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The effects of dapagliflozin on the neovascularization of carotid atherosclerosis plaques in type 2 diabetes mellitus patients

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Abstract: This study investigated the effect of dapagliflozin on the neovascularization of carotid atherosclerotic plaques in patients with type 2 diabetes mellitus (T2DM) who failed to meet the initial treatment standard of metformin. Sixty patients with HbA1c 7.0–11.0% after metformin (2000 mg/day) treatment were included and randomized into two groups: group A (dapagliflozin) and group B (glimepiride). After 12 weeks of treatment, group A had lower mean blood glucose (MBG) and higher time in range (TIR) compared to group B. After 48 weeks of treatment, group A showed significant differences in various indicators compared to group B, including lower MBG, higher TIR, lower fasting insulin (FINS), improved insulin resistance, reduced systolic blood pressure (SBP), and lower BMI, waist-to-hip ratio (WHR) and time intensity curve of carotid angiography. No statistical differences in HbA1c, fasting blood glucose (FBG), diastolic blood pressure, low-density lipoprotein cholesterol (LDL), ALT, AST, blood urea nitrogen (BUN), serum creatinine or glomerular filtration rate (eGFR) after 12- and 48-week treatment between either group. Dapagliflozin treatment in T2DM patients can effectively control blood glucose, improve insulin resistance, reduce SBP, lower BMI and WHR, and improve the time intensity curve of carotid angiography, delaying the progress of diabetic macrovascular complications.

Keywords: Dapagliflozin, type 2 diabetes, carotid atherosclerosis, macrovascular complications.

INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) is rising worldwide. Diabetic macroangiopathy is the main cause of disability and death in type 2 diabetes (Chen *et al.,* 2020; Anonymous 2020 and Yao *et al.,* 2022). Although many factors are related to the progression of diabetic macrovascular complications (Toya and Malik, 2012; Madonna *et al.,* 2018 and Ceriello *et al.,* 2008), researchers have found that hyperglycemia and insulin resistance are the two most important initiators (Katakami *et al.,* 2018).

Neovascularization caused by atherosclerosis is the main pathological change of diabetic vascular complications. Vascular endothelial cell dysfunction is one of the mechanisms of atherosclerosis, resulting in that chronic hyperglycemia and hyperlipidemia that can cause oxidative stress and elevated inflammation of endothelial cells (Wang *et al.,* 2022). The study found that the density of neovascularization in arterial plaque was significantly related to plate stability (Magnoni *et al.,* 2019), and cardio-cerebrovascular complications were more likely to occur with greater density (Feinstein *et al.,* 2006). Carotid atherosclerosis occurs earlier than other large blood vessels. Ultrasound can be used to evaluate the presence of atherosclerosis in the carotid artery, time intensity curve of carotid angiography, which can quantify the stability of carotid plaques, is the main indicator for evaluating carotid atherosclerotic plaque neovascularization (Tian *et al.,* 2019; Qin *et al.,* 2018).

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor, a drug which can reduce blood glucose level by inhibiting the reabsorption of glucose by the kidneys and increase excretion of urine sugar (DeFronzo *et al.,* 2013). Recent studies have found that dapagliflozin can significantly improve body mass index (Lazzaroni *et al.,* 2021), reduce triglycerides, increase high-density lipoprotein levels and improve various metabolic disorders in patients with type 2 diabetes (Strojek *et al.,* 2013; Bolinder *et al.,* 2012 and He *et al.,* 2022). Moreover, incidence and mortality rates of diabetes mellitus complicated by heart failure can also be lowered by dapagliflozin (Nassif *et al.,* 2021). Until now, there have been no specific studies examining whether dapagliflozin can delay macrovascular complications of diabetes (Nicolucci *et al.,* 2019; Saleem *et al.,* 2017). Therefore, we use a case-control study to elaborate the effect of dapagliflozin on neovascularization in carotid atherosclerotic plaques in patients with type 2 diabetes, and to explore whether dapagliflozin can delay the occurrence of macroangiopathy in type 2 diabetes.

