (1999)[18] and drug-naïve type 2 diabetes, had HbA1c levels between 58 ~ 85 mmol/mol (7.5%~10%), body mass index (BMI)  $\geq 23.0\text{Kg/m}^2$ . The key exclusion criteria were severe hepatic and renal dysfunction, acute diabetic complication, suffered from acute or chronic pancreatitis at any time, have received or planned to undergo gastric bypass bariatric surgery or restrictive bariatric surgery during the study period, or long-term use of drugs that directly affect the motility of the gastrointestinal tract. We enrolled 29 participants, all of them completed the study. The protocol and informed consent document were approved by the ethics committee of Nanjing First Hospital, and all participants gave written informed consent before enrolling in the study.

## Study design and laboratory analyses

Eligible participants were assigned randomly to receive one of two treatment with dapagliflozin 10 mg/d or placebo, all are taken orally before breakfast every day. All participants were received instructions of similar level of physical activity and the same nutritional value and equivalent energy intake of meals, and the original lipid-lowering and anti-hypertensive programs were maintained during the period.

At the beginning and end of 24 weeks treatment, height, weight, and blood pressure of all participants were measured by trained and certified nurse using standard protocols and techniques. After an overnight fast, fasting blood samples were acquired for the measurement of asprosin, FPG, HbA1c and lipid profiles in all participants. Serum asprosin was determined by the enzyme-linked immunosorbent assay kit from Eiaab Science INC. Wuhan, China (Catalogue Numbers, E15190h). The kit had a sensitivity of 0.938 ng/mL, with a range between 1.563 ng/mL and 100 ng/ml. The intra-assay coefficient of variation is 6.6% and inter-assay coefficient of variationis 7.6%.The plasma glucose level was assessed by glucose oxidase method using an automatic biochemistry analyzer (HITACHI-7180, Tokyo, Japan), HbA1c was measured by high-pressure liquid chromatography (BIO-RADD-10 TM, California, USA), and lipid profiles were assessed by enzymatic colorimetric assay using an automatic biochemistry analyzer (HITACHI-7180, Tokyo, Japan). BMI was calculated by weight divided by the square of height (kg/m<sup>2</sup>). All these tests were done in the clinical laboratory of Nanjing First Hospital.

## Statistical analyses

All analyses were conducted using SPSS26.0. all variables were tested for normal distribution by Shapiro-Wilk test. Data conforming to the normal distribution were expressed as means  $\pm$  standard deviation (SD). Paired t-test and independent-samples t-test were used to compare differences with groups. Data for non-normal distribution were expressed as median and interquartile range (IQR), Mann-Whitney U test was used in the comparisons between groups. Multivariate liner regression analysis was performed to identify the correlation between clinical and metabolic parameters. All comparisons were 2-sided at the 5% significance level. *P* value < 0.05 was considered to be statistically significant.

# Results

## Baseline characteristics

The study population consisted of 19 participants with T2DM in dapagliflozin group and 10 in placebo group. The demographic and baseline characteristics of study participants were balanced between two groups (Table 1).

## Effects of SGLT2 inhibitors on the levels of serum asprosin

At 24 weeks, the median levels of serum asprosin was significantly decreased in the dapagliflozin group from 36.88 to 22.87 ng/ml (*P*<0.001). Furthermore, the median levels of serum asprosin with dapagliflozin treatment was significantly reduced to 22.87 ng/ml compared with 45.06 ng/ml with placebo treatment at 24 weeks (*P*<0.001). (Fig. 1a)

## Effects of SGLT2 inhibitors on body weight and BMI

Modest but no significant changes were observed in body weight and BMI at 12 weeks in participants treated with dapagliflozin compared that of placebo(-2.80 versus -1.00,Kg and -0.71 versus -0.35 Kg/m<sup>2</sup>) $P>0.05$  for both ). but these clear declines were significant at 24 weeks in dapagliflozin group compared with the placebo group(-5.83 versus -1.06,Kg and -2.08versus -0.42 Kg/m<sup>2</sup>) $P<0.05$  for both )(Fig. 1b and c).

