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ORIGINAL ARTICLE

Assessment of plasma lipid parameters, exhaled nitric oxide fraction, and systemic immune-inflammation index on stable asthma patients

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Abstract

Asthma is a chronic disease characterized by the presence of inflammatory agents in the airways, and diagnosis and treatment are based on clinical questioning, physical examination, laboratory results, and spirometric analysis. This study investigated the effect of asthma alone on routine laboratory parameters in adults and whether an idea about the course of the disease can be obtained using these parameters. Two hundred and fourteen patients with known asthma history, diagnosed, and treated according to guidelines, were included in our study. Among all patients and between gender-specific groups, total cholesterol (CHOL), HDL, LDL, VLDL, triglyceride (TG), albumin, total protein (TP), lactate dehydrogenase (LDH), glucose, urea, creatinine, C reactive protein (CRP), FeNO, SII, INR, and complete blood count value parameters of the patients were analyzed. When we consider all asthma patients, we found that the mean glucose, LDH, CRP, TG, FeNO, and INR values outpaced the upper limit of the reference range. In contrast, the mean HDL value was below the reference range for all patients. In addition, our study found a significant correlation between triglyceride levels within the biochemical parameters with FeNO and SII). Finally, when we compared the mean values of gender-specific groups, we found a statistically significant difference between VLDL, HDL, TG, CRP, FeNO, creatinine, lymphocyte, eosinophile, basophile, and hemoglobin. CRP, LDH, TG, FeNO, SII, and INR levels may help clinicians in adult patients with stable asthma. In addition, differences depending on gender could be observed in the biochemical parameters of asthma patients.

Keywords: Asthma, biochemistry, adult, laboratory

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Introduction

Asthma is a chronic disease that interests more than 300 million people globally [1]. In the world's urban population, 100 million more people will develop asthma, according to estimated figures by 2025 [2]. However, the definition of asthma has not changed for many years. Pathophysiologically, asthma is a chronic inflammatory disease of the respiratory tract and causes bronchial remodeling in addition to the restriction of airflow [3]. Asthma is characterized by the presence of inflammatory agents in the airways, and diagnosis and treatment are based on clinical questioning, physical examination, laboratory results, and spirometric analysis [4]. The general clinical signs and symptoms are dyspnea, cough, chest tightening, and wheezing that may reflect airway hypersensitivity to a range of stimuli, such as exercise and inhaled irritants, with limitation in expiratory airflow, varying with time and intensity. Various genetic and environmental factors determine the disease's occurrence and the severity of the clinical course. Although most cases occur in childhood, the condition can also begin adulthood under allergens' influence [5].

In the classification of atopic asthma directed by interleukin (IL)-4, IL-5, and IL-13 cytokines, blood eosinophil counts with total, and allergen-specific IgE tests are used [6]. Studies have suggested that sputum eosinophils predict poor prognosis, especially in children with atopic asthma [7]. As a result of microarray studies, the TH2-high blood biomarker periostin has been identified as an IL-13 inducible protein produced by the respiratory epithelium [8]. High fractional NO [FENO] excretion by expiration has generally been reported as an inflammation indicator [9]. Blood biochemistry and hematological analyses are essential in supporting the diagnosis of asthma. The required blood volumes for cell count and most biomarker measurements are low and carry a low risk, especially for children [10]. Systemic immune-inflammation index (SII) has been assessed in several malignancies and vasculitis as an essential indicator of systemic inflammation and prognosis [11]. Although literature searches address routine laboratory parameters in asthma patients, studies have generally been carried out to discover possible specific biomarkers, and these parameters are not easy to reach. Hoping that routine laboratory analyzes can give an insight into the clinical course of asthma patients, we set out for research. Also, since the differences between male and female physiological mechanisms are known even in the healthy population, we aimed to find differences according to gender in asthma patients. Based on this, the effect of asthma alone on routine laboratory parameters and whether an idea about the disease can be obtained using these parameters was examined in our study. Standard laboratory parameters are easily reproducible globally and can easily compare with different workgroups. This logic is used in the preparation of the study.