MATERIALS AND METHODS

Patients

From December 2017 to December 2018, 60 patients with type 2 diabetes (including 36 males and 24 females) were selected from the department of endocrinology of the

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Affiliated Hospital of Qingdao University. Inclusion criteria were as follows: (1) individuals who met the criteria of the American Diabetes Association 2019 (Strojek *et al.,* 2013); (2) age 30–80 years old, HbA1c 7.0%-11.0% after 2000 mg/day metformin treatment ≥ 3 months; (3) carotid atherosclerotic plaque formation confirmed by cervical vascular ultrasound; and (4) standardized treatment with statins ≥ 3 months. Exclusion criteria: (1) the presence of acute and severe chronic complications of diabetes; (2) FINS <3.0 uIU/ml or fasting C-peptide < 1.1 ng/ml; (3) use of antihypertensive drugs, diuretics, anti-platelet drugs or total parenteral nutrition; and (4) diagnosis of serious hepatorenal disease or dysfunction, serious cardio and cerebrovascular disease, acute infection, urinary malformation, urinary calculi, genetic disease or mental illness. Selected individuals were randomly divided into groups A or B according to a computer-generated random number table. Of those selected, five individuals were lost to follow-up. Finally, 31 individuals were in group A and 29 were in group B. All individuals signed informed consents, and the research scheme was approved by the research ethics committee of Affiliated Hospital of Qingdao University.

Intervening measures

Based on diet and exercise treatment guidance, all individuals continued to use metformin 2000 mg/day. In addition, group A was given dapagliflozin 10 mg/day and group B was initially given glimepiride 2 mg/day. The dosage of glimepiride was individually adjusted according to blood glucose. The observation continued for 48 weeks, and relevant indicators were tested to evaluate efficacies at 12 and 48 weeks. All individuals continued to use statins at a dose of 20 mg/day.

Biochemical measurements

Weight, height, waist circumference, hip circumference, HbA1c, fasting blood glucose (FBG), fasting insulin (FINS), blood pressure, LDL, ALT, AST, BUN and Cr were measured before enrollment and subsequently at 12 and 48 weeks after treatment. Body mass index (BMI), waist to hip ratio (WHR), insulin resistance index (HOMA-IR) and glomerular filtration rate (eGFR) were calculated. Mean blood glucose (MBG) was calculated by dynamic blood glucose monitoring, which is an instant sense scanning glucose monitoring system. Subjects self-monitored blood glucose levels through their fingertips during fasting and 2h after a meal, every 2 weeks. All subjects underwent carotid ultrasonography, where after routine carotid ultrasonography, they were rapidly injected with a contrast agent into the elbow vein of the upper arm. The enhancement and regression of neovascularization in plaques were continuously observed and recorded under ultrasound. The acquired images were analyzed by acoustic quantitative analysis software (Sonoliver). The main parameters included: peak time, which is the time from the injection of contrast agent to the maximum concentration in the region of interest; peak intensity: contrast agent (the ratio of the maximum concentration of the agent in the region of interest to the reference region); and area under the curve (AUC), which reflects the total time-intensity of the contrast agent from entering the region of interest to completely cleared blood flow dynamics.

STATISTICAL ANALYSIS

Statistical analysis was conducted with SPSS 21.0 software. The Kolmogorov–Smirnov Z tests were used to determine whether the data were normally distributed. We used the mean ± SD or median (25th percentile, 75th percentile) as a description of the data. According to the distribution characteristics of the clinical data among groups, the measurement data were compared by ANOVA analysis for normally distributed data or Mann–Whitney U tests for abnormally distributed data. A P value < 0.05 (two-tailed) was considered statistically significant.

RESULTS

Clinical characteristics of the two groups before intervention

There was no significant difference in age, gender, course of diabetes, BMI, WHR, HbA1c, FBG, FINS, HOMA-IR, MBG, time in range (TIR), LDL, systolic blood pressure (SBP), diastolic blood pressure (DBP), alt, AST, bun, Cr, eGFR, or time intensity curve of carotid angiography between the two groups before intervention (P>0.05, table 1).

