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Original Article

Clinical, laboratory and endothelium-modulating changes in patients with arterial hypertension comorbid with hypothyroidism

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Abstract

Endothelial dysfunction is one of the early pathogenetic signs and a universal predictor of various diseases, including arterial hypertension, atherosclerosis, cerebrovascular pathology, metabolic syndrome, diabetes and others. Functional impairment of the vascular endothelium can deepen under the influence of innate and pathological factors. Up to the present, the effect of thyroid hormones on the state of the endothelium has not been sufficiently studied. The purpose of the research was to study the characteristics of changes in the functioning of endothelium in patients with arterial hypertension comorbid with hypothyroidism and to investigate the relationships between endothelium-dependent vasodilatation of the brachial artery and the main clinical and anthropometric indicators, blood pressure levels and biochemical blood parameters in this cohort of patients. The study included 99 patients with stage 2 arterial hypertension, who were divided into 3 groups depending on the functional state of their thyroid gland. All examinees were measured height, body weight, body mass index, waist circumference and blood pressure. Disorders of carbohydrate metabolism and imbalance of lipid spectrum were studied based on the results of biochemical blood analysis. Endothelium-dependent vasodilatation was evaluated based on the results of cuff test. The statistical analysis was performed using MS Excel 2016 and Statistica 10 software applications. The result of the research showed that among patients with hypertension comorbid with hypothyroidism a decrease in the hormone-producing function of their thyroid gland and an increase in the level of thyroid-stimulating hormone is an additional factor in endothelium dysfunction. A reliable negative correlation of medium strength was found between endothelium-dependent vasodilatation indicators and thyroid-stimulating hormone levels in such patients, which endorses the expediency of the reduced thyroid function compensation together with an adequate antihypertensive therapy.

Keywords: endothelial dysfunction, endothelium-dependent vasodilation, high blood pressure, hypothyroidism, lipids, thyroid-stimulating hormone, risk factor.

Introduction

Cardiovascular disease remains the leading cause of death worldwide, representing a major health, social and economic issue. In particular, the World Heart Federation has estimated that by 2030, the total global cost of cardiovascular disease is set to rise from approximately USD 863 billion in 2010 to a staggering USD 1044 billion [1]. Hypertension is a major risk factor for cardiovascular disease [2]. Currently, approximately 1 billion people worldwide suffer from arterial hypertension, which is the main cause of premature death, atrial fibrillation, heart failure, chronic kidney disease, peripheral artery disease, and even reduced cognitive ability [3, 4]. Hypothyroidism, both clinical and subclinical, without the indicated therapeutical management, may contribute to the progression of hypertension via plenty of mechanisms, such as dyslipidemia, systolic and diastolic myocardial dysfunction, as well as endothelial dysfunction [5, 6], which is an early step for the development of Atherosclerosis and cardiovascular disease [7].

Nowadays, the endothelium is considered a sophisticated, complex system at the border of the body's internal environments with unique endocrine, autocrine and paracrine properties, which play a significant role in maintaining vascular homeostasis [8]. Impairment of its function, endothelial dysfunction (ED), is one of the early pathogenetic signs and a universal predictor of the development of many diseases, in particular arterial hypertension, atherosclerosis, cerebrovascular pathology, metabolic syndrome, diabetes and, as a result, is one of the main causes of cardiovascular complications in various diseases and their adverse course [9, 10]. ED can worsen under the influence of both innate factors, such as age and pathological ones. Risk factors for ED development include hypertension, hypercholesterolemia and obesity, whereas violations of the body's hormonal status, climacteric syndrome, hypothyroid state and type 2 diabetes are associated with deepening of the vascular endothelium dysfunction and the progression of the pathological process [11, 12].

Thyroid hormones maintain vascular homeostasis by positive effects on endothelial and vascular smooth muscle cells [13]. There is data that thyroid hormone receptors can be found in the myocardium and in vascular endothelium, which allows for the regulation of these tissue processes, including endothelial nitric oxide production and vascular tone [14, 15]. However, the influence of thyroid hormones on the state of the endothelium in patients with arterial hypertension and hypothyroidism has not yet been sufficiently studied, and adequate methods for the correction of endothelial dysfunction in such comorbid patients have not been developed.

