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The relationship between serum thyrotropin and components of metabolic syndrome

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Abstract. To explore the relationship between serum thyrotropin and components of metabolic syndrome in a Chinese cohort. A total of 1534 adult inhabitants in DaDong district of Shenyang were asked to fulfill the questionnaire, complete physical examination and OGTT. Blood samples were collected to test thyrotropin (TSH), fasting plasma glucose (FPG), OGTT 2h PG, fasting insulin (FINS), triglyceride (TG) and high density lipoprotein cholesterol (HDL-C). Serum TSH in metabolic syndrome group was higher than that in the non-metabolic syndrome group (2.54 mIU/L *vs.* 2.22 mIU/L, $p<0.05$). TG level increased significantly in subclinical hypothyroid group compared with euthyroid subjects (1.73±0.12 mmol/L *vs.*1.47±0.03 mmol/L, $p<0.05$), and HDL-C decreased significantly in patients with subclinical hypothyroidism compared with euthyroid subjects (1.26±0.27 mmol/L *vs.* 1.33±0.27 mmol/L, $p<0.05$). The prevalence of hypertension was higher in the subclinical hypothyroid group than that in euthyroid group (42.86% *vs.* 33.2%, $p<0.05$). The serum TSH within the reference range was positively related with the prevalence of overweight/obesity. Slight increase in serum TSH maybe a risk factor for metabolic syndrome.

Key words: Metabolic syndrome, Thyrotropin, Subclinical hypothyroidism, Subclinical hyperthyroidism

THYROID dysfunction is a risk factor of cardiovascular diseases [1-3], even slight change in thyroid function may increase the risk of cardiovascular diseases [4, 5]. Recently, the effects of serum thyrotropin level on cardiovascular diseases in euthyroid subjects have become a hot topic to study.

Metabolic syndrome is a cluster of obesity, hyperglycemia, dyslipidemia and hypertension, which is a threat to human health. The prevalence of metabolic syndrome in western countries is about 20% to 30% [6-8], while it is about 10% to 21% in China [9]. Metabolic syndrome is a risk factor for type 2 diabetes and cardiovascular diseases [10], the risk for cardiovascular disease and cardiovascular death increased 3 times in subjects with metabolic syndrome, and the risk for diabetes increased 5 times in subjects with metabolic syndrome.

Now, there are several studies about the correlation between thyroid function and components of metabolic syndrome, but the results are disputed. A cross-sectional study [11] of 1581 euthyroid subjects found that there was positive correlation between TSH and index of insulin resistance as well as triglyceride. So we used our epidemiological data to analyze whether there was correlation between TSH and components of metabolic syndrome.

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Subjects and Methods

Subjects

A total of 1534 inhabitants, aged 18-85 years, of three communities in DaDong district, Shenyang city, participated in a stratified sample survey on thyroid

disease, diabetes and metabolic syndrome.

Exclusion criteria were (i) participants having a personal history of thyroid disease and have been taking thyroxine or antithyroid drugs for treatment; (ii) taking medication affecting thyroid function such as glucocorticoid, antiepileptic and contraceptive drugs; (iii) pregnant women or within the first year of postpartum period; (iv) participants with overt hypothyroidism or overt hyperthyroidism. Moreover, 5 participants with inaccurate height measured and 7 participants without complete data were also excluded from the study. Finally, 1399 participants were enrolled and evaluated (male 556, female 843). Of the 1399 enrolled participants, 102 were with subclinical hypothyroidism, 14 were with subclinical hyperthyroidism, 1283 participants were euthyroid.

Methods

Sample collection: All the participants were told to attend our survey in fasting status. A questionnaire was given to each participant including general information, such as name, gender, ethnicity, date of birth, address, identification card number, educational qualification, profession, family income, telephone number, duration of time living in DaDong district, history of childbearing, status of medical insurance, involvement in sports and their diet intake, history of smoking and drinking, family history and personal history of thyroid diseases, diabetes, hypertension and dyslipidemia and their treatment. All the patients were asked to rest at least 30 minutes and then blood pressure of their right arm was measured twice with a desk-model sphygmomanometer with the participants in a sitting position, there was a 3-min interval between the two measurements for each participant, and the mean value of the two measurements was used. Height and body weight were measured to calculate body mass index (BMI). BMI= body weight (kg)/height (m^2). Fasting blood samples were drawn for serum TSH, fasting plasma glucose, TG, HDL-C and insulin tests. Serum FT3 and FT4 were further examined if TSH was abnormal. OGTT 2h glucose was also tested in each participant. The Homoeostasis model of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR=fasting plasma glucose (mmol/L)×insulin(mIU/L)/22.5.