## Effects of SGLT2 inhibitors on glucose control

Decreased in HbA1c levels and FPG concentrations were both notable in the treatment group (Fig. 1d and e). At week 12 and 24, median changes from baseline in HbA1c levels were significant in the SGLT2 inhibitor group [-12.13mmol/mol (-1.11%) and -14.20mmol/mol (-1.30%), respectively] compared with the control group [-3.60mmol/mol (-0.33%) and-4.48mmol/mol (-0.41%);  $P<0.001$  and  $P<0.05$ , respectively]. Compared with the placebo group, the treatment group exhibited a significantly greater reduction in FPG concentrations after 12 weeks and 24 weeks [(-1.34 and -1.64 mmol/L) versus (0.04 and 1.10 mmol/L),  $P=0.005$  and  $P<0.001$ ].

## Effects of SGLT2 inhibitors on lipids metabolism

Lipid metabolism measurements, including total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C) were assessed at baseline and at 24 weeks. Decreased TG levels and increased HDL-C levels were detected with dapagliflozin treatment (-0.34mmol/L and 0.40mmol/L,  $P<0.05$  for both). The differences of TC and LDL-C levels were both no statistically significant between the SGLT2 inhibitors group and the placebo group. (Table 2)

## Correlation analyses

Multivariate liner regression analysis indicated that the lower levels of serum asprosin were not related to the change in body weight, BMI and glycolipid parameters. Further adjustment for baseline age or gender did not alter this finding.

## Discussion

The results of this study showed that lower levels of serum asprosin in the SGLT2 inhibitors group than in the placebo group after 24 weeks treatment. At 24 weeks, serum asprosin, body weight, BMI, and glucolipid parameters were improved in the 19 participants who received SGLT2 inhibitors treatment compared with the 10 participants who received placebo. No significantly statistical correlation was detected between serum asprosin and clinical metabolic parameters.

There are several possible explanations for decreased serum asprosin and improved glucose levels with SGLT2 inhibitors treatment. Firstly, serum aspsorin is directly related to glucose metabolism and may be used as a predictor of early diagnosis of T2DM. After secreted by white adipose tissue, asprosin in the circulation recruited to the liver and promotes hepatic glucose production, resulting in rapid elevated glucose levels[5]. Numerous clinical trials have analyzed that the levels of serum asprosin in patients with type 2 diabetes are

significantly higher than those in healthy volunteers[19], Zhang[3] found that the increased morbidity of T2DM is accompanied by higher asprosin levels and serum asprosin independently was associated with FPG and TG, which is consistent with results in our study. Li group[20] identified that mice knocked out the asprosin receptor gene have lower insulin levels, reduced fat accumulation, and significantly attenuated glucose release. These results reveal that serum asprosin may be used as a potential therapeutic target for patients with T2DM. Secondly, Xu[21] reported the SGLT 2 inhibitors can activate macrophages polarization to increase the utilization of white adipose tissue, which is likely to explain the loss of body weight in patients treated with SGLT2 inhibitors in current study and various randomized controlled trials[22, 23]. These effects SGLT2 inhibitors on enhancing adipose tissue expenditure, which could reduce synthesis and release of asprosin that is secreted by white adipose tissue. Therefore, when participants received SGLT2 inhibitors treatment, their improved glucose variations may result from decreased levels of serum asprosin.

It is clear that mechanisms of asprosin are related to obesity, glucose and lipid metabolism. Meanwhile, all of these are not good for cardiovascular system structure and function, particularly in patients with T2DM [24]. Actually, serum asprosin were found in liver, brain tissue and heart tissue in diabetic rats[25]. Besides animal experiments, a clinical study detected to the direct relationship between serum asprosin and coronary artery stenosis in acute coronary syndrome people with unstable angina pectoris, their results showed that there was a significant positive correlation and asprosin may be the first biochemical marker for predicting the severity of unstable angina pectoris [4]. Thus, to some extent, decreased levels of serum asprosin are beneficial to the cardiovascular system in patients with T2DM.

SGLT2 inhibitors are distinguished from traditional hypoglycemic drugs because of its unique hypoglycemic effect and excellent cardiovascular protection[26, 27].However the cardiovascular protective mechanism of SGLT2 inhibitors is not completely understood[28]. Previous studies have found that SGLT2 inhibitors may benefit the cardiovascular system through the reduced atrial natriuretic peptide and brain natriuretic peptide levels[29, 30]. Notwithstanding, researches have shown that adipokines involved in heart failure could be regulated by SGLT2 inhibitors[17, 31]. In the present study, the SGLT2 inhibitors reduced serum asprosin levels by -14.58 ng/ml in patients with newly diagnosed T2DM, which may be involved in cardiovascular protective mechanism of SGLT2 inhibitors.