The aim of the research was to study the features of changes in the functional state of the endothelium in patients with arterial hypertension comorbid with hypothyroidism and to investigate the relationships between endothelium-dependent vasodilatation (EDV) of the brachial artery and the main clinical and anthropometric indicators, the levels of blood pressure and biochemical blood parameters in this cohort of patients.

Material and methods

The research included 99 patients who were examined and treated in the cardiology department of the Ternopil Regional Clinical Hospital for stage 2 arterial hypertension. The average age of the patients was 58.62±1.12 years, among them 43 (43.43%) men and 56 (56.57%) women. All examinees were divided into three groups depending on the functional state of their thyroid gland: group 1– patients with subclinical hypothyroidism (n=31), group 2 – patients with primary hypothyroidism (n=34), group 3 – individuals with normal thyroid gland function (n=34). The diagnosis of arterial hypertension was made according to the protocol approved by the order of the Ministry of Health of Ukraine dated May 24, 2012, No. 384. Stage 2 arterial hypertension was defined as systolic blood pressure (SBP) in values ≥140–159 mmHg and/or diastolic blood pressure (DBP) in values ≥90–99 mmHg and the presence of asymptomatic hypertension-mediated organ damage and/or chronic kidney disease stage 3 while glomerular filtration rate within 30–59 ml/min, and/or diabetes mellitus without organ damage and assumed the absence of associated clinical conditions in accordance to national and European Societies of Hypertension and Cardiology (ESH/ESC 2018) requirements [16]. The study was conducted in accordance with bioethics requirements and in compliance with the provisions of the Declaration of Helsinki. The functional state of the thyroid gland was evaluated in a laboratory using the ELISA method by determining the concentration of thyroid-stimulating hormone (TSH) in blood serum. A TSH value of 0.270–4.20 mIU/l was considered normal. Subclinical hypothyroidism was diagnosed with TSH levels of 4.21–10.00 mIU/l and normal values of thyroid hormones.

Patients' height, body weight, body mass index (BMI) and waist circumference were measured. BMI was calculated using the formula: body weight (kg)/height^2 (m^2). Data were interpreted according to the WHO guidelines: normal weight in the range of 20.0–24.9 kg/m^2; overweight (pre-obesity): 25.0–29.9 kg/m^2; class 1 obesity: 30.0–34.9 kg/m^2; class 2 obesity: 35.0–39.9 kg/m^2, and class 3 obesity: >40 kg/m^2. Waist circumference measuring was used to detect the signs of insulin resistance [17]. Carbohydrate metabolism disorders and imbalance of the lipid spectrum were studied based on the results of biochemical blood analysis. The coefficient of atherogenicity (AC) was calculated according to the formula: AC = [total cholesterol – high-density lipoprotein (HDL) cholesterol/HDL]. All patients were measured for blood pressure.

All examinees underwent an ultrasound examination of the brachial artery diameter using the Alpinion E-Cube i7 device. The state of the vascular endothelium was determined by the method of calculating the EDV of the brachial artery proposed by D. Celermajier

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and co-authors [18]. An increase in the brachial artery diameter of less than 8–10% when performing a cuff test was considered a manifestation of ED.

Statistical analysis of the obtained data was carried out using MS Excel 2016 Statistica 10 software applications. The results of the study are presented in the form of arithmetic mean values with the error of the mean square deviation of the sample (M±m). The probability of data differences in groups was determined using the reliability coefficient P, which was estimated based on students' t-tests. The difference in indicators was considered statistically reliable at P<0.05. Pearson's pairwise correlation coefficient (r) was used to identify the degree of correlation between indicators.

Results and discussion

The average age of examinees was the highest in group 1 (Table 1), and it exceeded the average age of those in group 3 by 16.89% (9.13 years) (P<0.05).

The results of the lipid profile showed that indicators of total cholesterol and low-density lipoprotein (LDL) cholesterol were the highest in group 1 and reliably prevailed by 13.32% (0.83 mmol/l) and 16.70% (0.75 mmol/l) the parameters of group 2, whereas by 9.79% (0.61 mmol/l) and 14.92% (0.67 mmol/l) the parameters of group 3, respectively (P<0.05). AC was the highest among the group of patients with subclinical hypothyroidism and reliably prevailed this index in group 2 by 25.06% (P<0.05).

