Int J Clin Exp Med 2017;10(3):5363-5371
www.ijcem.com /ISSN:1940-5901/IJCEM0018670

Original Article

Ultrasonic features of carotid plaque and its influencing factors in ischemic stroke patients with Type 2 diabetes mellitus

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Received October 28, 2015; Accepted March 25, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: Objective: We investigated ultrasonic features of carotid plaque and its influencing factors in ischemic stroke patients with Type 2 diabetes mellitus (T2DM). Methods: Patients with ischemic stroke (n = 255) was classified into T2DM group (n = 121) and non-T2DM group (n = 134) based on whether these patients were complicated with T2DM. Ultrasonic inspection was conducted to identify intima-media thickness (IMT), plaque, location, vulnerability, echoes, numbers and size, as well as artery stenosis, degree and numbers in common carotid artery (CCA), carotid bulb (CB) and internal carotid artery (ICA). Logistic regression analysis was conducted to clarify the possible risk factors for increased IMT, carotid plaque and artery stenosis. Results: T2DM group had higher incidence of carotid plaque than non-T2DM group (76.45% vs. 58.20%, P < 0.001). Significant differences on plaque vulnerability, states and echoes in CCA, CB and ICA and plaque number in ICA were found between two groups (all P < 0.05). The percentage of vessel injuries caused by artery stenosis in T2DM group was 30.17%, higher than 11.19% in non-T2DM group (P < 0.001). The number and distribution of injured vessels in ICA was differenced (both P < 0.05). Logistic regression analysis demonstrated that T2DM, CHD state, Hcy and FBG levels were the factors influencing IMT increasing in CCA (all P < 0.05), T2DM, CHD state, alcohol consumption and hsCRP were the factors influencing the presence of plaque (all P < 0.05), and T2DM state, tobacco smoking and alcohol consumption were the factors influencing the presence of artery stenosis (all P < 0.05). Conclusion: Application of ultrasonic image of carotid plaque in ischemic stroke is recommended, which exhibits guiding significance for prediction of ischemic stroke patients with T2DM.

Keywords: Type 2 diabetes mellitus, ischemic stroke, ultrasonic inspection, carotid plaque, artery stenosis, intima-media thickness

Introduction

Diabetes mellitus (DM) is a pandemic chronic metabolic disorder throughout the entire world and is a high risk factor for ischemic stroke [1]. Type 2 diabetes mellitus (T2DM) makes up about more than 90% cases of DM [2]. Due to its chronic nature and multiple vascular complications, it is estimated that 439 million people worldwide will have T2DM by the year 2030 [3]. Both lifestyle and genetic factors are implicated in the etiology of T2DM, especially physical inactivity, sedentary lifestyle, cigarette smoking and generous alcohol consumption and obesity [4-6]. As a major risk factor for vascular complication, T2DM may result in vascular damage during its disease course, thus elevate the risk of developing ischemic stroke [7]. Specially, epidemiological study suggested that T2DM was associated with the increasing risk of vascular diseases which were the most prevalent cause of mortality in patients with T2DM [8]. Additionally, inflammation of atherosclerotic plaques is a well-defined risk factor in the development of ischemic stroke and myocardial infarction [9]. As the disruption of atherosclerotic plaque may lead a predominant part in the occurrence of cardiovascular diseases (CVD), it was considered of great importance to identify the tissue characterization of plaque lesions in patients with T2DM [10].

