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Uric Acid as a Predictor of Peripheral Arterial Disease as Indicated by Ankle Brachial Index

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ABSTRACT

Background: Peripheral arterial disease (PAD) is a chronic atherosclerotic progressive disorder that affects the arterial tree especially those of the lower limb which can be screened by the ankle-brachial index (ABI). Generally, uric acid (UA) has been accused of the initiation and progression of atherosclerosis in various arterial segments however, it is a less studied risk factor in PAD.

Objective: Our study aimed to evaluate the correlation between increased serum uric acid levels and PAD as indicated by ABI and whether there is a cut-off value for UA to predict PAD.

Patients and methods: A case-control study compared 100 patients with PAD as indicated by ABI with 100 cross-matched controls as regards serum UA levels and other risk factors. Moreover, the receiver operating characteristic curve (ROC) was plotted to determine the best cut-off point for UA to detect PAD as indicated by ABI.

Results: The BMI, DM, and dyslipidemia were highly significant among the patient's group (P- value= 0.001). Moreover, UA was significantly correlated to low ABI (P- value=0.003). Besides, UA cut-off value > 6.5 exhibited a specificity of 90% and a positive predictive value of 80% to diagnose PAD.

Conclusion: Low ABI was significantly associated with UA denoting its probable relation with lower limb atherosclerosis, with a good positive predictive value to predict it.

Keywords: Peripheral arterial disease, Uric Acid, Ankle-brachial index.

INTRODUCTION

Peripheral arterial disease (PAD) is a chronic progressive disorder caused mainly through the atherosclerotic process that affects peripheral vasculature, especially those of the lower limb causing gradual narrowing of their lumens with eventual complete obstruction& limb loss unless treated. It affects about 200 million people over the world [(1)].

Symptoms differ usually according to; the grade& location of stenosis. It diverges from asymptomatic to exercise- induced intermittent claudication, rest pain, and critical limb ischemia (CLI)[(2)]. Numerous risk factors have been linked to PAD. Age and male gender were correlated to PAD incidence in many epidemiological studies. DM, Smoking, Hypertension& Hyperlipidemia were reflected as the most evaluated modifiable risk factors. However, less studied risk factors such as Chronic Kidney Disease (CKD), elevated C-reactive protein (CRP)& other inflammatory markers, uric acid, hyperhomocysteinemia, and D-dimer, also have been accused.

Uric Acid (UA) has been associated with atherosclerosis, especially in PAD Moreover, treatment with hypouricemic drugs was associated with improvement in limb function in some trials[(3)]. Uric acid has been assumed to have a role in the initiation of inflammation & the upsurge in oxidative stress because of its accumulation in the arterial wall & activation of the Xanthine Oxidoreductase (XOR) enzyme[(4)]. Ankle Brachial Index (ABI) is a non-invasive modality to screen for PAD with a sensitivity that reaches 75%, subsequently, it is the utmost commonly used screening method, and it is recommended by American Diabetes Association (ADA) in people with DM above 50 years.

So, in the present study, we aim to evaluate the correlation between increased serum uric acid levels & peripheral arterial disease as indicated by ABI & whether there is a cut-off value for UA to predict PAD.

PATIENTS AND METHODS

This was a case-control study carried out on 200 subjects, divided into two groups: The group A (the case group) composed of 100 subjects identified as having a peripheral arterial disease (PAD), were recruited from the Vascular Surgery Department. Group B (the control group) was composed of 100 subjects who matched the participants in group A in age and sex and had traditional cardiovascular risk factors. Informed consent was done, and the steps of the research were explained to the subjects with the protection of their privacy and confidentiality.

The inclusion criteria:

We divided our subjects into two groups, Group A (included):

1. Patients presented with claudication pain.
2. Patients having low ABI <0.9.
3. Patients with critical limb ischemia (rest pain and/or tissue loss).
4. Patients having peripheral vascular disease diagnosed by arterial duplex or CT angiography & being treated medically or underwent angioplasty or surgical bypass.

Group B (included): People with normal ABI (0.9-1.2) & have one or more risk factors for PAD who matched the patients as regards age& sex.

We excluded patients with acute limb ischemia, Renal Failure on dialysis, recent TIA or stroke, and patients on chemotherapy or bedridden patients.