The further analysis of the lipid profile blood test didn't show reliable differences in other indicators between the three groups of examinees.

Pulse pressure (PP) was measured in order to characterize its effect on EVD. The value of PP depends on the cardiac output, the stiffness of the arteries and the reflection of the pulse wave from the surrounding tissues and should normally be from 30 to 50 mmHg. According to the literature data, including the Framingham study, PP is the best predictor of the development of ischemic heart disease in patients over 50 years old with hypertension and also has an independent and greater prognostic value than the levels of SBP and DBP in relation to the risk of adverse cardiovascular events [19, 20].

The highest levels of SBP, DBP and PP were found in patients of group 1 (Table 2). SBP and DBP levels in this group were 8.1% i 6.86% higher than those among the patients of group 2 (P<0.05). In group 3, the SBP DBP levels were 11.36% i 10.47% lower, respectively, while PP was lower by 12.71% than in group 1 (P<0.05).

When performing a cuff test, a deviation of the normal function of the endothelium was observed in 93 (93.94%) of the examined patients, while worse indicators of EDV were observed in people with reduced thyroid gland function (Figure 1), compared to individuals from group 3 (P<0.001).

According to the results of the clinical and laboratory examination of the patients and duplex scanning of the brachial artery, a correlation analysis of the main indicators and EDV was performed. A reliably negative impact of the age of patients on ED among the three groups examined was revealed (Table 3), while the strongest negative correlation relationship was established in the 3rd group of patients (r=-0.5464, p=0.001). According to the literature, aging-caused endothelial dysfunction is explained by a decrease in the synthesis of nitric oxide prostacyclin and an increase in the levels of endothelin-1 and thromboxane-A2 in the blood plasma [21]. These changes occur in parallel with age-dependent disorders of vascular, antithrombotic and anti-inflammatory (increase in the content of tumor necrosis factor α) functions of the endothelium, and they are facilitated by a decrease in the bioavailability of NO, metabolic deregulation, aging of the endothelium and apoptosis, age-related changes in systemic circulating factors that modulate the functions of the endothelium [22].

A number of independent factors capable of aggravation of the vascular ED, but can be improved with modification and treatment, have been established. They turned out to be different among the examined three groups depending on the functional state of the thyroid gland.

Thus, in patients of group 1, the EDV indicator was reliably correlated with AC (r=-0.3595, p=0.047). Among patients of group 2, the duration of hypertension (r=-0.4269, p=0.012) and the level of PP (r=-0.3924, p=0.022) affected the EDV indicator. In group 3, the EDV indicator was reliably correlated with BMI (r=-0.7458, p=0.001), waist circumference (r=-0.5502, p=0.001) and the level of triglycerides (r=-0.4001, p=0.019). Waist circumference, together with BMI, is considered to be the strongest predictor of reduced tissue sensitivity to insulin and the development of compensatory hyperinsulinemia [23], according to studies by Parikh, N. I *et al.* [24], excessive accumulation of visceral adipose tissue is accompanied by excessive deposition of lipids in hepatocytes and the development of nonalcoholic fatty liver disease, their ectopic deposition in epicardial and perivascular tissues, which is associated with the development of insulin resistance in this cohort of

Table 1: Characteristics of laboratory and anthropometric indicators in patients with arterial hypertension in combination with hypothyroidism (M±m).