Table 1. Comparisons on clinical data between T2DM group and non-T2DM group

	T2DM group (n = 121)	Non-T2DM group (n = 134)	t/χ²	*P*
Sex (male/female)	73/47	89/44	1.014	0.314
Age (years)	59.25 ± 9.72	60.64 ± 10.42	0.564	0.573
BMI (kg/cm²)	24.11 ± 4.01	22.85 ± 3.61	2.641	0.009
CHD (yes/no)	76/45	74/60	1.511	0.219
Tobacco smoking (yes/no)	91/30	88/46	2.763	0.097
Alcohol consumption (yes/no)	100/21	101/33	2.014	0.156
TC (mmol/L)	5.0 ± 0.9	5.1 ± 1.1	0.798	0.426
TG (mmol/L)	1.22 ± 0.22	1.15 ± 0.21	1.856	0.065
LDL-C (mmol/L)	3.01 ± 0.69	2.26 ± 0.51	9.932	< 0.001
HDL-C (mmol/L)	1.04 ± 0.13	1.31 ± 0.18	13.6	< 0.001
hs-CRP (mg/L)	13.17 ± 3.23	12.20 ± 4.02	2.133	0.034
FIB (g/L)	6.06 ± 0.99	3.79 ± 1.02	18	< 0.001
Hcy (umol/L)	11.13 ± 3.13	10.32 ± 4.21	1.728	0.085
FBG (mmol/L)	8.44 ± 1.29	5.14 ± 0.61	25.67	< 0.001
Leukocyte (×10⁹/L)	8.47 ± 0.84	7.81 ± 0.76	1.597	0.112

T2DM, Type 2 diabetes mellitus; BMI, Body mass indexes; CHD, Coronary heart disease; TC, Total cholesterol; TG, Triglyceride; LDL-C, Low density lipoprotein-cholesterol; HDL-C, High density lipoprotein-cholesterol; hs-CRP, High-sensitivity C-reactive protein; FIB, Fibrinogen; Hcy, Homocysteine; FBG, Fasting blood glucose.

Presently, various modalities including Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are being applied to detect the atherosclerotic plaque in CVD and carotid arteries [11, 12]. Carotid plaque mainly happens in carotid bulb (CB) and internal carotid artery (ICA), but it also occurs in common carotid artery (CCA) in severe atherosclerotic diseases [13]. It was widely recognized that several risk factor may influence the disruption of atherosclerotic plaque, including content of lipid, neovascular vessel, inflammation in plaque and plaque vulnerability [10]. Moreover, previous evidence implied that majority of patients with stroke had moderate or severe carotid stenosis caused by unstable carotid plaque [14]. Therefore, scanning on carotid arteries and assessment of plaque may contribute to the identification of CVDs [15]. Ultrasonic measurement on the carotid atherosclerosis is a simple, safe, and reliable method, and thus, the intima-media thickness (IMT) and plaque size have been utilized as index in the ultrasonography [16]. Doppler ultrasound can provide information both on the degree of carotid stenosis in carotid artery and the characteristics of the atherosclerotic plaques [17, 18]. Considering these points, we suspected that that the occurrence of ischemic stroke in patients with T2DM was related to the ultrasonic features of carotid atherosclerosis plaque. As majority studies have examined relationships between the occurrence of ischemic stroke and ultrasonic features of carotid atherosclerosis or blood glucose measurements in patients with T2DM [16, 19, 20], few study investigated the combined results of ultrasonic features of carotid atherosclerosis and blood glucose measurements. In currents study, we aims to clarify the association between ultrasonic features of carotid plaque in patients T2DM and the risk of ischemic stroke by comparing the ultrasonic features of carotid atherosclerosis and blood glucose measurements in patients with or without T2DM.

Methods and materials

Ethics statement

The study was carried out with the approval of the ethics committee of the First Affiliated Hospital of Xinxiang Medical College. Written, informed consent was collected for each patient before the study. Study protocols were based on the ethical principles for medical research of the Helsinki Declaration [21].

Subjects

Two hundred twenty five patients with ischemic stroke were included in this study, all of which were recruited prospectively from the First Affiliated Hospital of Xinxiang Medical College from March 2014 to March 2015. All included patients were diagnosed and confirmed by cranial CT or MRI, and met the criteria defined by the Fourth Academic Conference of National Cerebral Vascular Disease [22]. Included 255 patients were classified into T2DM group (n =

Table 2. The intima-media thickness (IMT) on common carotid artery, carotid bulb and two sides of internal carotid artery of patients in T2DM group and non-T2DM group (mm)

	Common carotid artery		Carotid bulb		Internal carotid artery	
	T2DM group	Non-T2DM group	T2DM group	Non-T2DM group	T2DM group	Non-T2DM group
Left	0.82 ± 0.46	0.76 ± 0.46	0.85 ± 0.45	0.82 ± 0.44	0.82 ± 0.43	0.78 ± 0.39
Right	0.80 ± 0.45	0.74 ± 0.45	0.85 ± 0.42	0.79 ± 0.44	0.79 ± 0.43	0.76 ± 0.40

T2DM, Type 2 diabetes mellitus.