Measurement of blood sample: Serum TSH, FT3 and FT4 were tested with super-sensitive chemiluminescence immunoassay (IMMULITE, Diagnostic Products Corporation, Los Angeles, CA, USA), plasma glucose was tested with hexokinase law (the first Japanese pharmaceutical kit), TG was tested with glycerol phosphate oxidase law and HDL-C with direct testing method (AU1000, Olympus, Japan), insulin was tested with radioimmunoassay (Biotechnology Research Institute of the North Port).

Diagnostic criteria: (1) Subclinical thyroid diseases [12]: ①Subclinical hyperthyroidism: TSH < 0.3 mIU/L, FT3 and FT4 within the reference range, ②Subclinical hypothyroidism: TSH > 4.8 mIU/L, FT3 and FT4 within the reference range. (2) Metabolic syndrome: The CDS (China Diabetes Society) criteria for metabolic syndrome was used in our study ①Overweight and/or obesity: BMI ≥ 25kg/m^2, ②Hyperglycemia: FPG ≥ 6.1mmol/L and/or 2hPG ≥ 7.8mmol/L and/or diagnosed diabetes, ③Hypertension: SBP/DBP ≥ 140/90mmHg and/or diagnosed hypertension receiving therapy, ④Dyslipidemia: Fasting TG ≥ 1.7mmol/L and/or fasting HDL-C < 0.9mmol/L(male) or HDL-C < 1.0mmol/L(female). Metabolic syndrome is diagnosed when there are 3 items or all the four items above.

Grouping: According to thyroid function, the participants were divided into subclinical hypothyroid group, subclinical hyperthyroid group and euthyroid group. According to our previous five-year follow-up study [12], baseline TSH of 1.0~1.9mIU/L is an optimal interval with the lowest incidence of abnormal TSH in five years, so we further divided the euthyroid group into relatively low TSH group (with TSH 0.3~1.0mIU/L), moderate TSH group (with TSH 1.0~1.9mIU/L) and relatively high TSH group (with TSH 1.9~4.8mIU/L) three subgroups. According to CDS diagnostic criteria of metabolic syndrome, the participants were divided into metabolic syndrome group and non-metabolic syndrome group.

Statistical analyses

Data processing and statistical analysis were performed by SPSS 11.5 software. We used covariance analysis to compare the difference between groups. TSH, TG, FPG, OGTT2hPG, FINS and HOMA-IR were analysed after log transformation was performed. Multiple linear regression was used to evaluate the correlation of the factors. Logistic regression was used to analyse multiplicity. Level of significance was set to 5%.

Ethical aspects

Research protocols were approved by the medical

Table 1 Comparison of the components of MS in groups with different serum TSH

	TSH (mIU/L)			
	<0.30 (n=14)	0.30-4.80 (n=1283)	>4.80 (n=102)	*p*
	$\bar{x}$±s	$\bar{x}$±s	$\bar{x}$±s	
Age (yr)	52±17	45±14	46±12	0.680
Waist[#] (cm)	78.6±13.2	80.8±10.3	80.7±9.6	0.121
BMI[#] (kg/m^2)	23.8±4.5	24.3±3.6	24.5±3.3	0.331
SBP[§] (mmHg)	128±22	123±18	122±19	0.818
DBP[§] (mmHg)	80±11	79±11	77±11	0.333
FPG[#] (mmol/L)	5.06±0.28	5.22±0.03	5.12±0.11	0.656
OGTT 2hPG[#] (mmol/L)	6.77±0.71	6.57±0.08	6.45±0.27	0.788
TG[†] (mmol/L)	1.85±0.31	1.47±0.03	1.73±0.12*	0.034
HDL-C[†] (mmol/L)	1.26±0.23	1.33±0.37	1.26±0.27*	0.011
FINS[#] (mIU/L)	11.20±6.17	12.22±23.69	10.78±5.16	0.656
HOMA-IR[#]	2.61±1.53	2.97±5.30	2.53±1.37	0.519