Materials and Methods

Afyonkarahisar Health Sciences University Ethics Committee approval was obtained for the study with 08.01.2021 date and 2021/1 number. Two hundred and fourteen patients with known asthma history, diagnosed and treated according to guidelines at Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Pulmonology, Afyonkarahisar, Turkey, were included in our study. Patients with chronic diseases other than asthma, using long-term medication other than asthma treatment, having organ failure or transplantation, diagnosed with obesity or metabolic syndrome, and not attending regular follow-up examinations were excluded from the study. Total cholesterol (CHOL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), triglyceride (TG), albumin, total protein (TP), lactate dehydrogenase (LDH), glucose, urea, creatinine, c reactive protein (CRP), FeNO, SII (neutrophil*platelet/lymphocyte), INR, and complete blood count value parameters of the patients were analyzed. Univariable and multivariable analyses were assessed to investigate the association between biochemical parameters, FeNO, SII, CBC, and INR. All blood tests were performed after an 8-hour overnight fast. Biochemistry parameters were studied from serum using spectrophotometric and enzymatic

methods in an autoanalyzer. CBC parameters were obtained from whole blood by electrical impedance and flow cytometry. We evaluated lung inflammation in three groups in terms of FeNO values; <25 ppb mild inflammation, 25-50 ppb moderate inflammation,> 50 ppb severe inflammation according to the American Thoracic Society 2011 guideline. INR data were determined from blood plasma by an optical method in a coagulometer. All patients and gender difference values were evaluated whether the results were within the test reference range and how far beyond the reference range limits. Besides, whether the data conformed to the normal distribution was found with the Excel (Microsoft Inc, Redmont, Washington, USA) application. Paired sample t-test was used to compare group means of normally distributed variables, and the Wilcoxon test was used to compare group means of variables that did not show normal distribution. We summarized variables as mean ± standard error (SE) mean ± standard deviation (SD). Pearson's correlation analysis test was used for correlation analysis of parametric variables. Spearman correlation analysis test was used for correlation analysis of non-parametric variables. P-values below 0.05 were considered significant. Statistical analyses were performed using JASP 0.14 statistical software (JASP team, Amsterdam, Netherlands). Descriptive statistics are given in Table 1. Graphical data analysis is demonstrated in Figure 1.

Results

We found that the mean glucose, LDH, CRP, TG, and INR values outpaced the reference range's upper limit when we considered all asthma patients. In contrast, the mean HDL value was below the reference range for the whole group. Mean values for other parameters remained within the reference range. When we evaluated gender differences in females, mean CRP, LDH, glucose, and INR levels were measured above the reference range, while the average HDL values were below. In males, mean CRP, TG, LDH, glucose, and INR were measured above the reference range, while the average HDL values were also found below the reference range. When we considered FeNO values, we found that our patients had moderate inflammation (mean: 28.167). In addition, we found a significant correlation between triglyceride levels within the biochemical parameters with FeNO and SII, ($R2 = 0.912$ and $p = 0.031$, $R2 = 0.894$ and $p = 0.042$, respectively). Other parameters were within the reference range in both genders. When we compared the mean values of both groups statistically, we found a statistically significant difference between VLDL, HDL, TG, CRP, creatinine, lymphocyte, eosinophile, basophile, and hemoglobin ($p=0.002$, $p<0.001$, $p=0.002$, $p=0.028$, $p=0.01$, $p=0.027$, $p=0.009$, $p=0.002$, and $p<0.001$ respectively). Statistical analysis results are shown in Table 2. Correlation analyses are demonstrated in Figure 2 and 3.

Discussion

Serum and sputum LDH levels have been reported to be high in asthma patients in studies [12,13]. The increased LDH subtype is thought to be the LDH-3 isoenzyme. It has been reported that the lungs contain 28% of the LDH-3 isoenzyme compared to the whole body [14]. At this point, it has been emphasized that increased LDH levels can be used directly or indirectly as a marker of airway inflammation. The results we obtained in our study are consistent with this information. It can be thought that LDH is released into the circulation from cells that die or break down due to respiratory tract damage in patients. Besides, the blood-air barrier may become more absorbent for LDH by losing its selective permeability over time in the lung damaged by chronic discomfort. Acting on the same logic, it can be thought that the high CRP levels in patients again reflect chronic airway inflammation. Even if there is no worsening due to the disease for many years, some increase in CRP is understandable, considering that asthma is not only a local but also a systemic disease. The investigators stated that serum CRP levels increased in steroid-independent asthma patients compared to healthy controls and demonstrated a negative correlation with lung function indexes and a positive correlation with sputum eosinophil counts [15]. However, this relationship could not be shown in steroid-dependent allergic asthma. The fact that our

patients are adults in our study may indicate that asthma subtypes are most likely non-atopic, which may explain why we found high CRP levels in our results.

