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ORIGINAL

Serum adropin levels are decreased in Chinese type 2 diabetic patients and negatively correlated with body mass index

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Abstract. Adropin has been identified as potent regulatory hormone implicated in insulin sensitivity and the maintenance of energy homeostasis. The aim of current study was to investigate serum adropin concentrations of type 2 diabetes mellitus (T2DM) patients in the fasting status, especially those overweight/obese and evaluate the relationships between adropin levels and metabolic parameters. A total of 116 T2DM patients and 60 controls with normal glucose tolerance (NGT) were recruited to the study. Adropin concentration was determined using commercial ELISA kits. Anthropometric characteristics were collected and biochemistry, glycosylated hemoglobin A_1c (HbA_1c) and fasting insulin (FIns) were detected by clinical laboratory. Insulin resistance was estimated by homeostasis model 2 assessment of insulin resistance (HOMA2-IR). Serum adropin levels in Chinese T2DM patients were decreased compared with the controls [3.8 (3.0–5.5) *vs.* 5.5 (3.7–7.9) ng/mL, $p < 0.01$]. Meanwhile, overweight/obese patients had more considerably reduced levels of adropin. Adropin level was negatively correlated with body mass index (BMI), high-sensitive C reactive protein (hs-CRP), triglycerides (TG), fasting plasma glucose (FPG), FIns, HOMA2-IR and HbA_1c, while positively with high-density lipoprotein cholesterol (HDL-C) in study participants ($p < 0.01$). The correlations of adropin with glucolipid variables (TG, HDL-C, FPG, FIns, HOMA2-IR, HbA_1c) still existed after adjusting the effect of BMI. Besides, HOMA2-IR and HbA_1c were independent factors associated with serum adropin levels. Binary logistic regression analyses showed that adropin was significantly associated with T2DM after removing confounding factors ($p < 0.01$). Receiver operating characteristic (ROC) curve demonstrated adropin concentration of 5.8 ng/mL could be used as a possible optimal cut-off value to identify T2DM from non-T2DM with sensitivity of 81.9% and specificity of 46.7%. Serum adropin concentrations are decreased in Chinese T2DM patients, especially those overweight/obese. Adropin, associated with glucolipid homeostasis and insulin sensitivity, may implicate in the pathogenesis of T2DM.

Key words: Adropin, Type 2 diabetes, Insulin resistance, Obesity

IN RECENT YEARS, the prevalence of diabetes has been steadily increasing around the world, with China having the largest number of patients [1, 2]. A nationwide survey of the Chinese adult population reported that the estimated overall prevalence of diabetes was 10.9%, and that for pre-diabetes was 35.7% in 2013 [3]. Type 2 diabetes mellitus (T2DM) is usually linked with obesity and insulin resistance, which develops when pancreatic β cells cannot compensate by producing more insulin [4]. Nowadays, there is growing evidence suggesting that liver-secreted factors play critical roles in modulation of systemic metabolism and energy homeostasis especially during periods of changed nutrition status [5-8].

Adropin, a secreted protein identified in 2008, is preferentially expressed in the liver [9]. It, encoded by the *Energy Homeostasis Associated (Enho)* gene, consists of

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76 amino acids, which is highly conserved in eutherian mammals such as human, mouse and rat [9]. As was reported that, tissue adropin levels in diabetic rats were as follows: Pancreas > liver > kidney > heart > brain > cerebellar tissues [10]. As dietary fat regulated adropin expression in mice [9, 11], Butler *et al.* further reported that dietary fat intake could rapidly increase circulating adropin levels in some individuals with low plasma adropin concentrations at baseline [12]. The stimulation of macronutrient consumption like fat on plasma adropin concentrations in humans requires further investigation by lack of critical evidence regarding the molecular mechanisms by which adropin expression is influenced. With the development of obesity, decreased adropin transcripts in liver or concentrations in serum was associated with the deterioration of metabolic homeostasis, including pronounced insulin resistance and increased adiposity in liver [9, 13]. Meanwhile, it was shown that adropin-knockout (AdrKO) mice on the C57BL/6J background exhibited remarkable insulin resistance, dyslipidemia and adiposity in liver [13]. In addition, adropin transgenic over-expression or administration treatment promoted glucose utilization, improved hyperinsulinemia and attenuated hepatic steatosis not only in diet-induced obesity (DIO) mice but also in streoptozotocin-induced type 2 diabetic rats [9, 14]. Except for observations on animals, reduced adropin concentration in human is usually related to increased risk of metabolic disorders, involving gestational diabetes mellitus (GDM), metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS) [15-19].