Indicator	Group 1			Group 2			Group 3		
	m, n=12	f, n=19	Total	m, n=9	f, n=25	Total	m, n=22	f, n=12	Total
Age, years	58.58±2.61	66.11±2.54**	63.19±1.93**	56.22±5.24	60.00±1.99	59.00±1.95	54.09±3.49	54.00±2.15	58.62±1.12
BMI, kg/m²	31.06±1.43	28.30±0.94	29.37±0.81	27.96±1.48	30.26±1.28	29.65±1.01	31.61±1.36	28.00±1.71	30.34±1.08
Waist circumference, cm	98.60±1.16	83.93±2.12*	89.99±1.95	96.54±1.97	89.29±1.33	91.21±1.22	98.26±1.28	85.09±2.18	93.62±1.56
Glucose, mmol/l	5.90±0.33	6.27±0.35	6.13±0.24	6.01±0.50	5.56±0.15	5.68±0.17	5.72±0.21	5.52±0.16	5.65±0.15
Total cholesterol, mmol/l	5.62±0.41	6.62±0.30*	6.23±0.25*,**	4.94±0.37	5.57±0.30	5.40±0.24	5.36±0.18	6.08±0.28	5.62±0.17
HDL, mmol/l	1.24±0.19	1.33±0.09	1.30±0.09	1.13±0.14	1.36±0.08	1.30±0.07	1.26±0.12	1.53±0.11	1.35±0.09
LDH, mmol/l	3.93±0.44	4.84±0.34	4.49±0.27*,**	3.17±0.27	3.95±0.30	3.74±0.24	3.48±0.19	4.44±0.38	3.82±0.19
Triglycerides, mmol/l	2.39±0.33	1.85±0.14	2.06±0.16	1.81±0.53	1.76±0.13	1.88±0.29	1.88±0.29	1.76±0.21	1.84±0.20
AC	4.43±0.80	4.42±0.44	4.43±0.40*	3.61±0.32	3.21±0.19	3.32±0.16	3.75±0.33	3.26±0.31	3.57±0.24
TSH, mIU/l	6.97±0.46**	6.75±0.43*,**	6.84±0.31*,**	6.01±1.32**	3.84±0.56**	4.41±0.55**	2.49±0.22	2.28±0.31	2.41±0.18

Note: * – the indicators are reliably different from the data in group 2 (P<0.05), ** – the indicators are reliably different from the data in group 3 (P<0.05). Abbreviations: m – male; f – female; HDL – high-density lipoprotein (HDL) cholesterol.

Table 2: Blood pressure levels in patients with arterial hypertension in combination with hypothyroidism (M±m).

Indicator	Group 1			Group 2			Group 3		
	m	f	Total	m	f	Total	m	f	Total
SBP, mmHg	163.33±7.53**	161.32±4.71	162.10±3.96*,**	153.33±4.33	152.60±3.65	152.79±2.85	143.86±4.76	143.33±7.45	143.68±3.92
DBP, mmHg	95.83±3.27	99.21±2.67*,**	97.90±2.02*,**	92.22±1.56	89.60±1.81	90.29±1.39	89.32±2.46	84.58±3.37	87.65±1.97
PP, mmHg	67.50±4.48*,**	62.11±3.22	64.19±2.58**	54.44±3.12	59.00±2.36	62.50±2.21	54.55±3.16	58.75±4.43	56.03±2.58

Note: * – the indicators are reliably different from the data in group 2 (P<0.05), ** – the indicators are reliably different from the data in group 3 (P<0.05).

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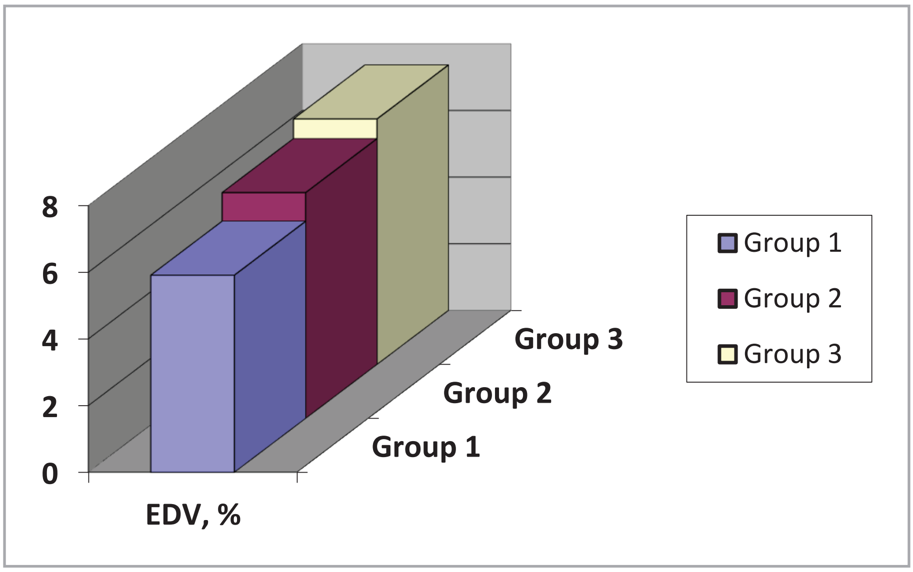

Figure 1: Changes in EDV in patients with arterial hypertension in combination with hypothyroidism.