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Methods:
Full history was taken with emphasis on different cardiovascular risk factors such as HTN, DM, and dyslipidemia, current medications, family history, smoking status, and previous operations, especially for Lower Limb vessels & different comorbidities.

Ankle-brachial index (ABI):

The systolic blood pressure was recorded both in the lower limb (LL) (at the dorsalis pedis or posterior tibial arteries) & in the upper limb (UL) (at the brachial artery) using an 8 MHZ vascular doppler ultrasound, and a sphygmomanometer was applied in the supine position after 10 minutes of rest. The occluding cuff (16x36 cm) was put just above the malleoli to measure the ankle pressure & 2-3 cm above the antecubital fossa to measure the UL pressure. The ABI was calculated as the ratio between the highest pressure in the lower limb to that in the upper limb on the same side, and the average of both limbs was taken. Normal ABI > 0.9, while any reading below that was considered abnormal & indicating PAD, ABI (0.4-0.9) usually indicates mild to moderate disease while ABI < 0.4 usually indicates severe disease.

Serum uric acid:

Samples were collected in a non-fasting status in the morning & were stored in vacuum tubes containing EDTA (Ethylene Diamine Tetra-acetic Acid) and processed and analyzed using an auto-analyzer. Hyperuricemia was defined as UA >7mg/dl in males & >6mg/dl in females.

Ethical Considerations:

The study protocol was approved by the local Ethical Committee of the Faculty of Medicine of Ain Shams University. Informed written consent for accepting participation in the study was obtained from every participating patient. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges. Also, qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitativedata was done by using the Chi-square test and/or Fisher exact test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data with parametric distribution was done by using an independent t-test. While the comparison between more than two independent groups with quantitative data and parametric distribution was done by using One Way ANOVA. Spearman correlation coefficients were used to assess thecorrelation between two quantitative parameters in the same group. The receiver operating characteristic curve (ROC) was used to assess the best cut-off point with its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). Univariate and multivariate logistic regression analysis was used to assess the risk factors associated with peripheral arterial disease. The confidence interval was set to 95% and the marginof error accepted was set to 5%. P-value < 0.05 was considered significant.

RESULTS

We collected data from 200 patients who were divided into case and control groups. The mean age in the case group was 58.28 ± 10.76 years, age ranging from 34 – 82 years, while in the control group was 57.80 ± 9.30 years, age ranged 32 – 78 years; In the case group, 64.0% (N=64) of patients were males, while in the control group, 44.0% (N=44) of patients were males. The mean Body Mass Index (BMI) in the case group was 29.52 ± 3.69, which ranged from 22 – 35, while in the control group was 27.72 ± 3.40, which ranged from 22 – 34, which showed statistical significance (P-value=0.013). In the case group, 56.0% (N=56) of patients were smokers, while in the control group, 32.0% (N=32) of patients were smokers, which is a significant difference (P-value=0.016) **(Table 1).**

Table (1): General characteristics of both groups

		Control group No. = 100	Patients group No. = 100	Test value	P-value	Sig.
Age	Mean±SD Range	57.80 ± 9.30 32 – 78	58.28 ± 10.76 34 – 82	-0.239•	0.812	NS
Gender	Female Male	56 (56.0%) 44(44.0%)	36 (36.0%) 64 (64.0%)	4.026*	0.045	S
BMI	Mean±SD Range	27.72 ± 3.40 22 – 34	29.52 ± 3.69 22 – 35	-2.536•	0.013	S
Smoking	Non- smoker Smoker	68 (68.0%) 32 (32.0%)	44 (44.0%) 56 (56.0%)	5.844*	0.016	S

Body Mass Index (BMI). P-value >0.05: Non significant (NS); P-value <0.05: Significant (S)
P-value< 0.01: highly significant (HS). *:Chi-square test; •: Independent t-test

The prevalence of hypertension (HTN) was slightly higher among the control group with a non-significant difference, while BMI, DM, Dyslipidemia & Uric acid were highly significant among the patient group (P- value= 0.001) **(Table 2).**

Table (2): Prevalence of risk factors among both groups.