Considering the evidence mentioned above [9, 10, 12-19], adropin might possess potent effects on metabolic adaptation to macronutrients, modulation of insulin sensitivity and maintenance of energy homeostasis. It is most likely, but still lack of evidence that adropin might be involved in the occurrence and development of T2DM. The current study was designed to investigate the serum adropin concentrations of Chinese T2DM patients in the fasting state, especially those overweight/obese and evaluate the relationships between adropin levels and metabolic parameters.

Materials and Methods

Subjects

A total of 116 T2DM patients hospitalized at the First Affiliated Hospital of Soochow University and 60 healthy controls from medical examination center were enrolled in our study. The diagnosis of T2DM was confirmed according to the American Diabetes Association diagnostic criteria 2011 [20]. Healthy controls all underwent standard 75 g oral glucose tolerance test to ensure normal glucose tolerance (NGT). Body mass index (BMI) ≥25 kg/m^2 was identified as overweight/obesity based on World Health Organization Technical Report, while BMI 18.5–25 kg/m^2 was known as normal weight [21]. Subjects with type 1 diabetes, secondary diabetes, GDM, infection, malignant tumor, severe hepatic insufficiency or end-stage renal failure were excluded. None have received antihypertensive or hypolipidemic therapies in the last month before enrollment. The protocol of the study approved by the local ethics committee. Details about the present study were explained to the eligible subjects and informed consents were obtained.

Anthropometric and biochemical measurements

Anthropometric and clinical characteristics were collected from hospital case files, including age, gender, blood pressure, height, weight, smoking, drinking and medical history. BMI, an assessment of general obesity, was calculated as body weight in kilograms/height square in meters (kg/m^2). Samples of venous blood were taken after overnight fasting for at least 10 h. Fasting plasma glucose (FPG) was immediately measured using the glucose oxidase technique. High-sensitive C reactive protein (hs-CRP) and lipid profiles including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined on the Hitachi 7600 analyzer (Kyoto, Japan). Glycosylated hemoglobin A_1c (HbA_1c) was measured using cation-exchange column chromatography on an automatic analyzer (Bio-Rad Company, Hercules, California, USA). Fasting insulin (FIns) was detected using ELISA kits (R&D company, USA). Insulin resistance was estimated by homeostasis model 2 assessment of insulin resistance (HOMA2-IR). HOMA2 Calculator (The Oxford Center for Diabetes, Endocrinology and Metabolism, England) was obtained to estimate insulin resistance index for an individual from simultaneously measured FPG (mmol/L) and FIns (uU/mL). Blood samples were centrifuged and then serum samples were stored at –80°C until laboratory analyses. Determination of serum adropin was based on commercially available ELISA kits (DL Sci & Tech Development Co., Ltd., Wuxi, CN). The detection range of the assay was 0.156–10 ng/mL. The minimum detect-

able dose of adropin is typically less than 0.065 ng/mL. The inter-assay and intra-assay coefficients of variation were less than 12% and 10%, respectively. The assay procedure strictly complied with instruction manual.

Statistical Analysis

Data analyses were performed using the SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). All values were presented as mean ± SD or median (25th and 75th percentiles) for continuous variables and as number or percentage for categorical data. Data that were not normally distributed were logarithmically transformed before analyses. Student's *t*-test was used to compare the differences between two groups, while One-way ANOVA was used for multiple comparisons. Categorical data were examined by χ^2 test. Pearson's correlation was performed to evaluate the associations between serum adropin levels and metabolic parameters. Partial correlation was then used to determine the associations after adjusting for the effects of BMI. To further explore independent factors associated with serum adropin levels, multiple regression analyses were performed, simultaneously examining related factors found in simple correlation analyses. Binary logistic regression analyses were applied to examine odds ratio per 1 ng/mL increase in adropin levels for prevalence of T2DM after removing confounding factors. Receiver operating characteristic (ROC) curve was drawn to ascertain whether serum adropin levels would become a biomarker of T2DM and determine the area under curve (AUC) and cut-off value. In the current study, a two-tailed p value < 0.05 was considered statistically significant.