MBG and TIR differed between the two groups after 12 weeks of treatment

After 12 weeks of treatment, there were no significant differences in HbA1c or FBG between the two groups (P > 0.05, table 2). However, compared with group B, group A had statistically significant lower MBG and higher TIR (P<0.05, table 2). Studies have suggested that the therapeutic effect of reducing HbA1c and FBG with dapagliflozin was like that of glimepiride, but dapagliflozin was better at reducing average blood glucose and improving TIR. There were no significant differences in BMI, WHR, fins, HOMA-IR, LDL, SBP, DBP, ALT, AST, BUN, Cr, EGFR, or time intensity curve of carotid angiography between the two groups at 12 weeks (P> 0.05, table 2).

Time intensity curves of carotid angiography were improved after 48 weeks of treatment

After 48 weeks of treatment, the MBG of group A was lower than that of group B, and TIR was higher than group B, and the differences were statistically significant (p<0.05). On the other hand, HbA1c and FBG of the two groups were not statistically different (table 3).

Table 1: Clinical characteristics of the two groups before intervention

	Group A	Group B	F	P-value
N(Male/Female)	31(18/13)	29(18/11)	0.097	0.757
Age	55.90±13.49	57.54±12.14	0.223	0.639
Course (year)	5.00±2.73	5.77±2.07	1.367	0.248
HbA1c (%)	8.80±1.45	8.83±1.11	0.006	0.939
FPG(mmol/L)	8.76±1.98	8.88±2.01	0.031	0.86
FINS(uIU/ml)	11.85±5.06	11.16±5.07	0.251	0.619
HOMA-IR	4.74±2.63	4.54±2.65	0.08	0.778
MBG(mmol/L)	10.69±1.75	10.92±1.44	0.305	0.583
TIR(%)	32.31±13.67	29.31±11.25	0.78	0.381
TP(S)	31.00±5.45	30.50±6.13	0.103	0.75
PI(%)	58.11±5.03	60.13±7.46	1.408	0.241
AUC(dB/s)	1423.28±118.73	1404.07±130.53	0.327	0.57
BMI(kg/m^2)	25.44±4.46	26.60±5.93	0.681	0.413
WHR(cm/cm)	0.92±0.14	0.96±0.14	1.1	0.299
LDL(mmol/L)	2.58±0.96	2.98±1.04	2.19	0.145
SBP(mmHg)	129.55±16.56	129.00±14.46	0.017	0.896
DBP(mmHg)	83.79±8.19	84.96±10.44	0.216	0.644
ALT(U/L)	26.03±12.2	26.00±11.72	0	0.992
AST(U/L)	30.00±13.29	25.42±9.06	2.175	0.146
BUN(U/L)	7.16±1.62	6.96±1.74	0.183	0.671
Cr(umol/L)	75.93±11.44	76.00±12.48	0	0.983
eGFR($ml/min/1.73m^2$)	95.06±18.05	95.55±16.58	0.011	0.917

HbA1c: glycated hemoglobin |glycosylated hemoglobin; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; MBG: mean blood glucose; TIR: time in range; TP: peak time (the time from the injection of contrast agent to the maximum concentration in the region of interest) ; PI: peak intensity [contrast (the ratio of the maximum concentration of the agent in the region of interest to the reference region)]; AUC: area under the curve; BMI: body mass index; WHR: Waist-to-Hip Ratio; LDL: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: blood urea nitrogen; Cr: Serum creatinine; eGFR: glomerular filtration rate.