121) and non-T2DM group (n = 134). T2DM patients were diagnosed and confirmed if they met one of the following three criteria set by the China guideline for T2DM (2007 version) [23], which were as followed: (1) presence of clinical indications (polydipsia, polydipsia or unexplained weight loss), fasting blood glucose ≥ 7.0 mmol/L or 2 h postprandial blood glucose ≥ 11.1 mmol/L; (2) absent with clinical indications with double checked fasting blood glucose ≥ 7.0 mmol/L or 2 h postprandial blood glucose ≥ 11.1 mmol/L; (3) patients with fasting blood glucose ≥ 7.0 mmol/L or 2 h postprandial blood glucose ≥ 11.1 mmol/L, 2-hours blood glucose after oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L. The patients were excluded from current study if they had hemorrhagic cerebrovascular disease, acute orchronic infectious diseases, diabetic ketoacidosis, severe liver dysfunction, severe renal dysfunction, hyperthyroidism, pulmonary fibrosis, collagenous diseases, tumors or hematological diseases.

Instruments and detection methods

All ultrasonography were done using an American GE LOGIQ700 ultrasound machine and an 8-12 MHz multiband linear transducer (GE Company, American) with 2 experienced doctors in our Diagnosis Department for the vascular examination. The subjects were in supine position with cervical and shoulder relaxed. When the patients were under inspection on the unilateral carotid, they were required to tilt their heads to the opposite side to fully expose the skin. The transducer were horizontally and longitudinally inspected the carotid area from clavicular fossae of sternocleidomastoid muscle to CCB, ICA and external carotid artery. The inspection on the ICA must extend to the intracranial part. The increased carotid IMT, atheromatous plaque and atheromatous plaque location and ultrasonic features (ultrasound echo, size and shape) were recorded. After Doppler spectrum was observed, Doppler sample volume (2~4 mm) was selected in the central of lumen, with 1.5 cm and 1.0~1.5 cm respectively to the proximal and distal part of bifurcation. Paralleled with the acoustic beam, the flow direction of vascular was in an angle of ≤ 60° with the acoustic beam direction. The carotid stenotic rate was calculated by observing the peak systolic velocity (PSV) and end of diastolic velocity (EDV).

Criteria for carotid atherosclerosis plaque

The absence with carotid IMT (IMT < 1.0 mm) or presence with carotid IMT (1.0 mm < IMT < 1.5 mm) can be considered as criteria for the presence of carotid atherosclerosis plaque. The criteria for carotid atherosclerosis plaque were: intimal single or multiple lesions were detected both transverse and vertical sectionaly in artery lumen. Moreover, the vertical dimension between fibrous cap on plaque surface and the front part of outer wall more than 1.5 cm. The diagnostic standards of carotid stenosis were strictly based on society of radiologists in ultrasound consensus conference: (1) slight stenosis: < 50%: PSV < 125 cm/s, EDV < 40 cm/s; (2) moderate stenosis: 50%~69%: 125 cm/s < PSV < 230 cm/s, 40 cm/s < EDV < 100 cm/s; (3) severe stenosis: 70%~99%: PSV > 230 cm/s, EDV > 100 cm/s; (4) total occlusion: missing blood flow signals in lumen and undetectable flow spectrum.

Biochemical indexes detection

Fasting blood glucose (FBG), high-sensitivity C-reactive protein (hs-CRP), total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), Fibrinogen (FIB) and Homocysteine (Hcy) were detected in each patients by extracting venous blood with empty stomach in the early morning.