Results

Characteristics of study participants (Table 1)

Gender, age, current smoker and alcohol drinking were comparable in study groups. There were no significant differences between T2DM and control group with respect to TC. Subjects in T2DM group had higher levels of BMI, blood pressure, TG, LDL-C, hs-CRP, FPG, HbA_1c, FIns and HOMA2-IR ($p < 0.05$ or $p < 0.01$), while lower levels of HDL-C ($p < 0.01$). Serum adropin levels in T2DM patients were remarkably decreased compared with the control group ($p < 0.01$).

Table 1 Anthropometric and biochemical characteristics of the study groups

Parameters	Control	T2DM	*p* value
N (Male/Female)	60 (32/28)	116 (68/48)	0.502
Age (years)	44.85 ± 9.92	48.24 ± 11.48	0.054
BMI (kg/m^2)	23.47 ± 2.45	25.21 ± 3.63	0.001
Current smoker (*n*)	14	24	0.686
Alcohol drinking (*n*)	5	6	0.622
SBP (mmHg)	119.27 ± 12.38	125.97 ± 9.80	0.000
DBP (mmHg)	73.72 ± 10.50	78.20 ± 9.05	0.004
TG (mmol/L)*	1.05 (0.80–1.52)	1.43 (0.89–2.07)	0.01
TC (mmol/L)	4.37 ± 0.67	4.41 ± 0.92	0.788
LDL-C (mmol/L)	2.45 ± 0.63	2.72 ± 0.79	0.025
HDL-C (mmol/L)	1.50 ± 0.26	1.27 ± 0.28	0.000
Hs-CRP (mg/L)*	1.07 (0.91–1.25)	1.71 (0.96–3.02)	0.000
FPG (mmol/L)	5.19 ± 0.32	8.34 ± 2.39	0.000
HbA_1c (%)	5.50 ± 0.25	9.46 ± 1.93	0.000
FIns (uU/mL)	7.25 ± 1.57	10.91 ± 5.54	0.000
HOMA2-IR*	0.96 (0.79–1.12)	1.54 (0.88–2.16)	0.000
Adropin (ng/mL)*	5.5 (3.7–7.9)	3.8 (3.0–5.5)	0.000

* Ln-transformed variable, values are given as median (25th and 75th percentiles).

The clinical and biochemical parameters of subjects based on the tertiles of adropin (Table 2)

Compared with subjects in the middle or upper serum adropin tertile, subjects in the lower tertile had higher levels of BMI, TG, FIns and HOMA2-IR ($p < 0.05$ or $p < 0.01$). In addition, subjects in the upper tertile had the lowest levels of FPG and HbA_1c, while highest levels of HDL-C among study groups ($p < 0.05$ or $p < 0.01$). The prevalence of T2DM was 79.7%, 70.7% and 47.5% in the low, medium and high serum adropin groups, respectively ($\chi^2 = 14.496$, $p = 0.001$). The percentage of overweight/obesity decreased as adropin concentrations elevated ($\chi^2 = 17.246$, $p = 0.000$).

Serum adropin level according to BMI (Table 3)

Serum adropin level of overweight/obesity group was lower than that of normal weight group within study participants ($p < 0.05$). Serum adropin level of T2DM patients was significantly lower than that of control group at each BMI rank ($p < 0.05$).