		Control group		Patients group		Test value	P-value	Sig.
		No.	%	No.	%			
BMI	≤ 28	68	68.00%	36	36.00%	10.256	0.001	HS
	>28	32	32.00%	64	64.00%			
HTN	No	32	32.00%	40	40.00%	0.694	0.405	NS
	Yes	68	68.00%	60	60.00%			
DM	No	48	48.00%	4	4.00%	25.156	0	HS
	Yes	52	52.00%	96	96.00%			
Dyslipidemia	No	56	56.00%	24	24.00%	10.667	0.001	HS
	Yes	44	44.00%	76	76.00%			
Uric acid	≤ 6.5	90	90.00%	60	60.00%	12	0.001	HS
	> 6.5	10	10.00%	40	40.00%			

Body Mass Index (BMI), Hypertension (HTN), Diabetes Mellitus (DM). P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS). *:Chi-square test

UA showed a highly significant difference between both groups. Its levels were (6.33 ± 2.94) among the patients group versus (4.89 ± 1.61) (in the controls) (P- value= 0.003) **(Table 3).**

Table (3): Uric acid levels in both groups.

		Control group	Patients group	Test value•	P-value	Sig.
		No. = 100	No. = 100			
Uric acid	Mean±SD	4.89 ± 1.1	6.33 ± 1.4	-3.028	0.003	HS
	Range	3 – 9.8	3.5 – 17			

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P- value< 0.01: highly significant (HS). •: Independent t-test

As regards UA, it showed a highly significant correlation with male gender (P-value= 0.02), hypertension (P-value= 0.01) & low ABI, however, it showed a non-significant correlation with dyslipidemia, DM, and smoking status **(Table 4).**

Table (4): Bivariate logistic regression between UA and different risk factors among the patient's group.

		Uric acid	P-value	Sig.
		Mean ± SD		
Gender	Female	5.02 ± 1.33	0.02	S
	Male	7.06 ± 3.34		
Smoking	Non-smoker	6.30 ± 3.19	0.95	NS
	Smoker	6.35 ± 2.79		
ABI	<0.9	7.94 ± 3.93	0	HS
	>0.9	5.42 ± 1.70		
CIMT	<=1	6.13 ± 2.87	0.65	NS
	>1	6.51 ± 3.06		
HTN	No	4.61 ± 1.00	0.01	HS
	Yes	7.47 ± 3.26		
DM	No	3.50 ± 0.00	0.17	NS
	Yes	6.45 ± 2.95		
Dyslipidemia	No	5.74 ± 1.62	0.43	NS
	Yes	6.51 ± 3.25		

P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P- value< 0.01: highly significant (HS). •: Independent t-test; ••: One Way ANOVA test

We subdivided UA levels into tertiles to evaluate the relationship with ABI. Similarly, it showed a significant negative difference with ABI (P-value= 0.01) **(Table 5).**

Table (5): Bivariate regression analysis of Uric acid tertiles with ABI.

		Uric acid (3-5)	Uric acid (>5-7)	Uric acid >7	Test value•	P- value	Sig.
ABI	Mean±SD	1.07 ± 0.18	1.12 ± 0.18	0.93 ± 0.25	5.418	0.01	HS

Among our subjects, UA showed a significant negative linear correlation with ABI (P-values =0.003), however, there was a non-significant positive correlation with increased advancing age &BMI **(Table 6).**

Table (6): Correlation of numeric data among the subjects of both groups.

	Uric acid		ABI	
	r	p-value	r	p-value
Uric acid	-	-	**-0.408****	**0.003**
ABI	**-0.408****	**0.003**	-	-
Age	0.077	0.595	-0.106	0.462
BMI	0.016	0.912	0.212	0.14

Logistic regression analysis showed that uric acid levels were significantly associated with PAD (Odds Ratio= 1.3, P-value= 0.006). However, after adjustment for other confounding risk factors, that association became non-significant (Odds Ratio= 2.165, P-value=0.227). It remained significant only with BMI<28, DM& dyslipidemia **(Table 7).**

Table (7): Univariate & multivariate logistic regression analysis for risk factors associated with PAD among the patient's group.