There are some limitations in current study that should be taken into consideration. First, the study population was not large enough and the research time was relatively short. Second, more clinical parameters for explaining the mechanism of serum asprosin should be detected, such as waist hip circumference and body fat analysis. Third, it is unknown whether better effects would be seen with different SGLT2 inhibitors dosage.

## Conclusions

In conclusion, we showed that SGLT2 inhibitors reduced the levels of serum asprosin in patients with newly diagnosed T2DM, which may be associated with SGLT2 inhibitors mechanisms for improving glucose and lowering cardiovascular diseases risks.

# **Abbreviations**

T2DM: type 2 diabetes mellitus; SGLT2:sodium-glucose co-transporter-2; BMI:body mass index; HbA1c:haemoglobin A1c; FPG:fasting plasma glucose; TG:triglyceride; HDL-C:lipoprotein-cholesterol; LDL-C:low density lipoprotein-cholesterol; TC:total cholesterol; AgRP:agouti-related peptide; POMC:proopiomelanocortin; SD:means ± standard deviation; IQR:interquartile range; cAMP:cyclic-AMP; PKA:protein kinase A

# **Declarations**

## **Ethics approval and consent to participate**

This study was approved by the ethics committee of Nanjing First Hospital and all participants provided written informed consent.

## **Consent for publication**

Not applicable.

## **Availability of data and materials**

All data generated and/or analyzed during this study is available from the corresponding authors upon reasonable request.

## **Competing interests**

The authors declare that they have no competing interests

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## **Authors' contributions**

Qian Li and Yuqing She conceived and designed the study; Lu Yuan, Ying Zhang and Zhanrong Feng performed data collection; Aijun Jiang and Qian Li performed statistical analysis; Aijun Jiang and Zhanrong Feng wrote the manuscript. All authors read and approved the final manuscript.

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## **Disclosure**

The authors report no conflicts of interest in this work.

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## Tables

Table1: Baseline clinical characteristics of participants

	SGLT2 inhibitor (n=19)	Placebo (n=10)	Z/t	P
Age,years	58.32±8.01	59.3±9.03	-4.301	0.766
gender, men/women	9/11	2/8	/	/
Body weight,Kg	71.97±8.31	66.20±1.93	1.930	0.064
BMI,kg/m <sup>2</sup>	26.60±1.32	25.64±1.41	1.809	0.082
SBP,mmHg	123.20±20.27	120.00 (120.00,137.00)	-0.786	0.432
DBP,mmHg	78.16±7.97	80.20±9.31	-0.612	0.541
BUN,mmol/L	6.43±1.30	5.82±1.14	1.248	0.213
Cr,umol/L	69.63±1.30	67.10±10.18	0.514	0.612
AST,U/L	18.00(15.00,24.00)	19.00(15.75,29.25)	-0.760	0.447
ALT,U/L	17.00(12.00,30.00)	20.50(15.25,36.00)	-0.599	0.599
ALP,U/L	85.00(4.00,97.00)	80.50±25.37	-0.689	0.689
FPG,mmol/L	9.12±1.75	7.93±0.84	2.018	0.054
Fasting C-pep,ng/ml	0.52±0.20	0.63±0.20	-1.507	0.143
2h C-pep,ng/ml	1.86±0.87	2.11±0.96	-0.715	0.481
HbA1c,%	8.10(7.70,8.90)	8.50(8.05,8.92)	-0.965	0.334
TC,mmol/L	4.88±0.89	4.75±2.18	0.238	0.814
TG,mmol/L	1.71(0.98,3.40)	1.23(1.04,2.96)	-0.964	0.335
LDL-C,mmol/L	2.93±0.83	2.342±0.62	1.989	0.057
HDL-C,mmol/L	1.28±0.27	1.15±0.31	1.170	0.252
asprosin,ng/ml	36.88(24.81,69.04)	33.43(19.64,49.94)	-0.620	0.535

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; FPG, fasting plasma glucose; Fasting C-pep, fasting C-peptide; 2h C-pep, 2h C-peptide; HbA1c, hemoglobinA1c; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; SGLT2, sodium-glucose co-transporter-2.