Table 2: Comparison of two groups after 12 weeks intervention

	Group A	Group B	F	P-value
N(Male/Female)	31(18/13)	29(18/11)	0.097	0.757
HbA1c (%)	7.32±1.69	7.10±1.42	0.255	0.616
FPG(mmol/L)	7.36±2.08	7.90±2.49	0.761	0.387
FINS(uIU/ml)	10.81±5.43	12.90±5.31	2.068	0.156
HOMA-IR	3.72±2.46	4.72±2.75	2.028	0.16
MBG(mmol/L)	8.99±2.25	10.26±2.07	4.708	0.035*
TIR(%)	66.72±16.89	49.73±12.35	17.786	0.000*
TP(S)	22.17±4.4	24.12±4.22	2.78	0.101
PI(%)	57.55±5.58	58.78±7.43	0.49	0.487
AUC(dB/s)	1379.20±133.65	1407.37±130.04	0.625	0.433
BMI(kg/m^2)	24.99±4.57	26.85±6.03	1.672	0.202
WHR(cm/cm)	0.91±0.14	0.96±0.14	1.771	0.189
LDL(mmol/L)	2.41±0.47	2.29±0.52	0.824	0.368
SBP(mmHg)	128.10±16.81	129.92±14.14	0.186	0.668
DBP(mmHg)	80.10±6.19	79.15±6.08	0.328	0.569
ALT(U/L)	32.17±9.29	29.12±12.02	1.126	0.293
AST(U/L)	26.24±13.71	25.85±12.49	0.012	0.912
BUN(U/L)	6.02±1.62	5.74±1.5	0.458	0.501
Cr(umol/L)	78.31±9.61	83.04±12.24	2.566	0.115
eGFR($ml/min/1.73m^2$)	90.42±17.42	88.95±19.67	0.086	0.77

FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; MBG: mean blood glucose; TIR: time in range; TP: peak time (the time from the injection of contrast agent to the maximum concentration in the region of interest) ; PI: peak intensity [contrast (the ratio of the maximum concentration of the agent in the region of interest to the reference region)]; AUC: area under the curve; BMI: body mass index; WHR: Waist-to-Hip Ratio;LDL: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: blood urea nitrogen; Cr: Serum creatinine; eGFR: glomerular filtration rate. * $p<0.05$

Table 3: Comparison of two groups after 48 weeks intervention

	Group A	Group B	F	P-value
N(Male/Female)	29(16/13)	26(16/10)	0.221	0.64
HbA1c (%)	6.36±1.81	6.92±1.44	1.678	0.207
FPG (mmol/L)	6.70±0.86	7.44±1.9	3.655	0.061
FINS (uIU/ml)	8.96±4.66	13.16±5.26	9.848	0.003*
HOMA-IR	2.89±1.9	4.38±2.28	6.996	0.011*
MBG (mmol/L)	8.84±2.53	10.32±1.95	5.8	0.021*
TIR (%)	69.17±17.72	49.46±13.79	20.848	0.000*
TP(S)	21.24±3.83	24.08±3.7	7.757	0.007*
PI (%)	54.19±6.07	61.52±6.78	17.869	0.000*
AUC (dB/s)	1291.17±162.25	1392.43±146.94	5.836	0.019*
BMI(kg/m^2)	23.93±4.25	26.92±6.03	4.599	0.037*
WHR	0.88±0.13	0.97±0.14	5.504	0.023*
LDL(mmol/L)	2.31±0.41	2.26±0.35	0.248	0.623
SBP(mmHg)	120.90±12.73	130.39±14.27	6.793	0.012*
DBP(mmHg)	79.90±4.99	79.54±6.48	0.053	0.818
ALT(U/L)	33.21±12.2	31.27±13.65	0.309	0.581
AST(U/L)	28.21±12.67	29.73±10.83	0.227	0.636
BUN(U/L)	6.20±1.63	6.32±1.73	0.065	0.815
Cr(umol/L)	78.48±13.84	79.42±14.83	0.059	0.809
eGFR($ml/min/1.73m^2$)	90.03±18.17	93.59±19.48	0.494	0.485

FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; MBG: mean blood glucose; TIR: time in range; TP: peak time (the time from the injection of contrast agent to the maximum concentration in the region of interest) ; PI: peak intensity [contrast (the ratio of the maximum concentration of the agent in the region of interest to the reference region)]; AUC: area under the curve; BMI: body mass index; WHR: Waist-to-Hip Ratio;LDL: low-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: blood urea nitrogen; Cr: Serum creatinine; eGFR: glomerular filtration rate. * $p<0.05$

This indicates that the blood glucose control of group A subjects was better. At the same time, FINS, HOMA-IR, BMI, WHR, and SBP of group A were lower than those of group B ($p<0.05$, table 3). Compared with subjects in group B, the parameters of carotid ultrasound contrast time-intensity curve in group A were statistically significant ($p<0.05$, table 3) and suggest that in carotid atherosclerotic plaques in group A, the density of neovascularization in the mass was lower and the plaques were more stable. There were no statistical differences in DBP, LDL, ALT, AST, BUN, Cr, or eGFR between the two groups of subjects ($p>0.05$, table 3).