Although different studies and evaluations about lipid metabolism changes in asthma patients have been proposed in the literature, the mechanism has not been fully elucidated. A study indicated that serum triglyceride levels decreased in patients with an asthma attack, while no change was found in stable patients similar to our study group [16]. It has also been determined that the use of LDL and VLDL increased, and their levels decreased due to the increase in surfactant production so that asthma patients could breathe more easily. It has been reported that HDL, which contributes little to surfactant production, remains in the tissues longer and increases proportionally [17,18]. Although we could not detect a difference in LDL and VLDL levels due to our data, we found decreased HDL levels for all patients and both sexes. These findings may have developed due to the morphological change and fibrous tissue formation in the lungs as a result of years of inflammation and the decrease in the surface to produce surfactant and the cells that will produce surfactant. A different explanation for these results may be advanced age. A severe reduction in estradiol levels, especially in women with aging and entering menopause, may explain our results.

Recent studies have found increasing evidence of coagulation activation in asthmatic patients' airways as a result of allergen stimulation [19]. It is widely known that the coagulation system is activated in diseases that develop systemic inflammation. The systemic coagulation pathway is activated during an asthma exacerbation by increasing airway and systemic inflammation. Therefore, even chronic asthma patients are often exposed to exacerbation attacks until they are brought under control. Also, subacute inflammation continues outside of the attack. In the light of all this knowledge, it is understood why INR levels increase in our patients.

Current National Institute of Health and Clinical Excellence (NICE) guidelines in the UK recommend using non-invasive FeNO as the first test for people with suspected asthma [20]. The FeNO measurement enables clinicians to have detailed knowledge of airway inflammation, which significantly changes treatment plans compared to clinical evaluation alone [21]. The increase is valuable in diagnosing asthma, steroid-responsive chronic obstructive pulmonary diseases, while the decrease is meaningful in primer ciliar dyskinesia, cystic fibrosis, interstitial lung disease, and systemic sclerosis [22]. Besides, it might help diagnose and monitor complications in lung transplant patients. For these reasons, it is crucial to keep other lung pathologies in mind while evaluating FeNO and focusing on differential diagnosis. Bringing a new perspective to the assessment of inflammation, the systemic immune inflammation index (SII) can comprehensively reflect the balance of host immune and inflammatory status [23]. We found a significant correlation between these two inflammatory indicators and triglyceride levels. This conclusion suggests that there may be a link between the course of inflammation and response to treatment in asthma and triglyceride levels. Perhaps the progression of inflammation may contribute to the increase in triglyceride levels by turning fatty acids and glycerol toward glucose utilization.

Our study's absence of a control group made it impossible to compare the biochemical parameters we evaluated in asthma patients with a healthy population since it was a retrospective analysis, and this was the missing part of our study. Studies involving healthy volunteers can provide more information by comparing values within the reference range. In addition, separating patients according to clinical severity and treatment groups and analyzing them as we could not do in our study may be beneficial for more efficient results.

Table 1. Descriptive statistics of biochemical, CBC, and INR parameters. SE: Standard Error, SD: Standard Deviation. High-level values are shown in red, low-level values are shown in blue, and values between reference ranges are shown in green. For FeNO results, the blue color indicates low inflammation, the yellow indicates moderate inflammation, and the red indicates severe inflammation