Correlation of adropin with clinic parameters and T2DM (Tables 4, 5, Fig. 1)

As to adropin level in all study participants, it was

Table 2 The clinical and biochemical parameters of subjects based on the tertiles of adropin

Parameters	Lower tertile	Middle tertile	Upper tertile
N (Male/Female)	59 (36/23)	58 (30/28)	59 (34/25)
Age (years)	46.00 ± 12.06	46.62 ± 11.59	48.63 ± 9.36
BMI (kg/m^2)	26.19 ± 3.63	24.50 ± 3.28^{a}	23.17 ± 2.44^{ab}
Current smoker (*n*)	12	12	14
Alcohol drinking (*n*)	2	4	5
SBP (mmHg)	125.19 ± 11.38	123.31 ± 11.82	122.56 ± 10.31
DBP (mmHg)	78.00 ± 10.33	75.26 ± 10.07	76.73 ± 8.84
TG (mmol/L)	1.81 (1.18–2.44)	1.02 (0.80–1.97)^{a}	1.06 (0.81–1.42)^{a}
TC (mmol/L)	4.43 ± 0.85	4.27 ± 0.82	4.49 ± 0.85
LDL-C (mmol/L)	2.73 ± 0.78	2.49 ± 0.75	2.66 ± 0.71
HDL-C (mmol/L)	1.26 ± 0.26	1.32 ± 0.30	1.46 ± 0.29^{ab}
Hs-CRP (mg/L)	1.78 (1.34–3.05)	1.25 (1.00–2.27)	0.95 (0.83–1.44)^{a}
FPG (mmol/L)	8.07 ± 2.61	7.32 ± 2.54	6.42 ± 1.91^{ab}
HbA_1c (%)	8.96 ± 2.41	8.32 ± 2.47	7.04 ± 2.10^{ab}
FIns (uU/mL)	12.29 ± 4.89	10.32 ± 4.92^{a}	6.39 ± 2.54^{ab}
HOMA2-IR	1.71 (1.21–2.19)	1.18 (1.01–1.97)^{a}	0.83 (0.71–0.96)^{ab}
T2DM (%)	79.7	70.7	47.5^{ab}
Overweight/obesity (%)	59.3	37.9^{a}	22.0^{ab}
Adropin (ng/mL)	2.9 (2.5–3.1)	4.3 (3.8–4.8)^{a}	7.1 (6.3–9.1)^{ab}

^{a} $p < 0.05$ *vs.* lower tertile, ^{b} $p < 0.05$ *vs.* middle tertile.

Table 3 Serum adropin level according to BMI

BMI (kg/m^2)		Control	T2DM
<18.5		—	—
18.5–25	*n*	43	63
		6.1 (4.1–9.0)	4.3 (3.3–6.4)*
≥25	*n*	17	53
		4.3 (2.9–6.9)$^{\#}$	3.2 (2.8–4.7)*$^{\#}$

* $p < 0.05$ *vs.* control, $^{\#}$ $p < 0.05$ *vs.* BMI 18.5–25. *n*, number of subjects. There were no subjects that had lower BMI than 18.5 in both groups.

negatively correlated with BMI, hs-CRP, TG, FPG, FIns, HOMA2-IR and HbA_1c, but positively correlated with HDL-C ($p < 0.01$). Except for hs-CRP, the correlations of adropin with glucolipid variables (TG, HDL-C, FPG, FIns, HOMA2-IR, HbA_1c) were still unchanged after adjusting the effect of BMI. HOMA2-IR and HbA_1c were independent factors associated with serum adropin levels after simultaneously examining related factors found in simple correlation analyses (Table 4).

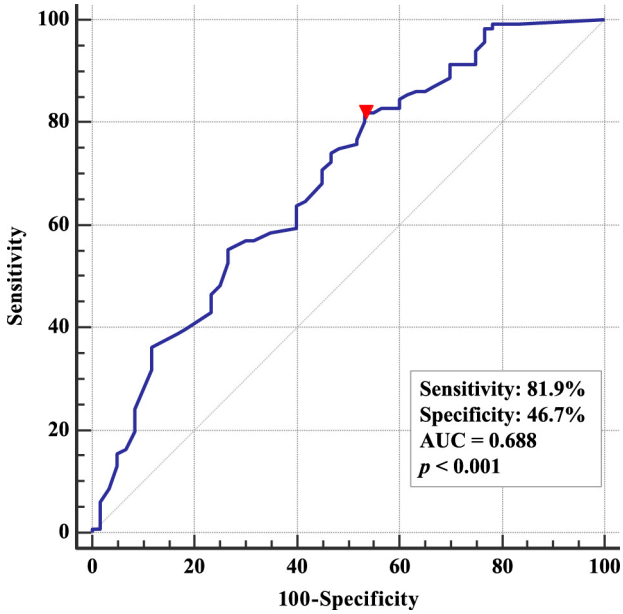

Fig. 1 The ROC curve for determining the adropin cut-off value for identifying T2DM

Binary logistic regression analyses showed that adropin was significantly associated with T2DM even after adjusting for demographic or anthropometric variable, smoking, drinking, lipid profile and hs-CRP (Table 5).