Table 3: Correlation coefficients (according to Pearson) between EDV and indicators of anthropometry and lipid profile in patients with arterial hypertension in combination with hypothyroidism.

Indicator	Group 1	Group 2	Group 3
Age, years	-0.5181* p=0.003	-0.4578* p=0.006	-0.5464* p=0.001
BMI, kg/m²	-0.1980 p=0.268	-0.0909 p=0.609	-0.7458* p=0.000
Waist circumference, cm	0.0346 p=0.853	-0.1798 p=0.309	-0.5502* p=0.001
Hypertension duration, years	0.2018 p=0.276	-0.4269* p=0.012	-0.0885 p=0.619
SBP, mmHg	0.2472 p=0.180	-0.1875 p=0.288	0.3189 p=0.066
DBP, mmHg	0.2816 p=0.125	0.2392 p=0.173	0.2843 p=0.103
PP, mmHg	0.1579 p=0.396	-0.3924* p=0.022	0.2677 p=0.126
Glucose, mmol/l	-0.1472 p=0.429	-0.1007 p=0.571	0.0557 p=0.754
Total cholesterol, mmol/l	-0.2090 p=0.259	-0.1560 p=0.378	0.0563 p=0.752
HDL, mmol/l	0.2470 p=0.180	-0.1431 p=0.419	0.3076 p=0.077
LDL, mmol/l	-0.2315 p=0.210	0.0154 p=0.931	0.1250 p=0.481
Triglycerides, mmol/l	-0.1991 p=0.283	-0.0224 p=0.900	-0.4001* p=0.019
AC	-0.3595* p=0.047	-0.0014 p=0.994	-0.2722 p=0.119
TSH, mIU/l	-0.4766* p=0.007	-0.4015* p=0.019	-0.5603* p=0.001

Note: * – marked indicators are reliably correlated with EDV.