DISCUSSION

According to our results, we found that dapagliflozin was significantly better than glimepiride in reducing MBG and improving TIR, and could more effectively stabilize blood glucose fluctuation. The long-term treatment of dapagliflozin has more advantages in reducing body weight, WHR, insulin level, insulin resistance, peak time, peak value and AUC of time intensity curve of carotid angiography, and in stabilizing and reducing carotid plaque and neovascularization.

In the past, HbA1c was used to evaluate blood glucose, and was used to describe the overall blood glucose control level of patients over the past three months. Compared with continuous glucose monitoring, HbA1c could not directly reflect blood glucose fluctuations. In 2019, the ADA considered TIR as the diabetes management standard, that is, the percentage of time that blood glucose was in the target range (3.9-10.0 mmol/L) within 24 hours as the indicator of continuous daily blood glucose monitoring. A recent study has found that in the relationship between HbA1C and TIR and TIR, a 10% change in TIR is equal to 9 mmol/mol change in HbA1C. Therefore, TIR is a good indicator for assessing glycemic control in individual patients (Tavarelli *et al.,* 2015). Our study found that there was no difference in HbA1c level reduction between the two groups, either at 12 or 48 weeks of treatment, but there was a significant difference in TIR that suggested that the ability of dapagliflozin in HbA1c reduction was similar to that of glimepiride, although dapagliflozin had a better effect in stabilizing blood glucose fluctuation. As a new type of hypoglycemic drug, the safety and effectiveness of dapagliflozin have been confirmed by some studies (Vigersky and McMahon, 2019; Mirabelli *et al.,* 2019 and Jabbour *et al.,* 2018). Diabetic patients were treated for 12 weeks (10 mg/d) continuously, and the amount of 24h urinary glucose could reach 70 g. The mechanism neither increased the secretion of insulin nor the accumulation of glucose and insulin, which stabilize blood sugar. A clinical study found that, compared with sulfonylureas, the incidence of hypoglycemia was lower (5.4% vs 51.6%) (Del Prato *et*

al., 2015), and the risk of hypoglycemia did not increase with long-term administration (Wilding *et al.,* 2013; Cox *et al.,* 2021). The lower the probability of hypoglycemia, the lower the frequency of rebound blood glucose fluctuations were observed.

Long-term poor blood glucose control is positively related to the incidence and mortality of micro vascular and macro vascular complications in T2DM patients (van Wijngaarden *et al.,* 2017). Jiao XM *et al*. found that the fluctuation of blood glucose could aggravate the injury of vascular endothelium in the lower extremity of T2DM patients, promoting progression of lower extremity angiopathy (Jiao *et al.,* 2014). Chronic hyperglycemia and acute glucose fluctuations caused by postprandial hyperglycemia can increase oxidative stress in diabetic patients leading to endothelial dysfunction (Maruhashi and Higashi*,* 2021). Endothelial cells produce and release some bioactive molecules to maintain the structure of intact vessels by balancing between oxidation and anti-oxidation (Katakami *et al.,* 2018). Long-term hyperglycemia or blood glucose fluctuation stimulation leads to a number of issues including excessive apoptosis and damage of vascular endothelial cells, activation of oxidative stress and inflammatory factors that cause macrophages to devour a large number of lipid substances, and increased platelet aggregation, all of which lead to atherosclerosis (Wu *et al.,* 2016; Terasaki *et al.,* 2015). The United Kingdom Prospective Diabetes study found that for every 1% decrease in HbA1c, the risk of diabetic micro vascular complications can be reduced by 37% (Stratton *et al.,* 2000). Kosiborod M found that HbA1c level was positively correlated with micro vascular complications, but not with macro vascular complications (Kosiborod *et al.,* 2018). As a new target to evaluate blood glucose fluctuation, TIR is not only closely related to risk of diabetic microangiopathy (Beck *et al.,* 2019), but it was also confirmed that the increase of TIR can reduce carotid intima-media thickness and the progress of diabetic macro vascular complications (Lu *et al.,* 2020).