Compared with euthyroid group, **p*<0.05; Age, after adjusting for gender; Waist and BMI, after adjusting for age, gender and HOMA-IR; HOMA-IR, after adjusting for age, gender and BMI; Others, after adjusting for age, gender, HOMA-IR and BMI; [#]exclusion of those having hypoglycemic drugs; [†]exclusion of those having hypoglycemic drugs and hypolipidemic drugs; [§]exclusion of those having hypoglycemic drugs and antihypertensive drugs.

Table 2 Comparison of the prevalence of MS and its components in groups with different serum TSH

			TSH (mIU/L)		
			<0.30 (n=14)	0.30-4.80 (n=1283)	>4.80 (n=102)
Overweight/ obesity	prevalence(%)		28.57	39.91	41.18
	p value	0.314	0.217	Ref.	0.390
Hypertension	prevalence(%)		42.86	33.2	42.16
	p value	0.045	0.590	Ref.	0.015*
Hyperglycemia	prevalence(%)		21.43	22.53	27.45
	p value	0.457	0.560	Ref.	0.275
Dyslipidemia	prevalence(%)		42.86	31.18	34.31
	p value	0.234	0.316	Ref.	0.159
Metabolic syndrome	prevalence(%)		28.57	18.55	24.51
	p value	0.246	0.239	Ref.	0.218

Ref. is control group; compared with euthyroid group, **p*<0.05, the prevalence of overweight/obesity, after adjusting for age, gender and HOMA-IR; others, after adjusting for age, gender, HOMA-IR and BMI.

ethics committee of the First Affiliated Hospital, China Medical University. All participants provided a written informed consent after the research protocols were carefully explained to them.

Results

The relationship between different serum TSH levels and risk of metabolic syndrome and its components

There were significant differences in serum TG and HDL-C levels between subclinical hypothyroid group and euthyroid group. The level of serum TG in subclinical hypothyroid group was obviously higher than that in euthyroid group (p=0.034), while the level of HDL-C in subclinical hypothyroid group was obviously lower than that in euthyroid group (p=0.011). (Table 1)

After adjusting for gender, age, HOMA-IR and BMI, the prevalence of hypertension in subclinical hypothyroid group was higher that in euthyroid group (p=0.015), the hazard ratio was 1.8. There was difference in the risk hypertension between subclinical hyperthyroid group and euthyroid group. No differences in the risk of overweight/obesity, hyperglycemia, dyslipidemia and metabolic syndrome among the three groups (p>0.05). (Table 2)

Comparison of TSH levels between metabolic syndrome group and non-metabolic syndrome group

According to the diagnostic criteria for metabolic syndrome made by China Diabetes Society, the prevalence of metabolic syndrome was 18.9% (53.2% were male and 46.8% were female). The TSH level in metabolic syndrome group was obviously higher than that

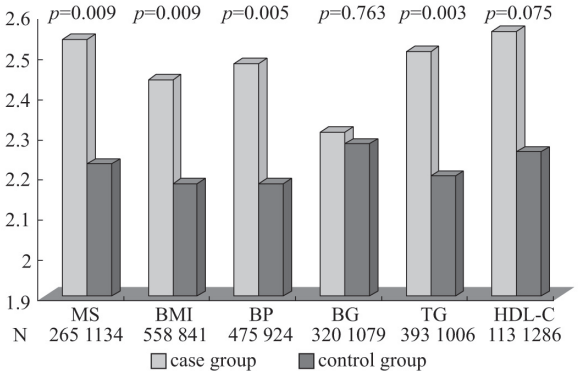

Fig. 1 Comparison of serum TSH level in different components of MS between case group and control group

in non-metabolic syndrome group (2.542mIU/L *vs.* 2.224mIU/L, p=0.009). After adjusting for age and gender, the level of TSH in overweight/obese subjects was higher than that in subjects with normal weight (2.436mIU/L *vs.* 2.184mIU/L, p=0.009). The level of TSH in hypertensive subjects was higher than that in subjects without hypertension (2.481mIU/L *vs.* 2.183mIU/L, p=0.005). The level of TSH in subjects with hypertriglyceridemia was higher than that in subjects with normal triglyceride (2.51mIU/L *vs.* 2.2mIU/L, p=0.003). No difference was found in the level of TSH between subjects with low level of HDL-C and subjects with normal level of HDL-C (2.56mIU/L *vs.* 2.26mIU/L, p=0.075). No difference was found in the level of TSH between subjects with hyperglycemia and subjects with normoglycemia (2.311mIU/L *vs.* 2.277mIU/L, p=0.763). (Fig. 1)