Adropin could be a novel biomarker for distinguishing T2DM form non-T2DM according to ROC curve in the present study (AUC: 0.688, 95%CI: 0.614–0.755, $p < 0.01$). The optimal cut-off value of adropin to identify T2DM was 5.8 ng/mL with sensitivity of 81.9% and specificity of 46.7%. Notably, a cut-off value of 3.3 ng/mL had a high specificity of 88.3%, although the sensitivity decreased to 36.2% (Fig. 1).

Discussion

In the present study, we have reported that serum concentrations of adropin were significantly decreased in Chinese T2DM patients compared with control subjects. Besides, serum adropin levels of overweight/obesity group were lower than that of normal weight group within study participants.

Adropin has been identified as potent regulatory hormone implicated in the maintenance of insulin sensitivity and glucose tolerance in mice [9, 13]. Aydin *et al.* demonstrated that serum and tissue adropin levels were

Table 4 Simple correlation and multiple regression analyses of serum adropin levels associated with other biochemical parameters in study population

	Adropin		Adropin (BMI adjusted)		Multiple regression	
	r	*p*	*r*	*p*	β	*p*
Age	0.078	0.305	0.051	0.499	—	—
BMI	–0.346	<0.01	—	—	–0.134	0.065
Smoking	–0.038	0.614	–0.044	0.559	—	—
Drinking	0.013	0.864	0.039	0.607	—	—
SBP	–0.080	0.291	–0.029	0.701	—	—
DBP	–0.029	0.702	0.034	0.657	—	—
Hs-CRP	–0.230	<0.01	–0.111	0.142	0.003	0.968
TG	–0.270	<0.01	–0.193	0.011	–0.090	0.190
LDL-C	–0.058	0.443	–0.010	0.891	—	—
HDL-C	0.313	<0.01	0.226	<0.01	0.103	0.146
TC	0.018	0.814	0.036	0.637	—	—
FPG	–0.349	<0.01	–0.302	<0.01	–0.068	0.429
FIns	–0.502	<0.01	–0.408	<0.01	—	—
HOMA2-IR	–0.513	<0.01	–0.424	<0.01	–0.378	<0.01
HbA_1c	–0.359	<0.01	–0.312	<0.01	–0.165	0.022

both increased in streptozotocin-induced diabetic rats [10]. In addition to animal based researches, a series of studies in humans have been implemented to further ascertain the correlation of serum adropin levels with systemic insulin resistance and metabolic disorders. Celik *et al.* assumed that decreased adropin level in maternal and cord serum of the GDM patients was associated with the underlying pathogenesis of GDM [15], which was in accordance with another case-control study conducted in Iranian pregnant women [16]. Besides, previous researches have also shown that low levels of plasma adropin were associated with metabolic syndrome, NAFLD and PCOS [17-19]. Nevertheless, the concentrations of adropin in T2DM patients were not as clear. We found in the present study that serum adropin levels in T2DM patients were significantly decreased compared with control subjects. The result was consistent with findings by Wu *et al.* reporting that serum adropin level was lower in T2DM patients than in non-diabetic patients, which were observed in individuals with chest pain and suspected coronary artery disease [22]. Furthermore, we reported for the first time that subjects in the lower serum adropin tertile had highest levels of FIns, HOMA2-IR and the prevalence of T2DM, while the upper tertile subjects had the lowest levels of FPG and HbA_1c among study groups. Binary logistic regression analyses showed that adropin was significantly associated with T2DM even after removing confounding factors (age, gender, SBP, DBP, smoking, drinking, BMI, lipids, hs-CRP).