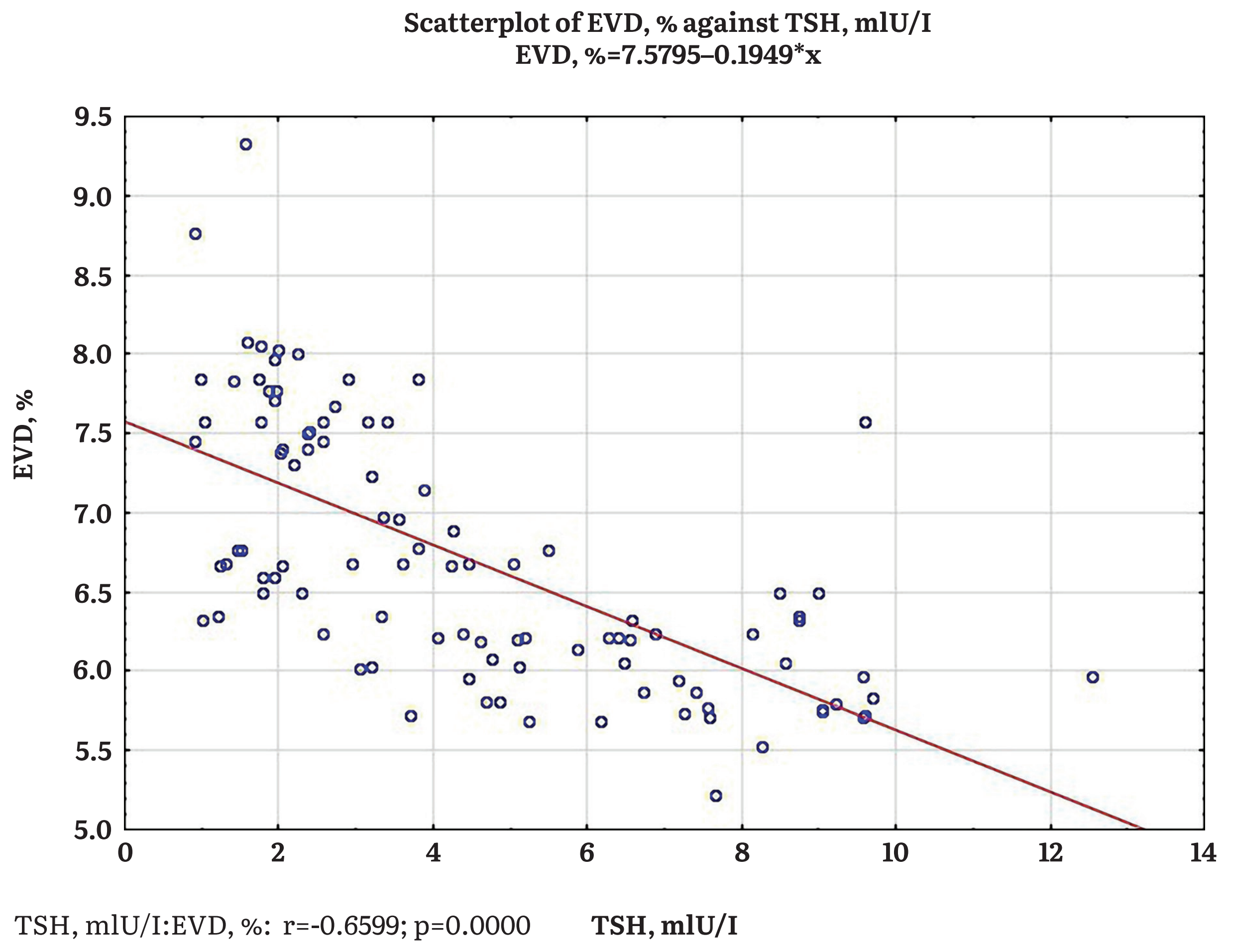

Figure 2: Scatterplot of EDV dependence on TSH level.

patients and an increased risk of cardiovascular complications.

A reliable negative relationship of medium strength was established between EDV and TSH level (Figure 2), which was observed among all groups of the examined patients and was stronger in patients of groups 1 and 3.

It is known that under normal conditions, thyroid hormones exhibit vasodilator properties, acting mainly on vascular smooth muscles. The hypothyroid state leads to an increase in vascular resistance and vasoconstriction in systemic and renal vessels and deterioration of EDVD in arterioles in patients with TSH levels higher than 4.1 mIU/l [25]. In the study of J. Lekakis and co-authors, it was shown that ED in patients with hypothyroidism is detected even within normal TSH values and worsens as its level increases [26]. Thus, the results obtained in the study confirm that in patients with arterial hypertension, the functional state of the endothelium significantly depends not only on the severity and duration of hypertension but also on the degree of violation of the hormonal status of the thyroid gland.

Conclusions

Unmodified (age of patients, duration of hypertension) and modified (overweight, increased blood pressure, signs of insulin resistance, impaired lipid metabolism) factors affecting the functional state of the vascular endothelium have been determined. An additional factor of ED in patients with arterial hypertension in combination with hypothyroidism is a decrease in the hormone-producing function of the thyroid gland and an increase in the TSH level.

The development of hypothyroidism in patients with arterial hypertension is associated with disturbances in carbohydrate and lipid metabolism, which leads to the development of metabolic obesity (BMI ≥30 kg/m^2), insulin resistance, and increased cardiovascular risk (CA>3).

In patients with arterial hypertension, a reliable negative correlation of medium strength was established between the EDV indicator and the TSH level (r=-0.6599), which endorses the expediency of the reduced thyroid

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gland function compensation simultaneously with adequate antihypertensive therapy.

Research on the use of nitric oxide donors to correct endothelial function in patients with arterial hypertension in combination with hypothyroidism.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine (approval ID: 123/21 – 21.09.2021).

Consent to participate

Written informed consent was obtained from all participants in this study.

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