Comparison of TSH levels within normal range and metabolic syndrome as well as its components

Differences were found in BMI and waist circumference among low TSH group, moderate TSH group and relatively high TSH group. BMI and waist circumference were both higher in relatively high TSH group than in moderate TSH group (p=0). (Table 3)

There was correlation between the level of TSH within the normal range and risk of overweight/obesity (p=0.006). (Table 4) The risk of overweight/obesity in relatively high TSH group was higher than that in moderate TSH group (p=0.001), the hazard ratio was 1.545.

In linear regression model, there was positive correlation between TSH within normal range and BMI (β=0.921, p=0.022). In multiple linear regression model, after adjusting for gender, age and HOMA-IR, the positive correlation between TSH within normal range and BMI became more obvious (β=1.316, p=0.001), also there was positive correlation between TSH within normal range and waist circumference (β=3.073, p=0.002), however, no correlations were found between TSH within normal range and SBP, DBP, TG, HDL-C, FPG, OGTT2hPG as well as HOMA-IR (p>0.05). There was correlation between serum TSH and FINS, however, after adjusting for gender, age, HOMA-IR and BMI, the correlation no longer existed. (Table 5)

Table 3 Comparison of the components of MS in groups with normal TSH

	TSH (mIU/L)			p
	0.30-0.99 (n=242) $\bar{x}$±s	1.0-1.90 (n=484) $\bar{x}$±s	1.91-4.80 (n=557) $\bar{x}$±s	
Age (yr)	45±15	44±13	45±13	0.680
Waist[#] (cm)	81.1±10.0	80.0±10.0	81.3±10.6*	0.000
BMI[#] (kg/m^2)	24.3±3.5	23.9±3.5	24.7±3.9*	0.000
SBP[§] (mmHg)	127±20	126±20	128±22	0.652
DBP[§] (mmHg)	80±12	81±12	81±12	0.439
FPG[#] (mmol/L)	5.58±1.91	5.38±1.65	5.30±1.20	0.279
OGTT 2hPG[#] (mmol/L)	7.34±4.38	6.90±3.54	6.91±3.42	0.571
TG[†] (mmol/L)	1.46±1.30	1.58±1.39	1.50±1.17	0.096
HDL-C[†] (mmol/L)	1.31±0.43	1.32±0.33	1.34±0.38	0.818
FINS(mIU/L)[#]	11.33±7.27	12.83±37.32	12.02±8.35	0.279
HOMA-IR[#]	2.93±2.51	3.04±8.06	2.92±2.45	0.707

Compared with moderate TSH subgroup, *p<0.05, Age, after adjusting for gender; Waist, BMI, after adjusting for age, gender and HOMA-IR; HOMA-IR, after adjusting for age, gender and BMI; others, after adjusting for age, gender, HOMA-IR and BMI; [#]exclusion of those having hypoglycemic drugs; [†]exclusion of those having hypoglycemic drugs and hypolipidemic drugs; [§]exclusion of those having hypoglycemic drugs and antihypertensive drugs.

Table 4 Comparison of the prevalence of MS and its components in groups with normal TSH

			TSH (mIU/L)		
			0.3-0.99 (n=242)	1.0-1.9 (n=484)	1.91-4.8 (n=557)
Overweight/ obesity	prevalence(%)		38.84	35.74	43.81
	p value	0.006	0.350	Ref.	0.001*
Hypertension	prevalence(%)		33.88	31.82	34.11
	p value	0.655	0.143	Ref.	0.119
Hyperglycemia	prevalence(%)		25.62	22.31	21.36
	p value	0.095	0.132	Ref.	0.448
Dyslipidemia	prevalence(%)		27.27	30.79	33.21
	p value	0.173	0.168	Ref.	0.554
Metabolic syndrome	prevalence(%)		18.18	17.77	19.57
	p value	0.965	0.965	Ref.	0.798

Ref. is control group; compared with moderate TSH subgroup, *p<0.05, the prevalence of overweight/obesity, after adjusting for age, gender and HOMA-IR; others, after adjusting for age, gender, HOMA-IR and BMI.