Table 3. The ultrasonic features of carotid plaque of different position in carotid artery between T2DM group and non-T2DM group

	n	Carotid plaque vulnerability		State of plaque		Echo intensity				Plaque location			Plaque number	
		Stable plaque	Vulnerable plaque	Regular	Irregular	Low	Middle	Strong	Inhomogeneous	Left	Right	Both sides	Single	Multiple
Carotid artery														
T2DM group	35	10	25	14	21	15	5	4	11	18	7	10	20	15
Non-T2DM group	33	25	8	26	7	2	12	11	8	17	4	12	23	10
χ^2		15.14		10.55		16.52				2.636			1.151	
P		< 0.001		0.001		< 0.001				0.268			0.283	
Carotid bulb														
T2DM group	78	20	58	36	42	4	14	21	39	18	20	40	27	51
Non-T2DM group	88	44	44	60	28	1	32	42	13	11	17	60	20	68
χ^2		12.1		8.227		28.34				4.37			2.879	
P		< 0.001		0.004		< 0.001				0.113			0.09	
Internal carotid artery														
T2DM group	72	25	47	23	49	23	14	10	25	18	20	34	18	54
Non-T2DM group	35	20	15	27	8	2	4	18	11	10	11	14	18	17
χ^2		4.858		19.33		20.59				0.338			7.368	
P		0.028		< 0.001		< 0.001				0.845			0.007	

T2DM, Type 2 diabetes mellitus.

Table 4. The degree, distribution and number of damaged vessels by artery stenosis in T2DM group and non-T2DM group

Degree of artery stenosis	Carotid artery		Carotid bulb		Internal carotid artery	
	T2DM group	Non-T2DM group	T2DM group	Non-T2DM group	T2DM group	Non-T2DM group
Slight stenosis	2	3	6	8	18	10
Moderate stenosis	3	1	3	2	17	4
Severe stenosis	1	0	1	1	15	0
Total occlusion	2	0	0	1	5	0
χ^2	3.225		1.315		9.23	
P	0.358		0.726		0.026	

T2DM, Type 2 diabetes mellitus.

Table 5. Logistic regression analysis on the increased intima-media thickness (IMT) in common carotid artery (CCA)

	B	S.E.	Wald	Sig.	Exp (B)	95% CI
T2DM	1.86	0.95	3.86	0.049	6.43	1.01-41.21
CHD	0.9	0.36	6.45	0.011	2.47	1.23-4.95
Hcy	0.17	0.05	11.63	0.001	1.18	1.07-1.31
FBG	0.6	0.19	9.62	0.002	1.82	1.25-2.66

T2DM, Type 2 diabetes mellitus; CHD, Coronary heart disease; Hcy, Homocysteine; FBG, Fasting blood glucose; S.E., Standard error; 95% CI, 95% confidence interval.

Statistics analysis

Data analysis was conducted using SPSS 22.0 software. Continuous data were expressed mean ± standard deviation (SD). Comparisons between two groups were determined by *t* test. Categorical data were calculated using χ^2 or Fisher's exact probability. The multivariate statistical analysis between the increased carotid IMT, the presence of carotid atherosclerosis plaque, carotid stenosis and biochemical indexes were identified by non-conditional logistic regression analysis. *P* value of less than 0.05 was regarded as statistical significance.

Results

Comparisons on clinical data

The comparisons on clinical data between T2DM group and non-T2DM group were presented in **Table 1**. T2DM group included a total of 121 patients with 73 male and 47 female. The mean age for T2DM group were 58.76 ± 19.7 years, ranged from 40~83 years. The clinical symptoms for T2DM group includes dizziness (n = 66), weakness of extremities (n = 52), limb numbness (n = 21), trouble in speaking (n = 18), headache (n = 9) and unconsciousness (n = 3). A sum of 134 patients was included in the non-T2DM group, consisting of 89 male and 44 female. The age range was 38~86 years with a mean age of 60.64 ± 10.42 years. The clinical symptoms for non-T2DM group includes dizziness (n = 70), weakness of extremities (n = 36), limb numbness (n = 18), trouble in speaking (n = 10), headache (n = 6) and unconsciousness (n = 4). Compared with the non-T2DM group, patients in T2DM group had an increased trend in body mass index (BMI), plasma LDL-C, hs-CRP, FBG, FIB levels and a decreased HDL-C level (all $P < 0.05$). The comparisons on sex, coronary heart disease (CHD) rate, tobacco smoking, alcohol consumption, TC, TG, Hcy, leukocyte between two groups were not statistically significant (all $P > 0.05$).