	Mean	SE	SD	Minimum	Maximum
CRP	1.154	0.134	1.732	0.100	11.300
CHOL	178.291	3.207	46.913	43.700	332.400
VLDL	30.509	1.172	17.072	5.940	117.580
LDL	121.496	2.829	41.286	25.700	251.300
HDL	46.543	0.977	14.192	7.900	98.500
TG	151.851	5.893	85.810	10.700	587.900
ALBUMIN	4.335	0.041	0.554	1.360	5.520
T. PROTEIN	66.319	1.178	15.133	6.490	80.700
LDH	235.640	6.444	87.889	41.000	674.000
GLUCOSE	118.148	4.185	56.917	10.600	525.000
INR	1.407	0.149	0.879	0.870	4.530
UREA	38.333	1.817	26.578	10.600	197.600
CREATININE	0.915	0.052	0.760	0.390	8.090
WBC	8.299	0.189	2.752	2.870	24.960
NEU	5.140	0.161	2.343	1.550	19.120
LEN	2.619	0.259	3.785	0.590	51.200
EOS	0.232	0.015	0.221	0.000	1.390
BAS	0.054	0.002	0.032	0.010	0.210
HGB	13.317	0.128	1.864	7.700	17.800
PLT	268.615	5.262	76.800	61.000	617.000
AGE	59.860	1.019	14.900	20.000	87.000
FeNO	28.167	0.918	7.611	2.000	59.000
SII	700.817	71.812	156.594	258.125	3459.67

Table 2. Statistical analysis results of asthma patients' parameters between genders. SE: Standard Error, SD: Standard Deviation. High-level values are shown in red, low-level values are shown in blue, and values between reference ranges are shown in green. For FeNO results, the blue color indicates low inflammation, the yellow indicates moderate inflammation, and the red indicates severe inflammation

		Mean	SE	SD	p-value
CRP	**F**	1.277	0.163	1.868	**0,028**
	M	0.717	0.169	1.027	
CHOL	**F**	179.190	3.641	47.053	0,598
	M	175.098	6.823	46.774	
VLDL	**F**	28.638	0.989	12.740	**0,002**
	M	37.263	3.934	26.681	
LDL	**F**	121.751	3.291	42.398	0,866
	M	120.594	5.471	37.506	
HDL	**F**	48.891	1.085	13.900	**<0,001**
	M	38.351	1.767	12.111	
TG	**F**	142.302	4.994	64.339	**0,002**
	M	186.311	19.670	133.408	
ALBUMIN	**F**	4.303	0.045	0.547	0,123
	M	4.458	0.092	0.569	
T. PROTEIN	**F**	65.769	1.360	15.624	0,352
	M	68.521	2.257	12.966	
LDH	**F**	241.221	7.257	87.388	0,104
	M	215.902	13.723	87.872	
GLUCOSE	**F**	120.331	5.142	61.272	0,948
	M	110.937	5.944	38.980	
INR	**F**	1.403	0.164	0.866	0,951
	M	1.426	0.379	1.002	
UREA	**F**	37.432	1.782	23.031	0,351
	M	41.534	5.346	36.651	
CREATININE	**F**	0.844	0.045	0.583	**0,01**
	M	1.166	0.171	1.169	
WBC	**F**	8.287	0.199	2.562	0,905
	M	8.341	0.492	3.370	
NEU	**F**	5.152	0.173	2.228	0,884
	M	5.096	0.399	2.738	
LEN	**F**	2.315	0.098	1.262	**0,027**
	M	3.693	1.119	7.669	
EOS	**F**	0.211	0.016	0.212	**0,009**
	M	0.306	0.034	0.236	
BAS	**F**	0.050	0.002	0.027	**0,002**
	M	0.067	0.006	0.042	
HGB	**F**	12.911	0.123	1.582	**<0,001**
	M	14.751	0.304	2.084	
PLT	**F**	273.777	6.065	78.140	0,065
	M	250.383	10.155	69.616	
AGE	**F**	60.479	1.114	14.399	0,253
	M	57.660	2.412	16.536	
FeNO	**F**	37.263	3.248	8.642	**<0,001**
	M	24.712	1.547	3.189	
SII	**F**	764.123	37.916	94.152	0,358
	M	694.763	35.614	84.254	