Table 5 Binary logistic regression analyses of association between adropin and T2DM

Adjusted model	OR	95%CI	*p*
Model 1	0.700	0.594–0.824	0.000
Model 2 (Model 1 + BMI)	0.732	0.618–0.868	0.000
Model 3 (Model 2 + lipids)	0.736	0.610–0.889	0.001
Model 4 (Model 3 + hs-CRP)	0.758	0.625–0.919	0.005

OR, odds ratio; 95%CI, 95% confidence interval; Model 1 was adjusted for age, gender, SBP, DBP, smoking and drinking; lipids, including TG, LDL-C, HDL-C, TC.

Up to now, the mechanisms underlying decreased adropin levels in T2DM patients remain elusive. Studies performed by Gao *et al.* showed that adropin played a crucial role in modulating glucose utilization in mice [23, 24]. First, adropin could promote carbohydrate oxi-

dation in skeletal muscle, with fat oxidation limited, which was mediated by suppressed activity of Sirtuin-1 (SIRT1) and peroxisome proliferator-activated receptor-gamma coactivator-1a (PGC-1a) [23]. Second, adropin sensitized insulin signal pathways, by increasing insulin-induced Akt phosphorylation and cell-surface expression of glucose transporter 4 (GLUT4) [24]. Kumar *et al.* demonstrated that adropin over-expression attenuated hepatic steatosis in DIO mice, which was partly associated with reduced expression of key enzymes involved in lipogenesis and triglyceride synthesis [9]. Thus, it is not hard to speculate that adropin might have positive influence on insulin resistance and T2DM by improvement of hepatic steatosis. In addition, adropin induced activation of endothelial nitric oxide synthase (eNOS), along with consequent enhancement of blood perfusion in peripheral tissues, thus to some extent resulting in rise of glucose availability [25]. In current study, we then explored the correlations of adropin with clinic parameters in all participants and observed negative correlations between adropin concentrations and TG, FPG, FIns, HOMA2-IR and HbA_1c even after adjusting the effect of BMI and that HOMA2-IR and HbA_1c were independent factors associated with serum adropin levels. Our findings were in agreement with previous researches [9, 13, 23, 24], suggesting the reasonable link of adropin with glucolipid metabolism and insulin sensitivity.

It is worth noticing that adropin has been demonstrated closely related to obesity. With the progress of obesity, adropin levels proved declined both in mice and human beings [9, 13, 17, 18, 26]. Besides, adropin levels appeared to increase after Roux-en-Y gastric bypass surgery and peak 3 months later [26]. Based on these findings, we presumed there would be a discrepancy in serum adropin concentrations between subgroups divided by BMI. Data in the present study suggested that adropin levels were lower in overweight/obesity group than normal weight group both in T2DM patients and control subjects and that adropin concentrations were negatively correlated with BMI in study participants.

Sayın *et al.* found that adropin concentrations were decreased in obese children, further fall of which could be an independent risk factor for NAFLD [18]. Similarly, obese individuals with normal metabolic function were accompanied with relatively higher levels of adropin compared with obese metabolic syndrome patients, which was so-called "healthy obese phenomenon" [17]. Interestingly, we demonstrated for the first time that overweight/obese patients represented more seriously decreased level of adropin than healthy overweight/obese control. The evidence mentioned above [17, 18], including ours, suggested that adropin level was expected to be a biomarker of the individual risk for metabolic diseases even in overweight/obese subjects. Serum adropin concentration of an individual falling to a certain level might demonstrate his/her risk of suffering from T2DM greatly increases.

Several limitations of the present study should be noted. First, the cross-sectional study design could not distinguish whether the decreased adropin level was causal for the development of T2DM. Second, this study was conducted in a single site with a relatively small sample size. Thus, the individuals enrolled in the research might not accurately represent the study population. Third, our study was based on a single measurement of serum adropin in the fasting state, which could not reflect adropin concentration fluctuation over time especially after the stimulation of macronutrient consumption.

In summary, serum adropin concentrations are decreased in Chinese T2DM patients. Besides, overweight/obese T2DM patients are found to have more considerably reduced levels of adropin. Peptide hormone adropin, involved in glucolipid metabolism and insulin sensitivity, is necessary to be further explored of its variation characteristics after macronutrient consumption and pathophysiological mechanism in T2DM.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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