Comparisons on carotid IMT in two groups

The IMT in CCA, CB and two sides of ICA were increased in T2DM group than non-T2DM group, failed to achieve significance (all $P > 0.05$) (**Table 2**). The percentage of increased IMT in CCA, CB and ICA in T2DM group were respectively 37.60% (91/242), 40.91% (99/242), 40.08% (97/242), comparing to 38.06% (102/268), 41.04% (110/268), 33.21% (64/268) in non-T2DM group without statistical significance (CCA: $\chi^2 = 0.011$, $P = 0.916$; CB: $\chi^2 = 0.112$, $P = 0.738$; ICA: $\chi^2 = 2.593$, $P = 0.107$).

Ultrasonic features of carotid plaque

The incidence of carotid plaque in T2DM group were 76.45% (185/242), which was significantly higher than 58.20% (156/268) in non-T2DM group ($\chi^2 = 19.09$, $P < 0.001$). Carotid plaque vulnerability, state of plaque and echo intensity between two groups were remarkably different (all $P < 0.005$), as well as in CCA, CB and ICA (all $P < 0.005$). No significance on the plaque location and plaque number in CCA, CB was detected between two groups (all $P > 0.05$). The

Table 6. Logistic regression analysis on the plaque in common carotid artery (CCA)

	B	S.E.	Wald	Sig.	Exp (B)	95% CI
T2DM	1.55	0.75	4.34	0.037	4.73	1.1-20.38
CHD	0.64	0.28	5.3	0.021	1.89	1.1-3.26
Alcohol consumption	0.82	0.35	5.63	0.018	2.28	1.15-4.49
hsCRP	0.09	0.04	5.44	0.02	1.09	1.01-1.18

T2DM, Type 2 diabetes mellitus; Hcy, Homocysteine; S.E., Standard error; 95% CI, 95% confidence interval.

Table 7. Logistic regression analysis on the carotid stenosis in common carotid artery (CCA)

	B	S.E.	Wald	Sig.	Exp (B)	95% CI
T2DM	2.12	0.91	5.49	0.019	8.37	1.42-49.51
Tobacco smoking	0.84	0.38	4.87	0.027	2.33	1.1-4.93
Alcohol consumption	0.86	0.42	4.13	0.042	2.35	1.03-5.37

T2DM, Type 2 diabetes mellitus; S.E., Standard error; 95% CI, 95% confidence interval.

plaque number in ICA between two groups was statistically significant ($P < 0.05$), but no significance was detected on the plaque location ($P > 0.05$) (**Table 3**).

Artery stenosis

The number of injured vessels caused by artery stenosis in T2DM group were 73/242 (30.17%), which was significant higher than 30/268 (11.19%) in non-T2DM group ($\chi^2 = 25.84$, $P < 0.001$). The injured vessels caused by artery stenosis in CCA and CB failed to show any significant difference between T2DM group and non-T2DM group (CCA: T2DM group vs. non-T2DM group: 8/242 (3.31%) vs. 4/268 (1.49%), $\chi^2 = 1.82$, $P = 0.177$; CB: T2DM group vs. non-T2DM group: 10/242 (4.13%) vs. 12/268 (4.48%), $\chi^2 = 0.038$, $P = 0.848$). However, the number of injured vessels caused by artery stenosis in ICA was notably higher in T2DM group than non-T2DM group (55/242 (22.73%) vs. 14/268 (5.22%), $\chi^2 = 29.80$, $P < 0.001$). The degree of artery stenosis in vessels in ICA was higher in T2DM group compared with non-T2DM group ($\chi^2 = 9.230$, $P = 0.026$), while no significance was detected in CCA, CB on artery stenosis between two groups (CCA: $\chi^2 = 3.225$, $P = 0.358$; CB: $\chi^2 = 1.315$, $P = 0.726$) (**Table 4**).

Logistic regression analysis

With the presence of increased IMT in CCA, plaque and artery stenosis as dependent variables, and T2DM, sex, age, BMI, CHD state, tobacco smoking, alcohol consumption, TC, TG, LDL-C, HDL-C, hs-CRP, FIB, Hcy, FBG and leukocyte as independent variables, multivariate and non-conditional logistic regression analysis was performed. The results demonstrated that T2DM, CHD state, Hcy and FBG levels were the factors influencing IMT increasing in CCA (all P < 0.05) (**Table 5**), T2DM, CHD state, alcohol consumption and hsCRP were the factors influencing the presence of plaque (all P < 0.05) (**Table 6**), and T2DM state, tobacco smoking and alcohol consumption were the factors influencing the presence of artery stenosis (all P < 0.05) (**Table 7**).