In addition, insulin resistance is also an important cause of atherosclerosis in diabetic patients (Yahagi *et al.,* 2017). Insulin resistance can lead to lipid metabolism disorder, resulting in increased production of FFA, VLDL and triglycerides. Meanwhile, insulin resistance can promote mononuclear phagocytes through vascular endothelial cells, which increase foam cells, and accelerate the progression of atherosclerosis. Therefore, reduction of oxidative stress and insulin resistance are important means to delay diabetic macrovascular complications. A recent meta-analysis has found that a novel insulin resistance replacement index (triglyceride-glucose index, TyG) was positively associated with atherosclerotic cardiovascular diseases (HR 1.61, 95% CI1.29-2.01) and was an independent risk factor for coronary artery disease (Ding *et al.,* 2021). This study also found that compared with the glimepiride group (B), insulin level, HOMA-IR, BMI, and WHR were significantly lower in the dapagliflozin group after 48 weeks treatment. Moreover, the indexes of the time intensity curve of carotid angiography were significantly lower, suggesting that dapagliflozin can reduce the generation of new blood vessels in the carotid plaque, increasing its stability, and it has good efficacy in delaying the progression of macroangiopathy in diabetes patients. We believe that it may be related to the improvement of TIR but not the increase of insulin levels in the treatment group.

Studies have reported that SGLT2i has antioxidant properties (Dhillon *et al.,* 2019). It can reduce oxidative stress through inhibiting the generation of free radicals, thereby improving vasodilation to keep the blood flowing (Solini *et al.,* 2017). Due to reducing the occurrence of insulin resistance, dapagliflozin can increase insulin sensitivity and reduce the damage of insulin accumulation to the vascular endothelium (Daniele *et al.,* 2016). Another study found that dapagliflozin can improve endothelial cell function, reduce the expression of vascular adhesion molecules and inflammatory factors, inhibit macrophage overactivation and reduce foam cell production, thereby retarding the occurrence of atherosclerosis (Gaspari *et al.,* 2018). In animal experiments, dapagliflozin was shown to improve blood lipid levels, inhibit ROS-NLRP3-caspase-1 bypass, and reduce the release of inflammatory factors, thus delaying the progression of atherosclerosis in diabetic mice (Leng *et al.,* 2016). In recent studies, dagliazine has been found to reduce the risk of cardiovascular disease, chronic kidney disease, and all-cause mortality in patients with (HR 0.64 95%CI0.52 -- 0.79) and without (HR 0.95 -- 0.72) diabetes (Wheeler *et al.,* 2021). In our study, after 48 weeks of treatment, fasting insulin, HOMA-IR index, BMI, WHR and SBP of the dapagliflozin subjects were significantly lower than those in the glimepiride group. Considering that the improvement of the above indexes is closely related to the neovascularization in carotid atherosclerotic plaque, dapagliflozin has more advantages than glimepiride in improving diabetic macrovasculopathy and long-term application can significantly improve the occurrence and development of diabetic macroangiopathy.

In this study, we discussed the effect of dapagliflozin on the improvement of diabetic macrovascular complications, however, there are some limitations. The number of samples included was small and the observation time was short, so we cannot draw a definitive conclusion about causality. Repeating the design of dapagliflozin and diabetic macroangiopathy using animal models and long-term intervention experiments will lend greater validity to our findings. Furthermore, the thickness of intima media as a parameter of endothelial dysfunction should also be considered in future studies.

CONCLUSION

Compared with glimepiride, dapagliflozin has more advantages in improving TIR, MBG, SBP, BMI, WHR, and insulin resistance. At the same time, long-term application of dapagliflozin can improve the stability of carotid plaque in diabetic patients and delay the progression of macrovascular complications.

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