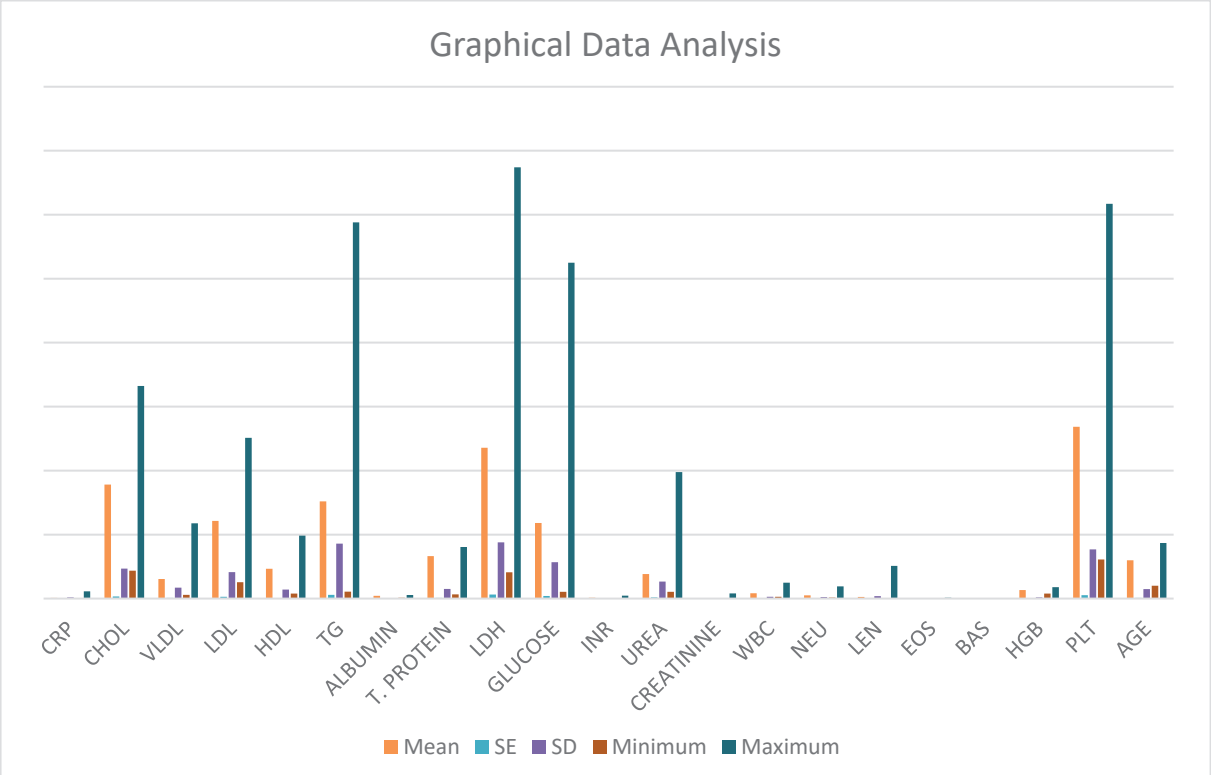

Figure 1. Graphical data analysis. SE: Standard Error, SD: Standard Deviation

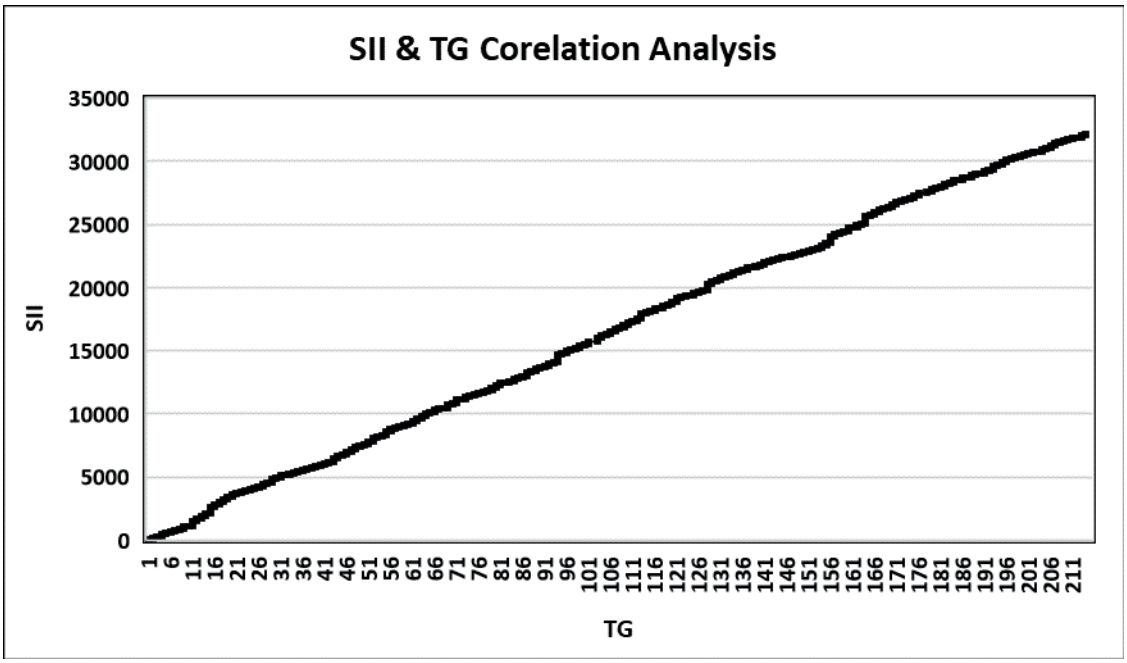

Figure 2. Correlation analysis of SII and TG values. SII: Systemic immune-inflammation index. TG: Triglyceride

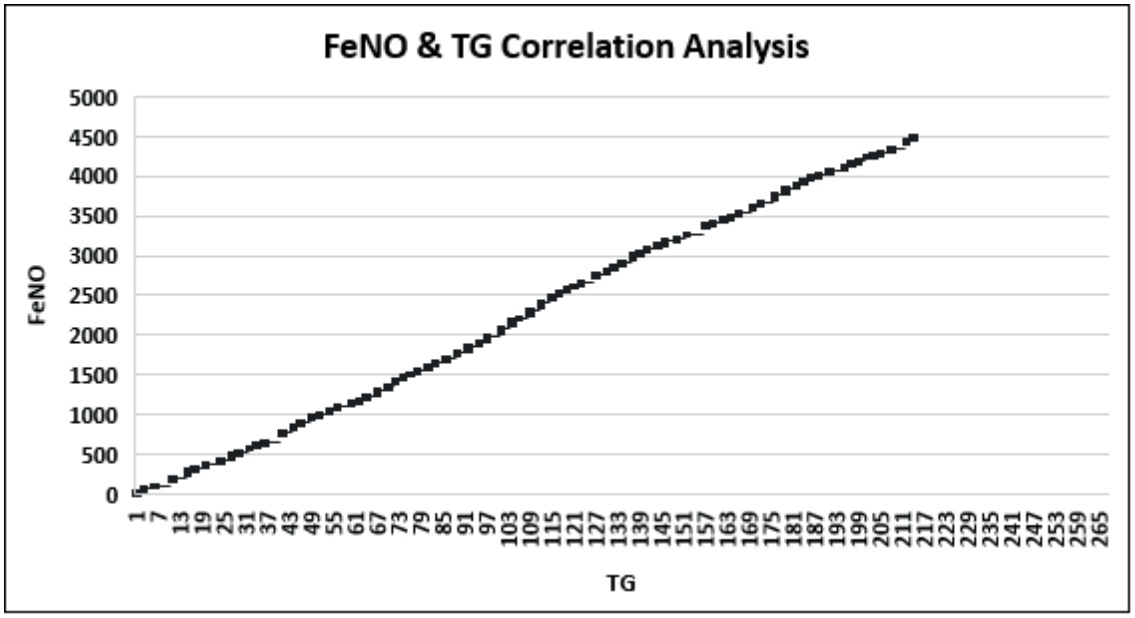

Figure 3. Correlation analysis of FeNO and TG values. SII: Systemic immune-inflammation index. TG: Triglyceride

Conclusion

In conclusion, as a result of comparing parameters between genders, we found increased levels that would make a statistically significant difference in men compared to women in terms of CRP, VLDL, HDL, TG, creatinine, lymphocyte, eosinophil, basophil, FeNO, and hemoglobin. However, we could not interpret our findings as a variable depending on gender associated with asthma. Studies involving control, clinical course, and treatment groups can guide more informative data.

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Conflict of interest

There is no conflict of interest.

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