Discussion

The present study was conducted to investigate ultrasonic features of carotid plaque and its influencing factors in ischemic stroke patients with. Our results confirmed that ischemic stroke patients with T2DM had increased IMT in CCA compared with patients without T2DM, implying that patients with T2DM had a great chance of developing atherosclerosis plaque. In support with our main findings, our results also defined that the carotid plaque and carotid artery stenosis was more severed in patients with T2DM compared to patients without T2DM. Also, the logistic regression analysis demonstrated that the risk factors for increased IMT in CCA include T2DM, CHD state, Hcy and FBG levels in patients with T2DM. Moreover, we also identified that the presence of carotid plaque might mainly depends on T2DM, CHD state, alcohol consumption and hsCRP, and carotid artery stenosis on T2DM, tobacco smoking and alcohol.

T2DM is an important risk factor for atherosclerotic diseases like CHD, ischemic stroke, and other CVD events [24, 25]. Our analysis suggested that smokers had a higher prevalence of having increased carotid IMT, which was consistent with previous study reported by kota et al. [8]. Our results also implied that patients with T2DM had an elevated chance of developing increased carotid IMT than patients without T2DM. Considering the potential correlations between atherosclerosis and CVD events, it is of great importance to find ultrasonic indexes for atherosclerosis identification. Carotid IMT is a reliable marker of preclinical atherosclerosis and predicts future risk for CHD and stroke [26]. Increased IMT, visualized with ultrasonography, was of curial important in the prognostic value for the development of CVD, as well as for the development of atherosclerotic plaque in carotid and peripheral arteries [19]. Epidemiologic studies have also reported the positive association between duration of DM, hypertension and IMT [27, 28]. In agreement with our results, a meta-analysis comprising of 102 prospective studies clarified that DM alone confers a more than 2-3 fold excess risk for CVD events [29]. Agarwal *et al.* found a higher carotid IMT in patients with both DM and coronary artery disease (CAD), which once again lead to the conclusion that carotid IMT is a reliable marker for CAD in patients with DM [30]. Major determinants of increased IMT among diabetic patients include obesity, lipid abnormality and hyperinsulinaemia, which formed the cardinal features of insulin resistance syndrome [19]. Furthermore, a study conducted by DeFronzo et al. identified that the accelerate incidence of CVD in patients with T2DM may be explained by insulin resistance, which was resulted from impaired insulin signaling through the phosphoinositol-3 kinase pathway with intact signaling through the mitogen-activated protein kinase pathway [31].

Our results found that patients without T2DM had a decreased LDL-C, HDL-C, FIB and FBG levels compared with patients with T2DM, implying the benefits of lipoprotein reduction in patients with ischemic stroke. Our results also found that the increased LDL-C level, FIB level and FBG level were correlated with the carotid plaque and artery stenosis in patients with T2DM. T2DM is a gradual developed disease with the failure of β-cell function in the presence of chronic insulin resistance [32]. Patients with T2DM were presented with atherogenic lipoprotein abnormalities with an increase of LDL-C, TG levels and lowering of HDL level [33]. Cholesterol plays a major role in atherosclerosis and LDL-C is the major carrier of cholesterol in the blood [34]. In patients with abnormal lipoprotein, elevated lipid parameters have been associated with increased subclinical atherosclerosis and an increased risk for CVD [35]. Plasma TG, HDL-C and LDL-C are independently related with insulin resistance and risk factors of CVD since the insulin could affect the HDL-C and LDL-C metabolism [36]. Supported with our results, Anderwald et al. also confirmed that elevated LDL-C was related to increased carotid IMT in patients with family history of T2DM [37].

In summary, our study demonstrated that application of ultrasonic image of carotid plaque in ischemic stroke is recommended, which exhibits guiding significance for prediction of ischemic stroke with T2DM. With regard to using ultrasonic features of carotid plaque to predict the risk of ischemic stroke patients with T2DM, we plan to investigate this interesting aspect in more detailed in the future.

Acknowledgements

We are grateful for the reviewers for their helpful comments in this manuscript.

Disclosure of conflict of interest

None.

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