Table 2: changes in lipids parameters at 24 weeks between groups with different treatment

SGLT2 inhibitor (n=19)		placebo(n=10)					
parameters	baseline	24 weeks	P-value	baseline	24 weeks	P-value	P-value b/w group at 24 weeks
TC,mmol/L	4.88±0.89	5.12±0.85	0.061	4.75±2.18	4.79 (3.77,5.31)	0.785	0.094
TG,mmol/L	1.71(0.98,3.40)	1.16±0.56	0.020	1.23(1.04,2.96)	5.00±1.78	0.878	0.501
LDL-C,mmol/L	2.93±0.83	3.15±0.75	0.108	2.342±0.62	1.94±0.54	0.990	0.379
HDL-C,mmol/L	1.28±0.27	1.68±0.39	<0.001	1.15±0.31	1.24±0.25	0.173	0.012

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; SGLT2, sodium-glucose co-transporter-2.

## Figures

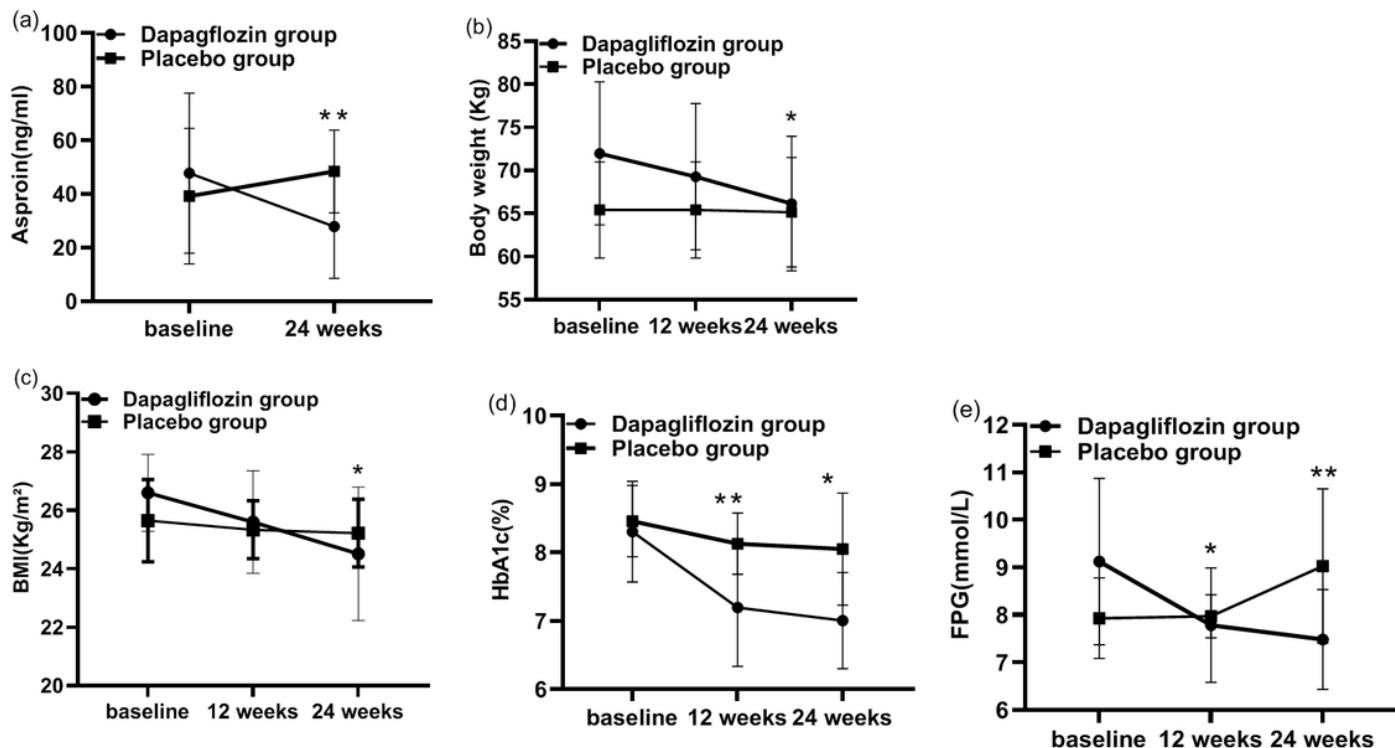


Figure 1

Change from baseline in asprosin, body weight, body mass index (BMI), glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG) levels in the sodium-glucose transporter-2 (SGLT2) inhibitors and placebo group at baseline, 12 weeks and 24 weeks. \*P <0.01. \*\* P <0.001.