Table 5 Comparison of the components of MS and insulin resistance in subjects with normal TSH

	Model	β	*p* value
BMI	1	0.921	0.022*
	2	1.454	0.000*
	3#	1.316	0.001*
SBP†	1	-1.476	0.5000
	2	2.628	0.1870
	3#	2.379	0.2310
	4#	0.574	0.7640
DBP†	1	0.260	0.8430
	2	2.547	0.0420*
	3#	2.167	0.0810
	4#	1.056	0.3760
FPG#	1	-0.006	0.4570
	2	-0.006	0.5160
	3	-0.013	0.0900
	4	-0.012	0.1140
OGTT 2h PG#	1	-0.006	0.7340
	2	0.001	0.9380
	3	-0.008	0.6100
	4	-0.015	0.3290
TG§	1	0.030	0.1640
	2	0.069	0.001*
	3#	0.066	0.016*
	4#	0.044	0.0960
HDL-C§	1	-0.001	0.9830
	2	-0.045	0.1270
	3#	-0.005	0.9020
	4#	0.017	0.6700
Waist	1	0.373	0.7440
	2	3.371	0.001*
	3#	3.073	0.002*
FINS#	1	0.057	0.024*
	2	0.059	0.021*
	3	0.013	0.0900
	4	0.012	0.1140
HOMA-IR#	1	0.051	0.0690
	2	0.053	0.0610
	4	0.019	0.4840

*p<0.05, Values of β are standardized regression coefficients. model 1, crude; model 2, after adjusting for age and gender; model 3, after further adjusting for HOMA-IR; model 4, after further adjusting for BMI. #exclusion of those having hypoglycemic drugs; †exclusion of those having antihypertensive drugs; §exclusion of those having hypolipidemic drugs.

Discussion

Metabolic syndrome is a cluster of diseases, and it's focused on because it is a risk factor of type 2 diabetes and cardiovascular diseases. The components of metabolic syndrome vary with different diagnostic criteria. The CDS diagnostic criteria for metabolic syndrome contain overweight/obesity, hyperglycemia, hypertension and dyslipidemia. Besides, metabolic syndrome contains other metabolic dysfuction and diseases. Recent studies showed that subclinical thyroid dysfunction [13], even TSH within normal range [14] may be related to metabolic syndrome and its components. A study indicated the level of insulin in subclinical hypothyroid group was obviously higher than that in normal controls; however no difference was found in HOMA-IR [15]. Annemieke Roos's study also showed there was no correlation between and HOMA-IR, he also found FT_4 correlated with fasting insulin [11]. Recently, Ashizawa K, *et al* published a study conducted in Japanese people, they found there was a significant increase in a cluster of metabolic cardiovascular disease risk factors among people with subclinical hypothyroidism [16]. So more epidemiological studies were needed to determine whether we should measure TSH in people with metabolic syndrome or not. Our study found the level of TSH in metabolic syndrome group was obviously higher than that in non-metabolic syndrome group. After adjusting for gender, age and BMI, there was no correlation between TSH within normal range and HOMA-IR. We also found when TSH was within normal range, after adjusting for gender, age and BMI, there was positive correlation between TSH and waist circumference. So far, most studies believed metabolic syndrome is related to insulin resistance, and central obesity in one cause of insulin resistance. Our study indicated we should pay attention to the level of serum TSH in people with central obesity.

The correlation between serum TSH and the components of metabolic syndrome varied in different studies. The prevalence of subclinical hypothyroidism in normal population is about 2%~20% [17], most of the patients were women over fifty. Hypothyroidism is a main factor affecting blood lipid metabolism. In patients with overt hypothyroidism, the LDL-C receptors on hepatocytes was down regulated, so the clearance of LDL-C was delayed, usually it is characterised by high levels of serum cholesterol and LDL-C and low level of HDL-C [18, 19], after L-T_4 therepy, HDL-C increased obviously [19]. Another study showed the levels of TC, LDL-C and TG in subclinical hypothyroid group were higher than in euthyroid group, however no difference was found in HDL-C level between the two groups [20], also there was a study which found no differences in the levels of TC, TG and HDL-C between subclinical hypothyroid group and euthyroid group [21]. Our study found the level of TG increased while the level of HDL-C decreased in subclinical hypothyroid group. Although the results were different in different studies, we could also find elevation of TSH in subclinical hypothyroidism may cause dyslipidemia.

In our study, there was positive correlation between serum TSH within normal range and TG, after adjusting for gender, age and HOMA-IR, the correlation still existed, which was similar the result of Annemieke Roos [11]. Waterhouse DF *et al* [22] found the correlation between TSH and TG when TSH was within normal range, TG increased 0.115 mg/dL with TSH increasing by 1mIU/L. However, after adjusting for BMI, the correlation between TSH and TG no longer existed, which indicated gender, age, obesity and diet may influence the correlation between TSH and TG. A study [23] showed that in euthyroid population, the correlation between TSH and blood lipid was regulated by the insulin sensitivity, as a result, subjects with relatively high TSH and insulin resistance had more possibility for dyslipidemia.

Researchers still argued the relationship between serum TSH and blood pressure in subjects with subclinical thyroid function and euthyroidism. Some researchers thought TSH positively correlated with SBP and/or DBP [22, 24-26], while some other researchers did not get such results [11, 21]. One study of Annemieke Roos *et al* showed that when TSH was within normal range, there was no correlation between TSH and SBP and DBP. Waterhouse *et al* [22] took 728 healthy women as subjects and found TSH positively correlated with SBP, with TSH increasing by 1mIU/L, SBP increased 1.53mmHg, no correlation was found between TSH and DBP. Our study indicated after adjusting for gender, age, HOMA-IR and BMI, there was no correlation between TSH and blood pressure, however the prevalence of hypertension in subclinical hypothyroid group was higher than that in euthyroid group, the hazard ration was 1.8, but the level of TSH within normal range had no correlation with the prevalence of hypertension.

In euthyroid subjects, we found TSH positively correlated with BMI, and the risk of overweight/obesity increased with TSH increasing, which was similar to some other studies [14, 27, 28]. Some studies showed adipocytes and preadipocytes expressed TSH receptors, TSH binded with TSH receptors and induced preadipocytes to produce and release adipokines, some of them such as leptin played a very important role in the onset of metabolic syndrome and cardiovascular diseases [27]. Acute administration of TSH to biochemically euthyroid patients caused endothelial dysfunction and increased serum levels of C-reactive protein, TNF-α, several indices of oxidative stress and IL-6 [29, 30]. Perhaps TSH elevation stimulates the secretion of inflammatory cytokines which leads to an increase in the components of metabolic syndrome, but this is only our hypothesis and further investigations are needed to explain the relationship between TSH elevation and the increase of components of metabolic syndrome.

This study did not find the relationship between TSH and metabolic syndrome as well as its components in people with subclinical hyperthyroidism, and the reason might be there were few subjects with subclinical hyperthyroidism. Also, we didn't see the correlation between TSH and blood glucose, maybe it was because the effect of thyroxine on blood glucose was stronger than that of TSH [11]. Our study was a cross-sectional study and did not design whether patients with subclinical hypothyroidism should receive LT4 replacement, and now there is no consensus on this issue, further prospective studies should be carried out to answer this question. Our recommendation is that those who are pregnant, whose TSH is over 10mIU/L and who are thyroid autoantibodies positive should receive LT4 replacement therapy. Recently, Paul W. Ladenson *et al* used thyroid hormone analogue eprotirome in patients receiving treatment with statins and found it was associated with decreases in levels of atherogenic lipoproteins without adverse effects on heart and bone [31], maybe in the future this kind of drug can be used in the treatment of metabolic syndrome in order to lower weight and control serum cholesterol without adverse effects caused by LT4.

Our study suggests that a slight increase in serum TSH might be a risk factor for metabolic syndrome. Further investigations are needed to evaluate the mechanism of this correlation.

Declaration of Interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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