	Uni-variate regression				Multivariate regression			
			95% C.I.				95% C.I.	
	P-value	Odds ratio (OR)	Lower	Upper	P-value	Odds ratio (OR)	Lower	Upper
BMI >28	**0.002**	3.778	1.65	8.651	**0.001**	7.704	2.298	25.83
Smoking	**0.017**	2.705	1.197	6.113	0.121	2.307	0.801	6.645
DM	**0**	22.154	4.848	101.23	**0.001**	16.722	3.008	92.96
Dyslipidemia	**0.001**	4.03	1.712	9.488	**0.034**	3.843	1.104	13.38
Uric acid >6.5	**0.006**	1.374	1.093	1.726	0.227	2.165	0.618	7.587

The receiver operating characteristic curve (ROC) curve was plotted to determine the best cut-off point for UA to detect PAD. It showed that the UA cut-off value > 6.5 exhibited a specificity of 90% and a positive predictive value of 80% to diagnose PAD as diagnosed by ABI **(Figure 1 and Table 8).**

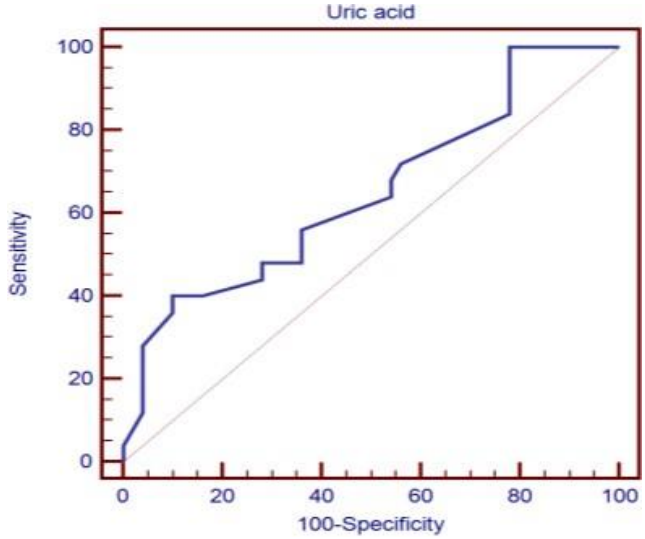

Figure (1): ROC curve of Uric acid as a predictor for PAD.

Table (8): Cut-off values of uric acid.

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
Uric acid	0.649	>6.5	40	90	80	60

DISCUSSION

There are numerous studies evaluating the relation between uric acid (UA) & atherosclerosis in the general population, in those with metabolic syndrome, and in those with one or more risk factors for arteriosclerosis such as DM, HTN, dyslipidemia, CKD, etc…. However, there is scanty data about the correlation between hyperuricemia & PAD. PAD can be simply assessed by measuring the ankle-brachial index (ABI).

Diagnosis of PAD is usually non-invasive, ABI is the best screening test with a sensitivity that reaches 75% & specificity of 86% for its diagnosis [(5)]. So it is recommended by the American Diabetes Association (ADA) & European Society of Cardiology (ESC) to be performed in asymptomatic people < 65 years of age, people >65 years who have high CV risk & people >50 years who have a family history of PAD. The association between serum UA and subclinical atherosclerotic diseases in general and PAD specifically remains controversial. So, our study aimed to evaluate the correlation between increased serum uric acid with PAD as indicated by low Ankle Brachial Index (ABI). We performed a case-control study which included 200 subjects subdivided into 100 patients diagnosed as having PAD (had symptoms, signs of PAD, and/or low ABI< 0.9) & 100 normal subjects (free from symptoms, signs of PAD & had normal ABI≥0.9).

The mean age of the patient group was 58.28±10.67, they were predominantly males representing 64%, with a mean BMI of 29.52±3.69, and they were predominantly smokers 56%. Male gender, high BMI, Age & Smoking were higher in the patient's group. Hyperuricemia was higher in males at 7.06 ± 3.34 than in females at 5.02 ± 1.33. It was higher in smokers 6.35 ± 2.79, it increased also with age & higher BMI.

In comparison to a study by Langlois, which included 156 hypertensive patients with PAD & 145 cohorts free from PAD, the mean age of PAD patients was 67.3±8.6, they were predominantly males 74%, their mean BMI was 27±4.3, and smokers represented only 30% of them [(6)]. Another prospective study was done by **Di Stolfo *et al.*[(7)],** who evaluated patients affected with established atherosclerotic CardioVascular diseases (defined as significant carotid stenosis, lower limb ischemia Leriche-Fontaine stage II or III). The patients were predominately males (279) with only 59 females. Their mean age was 71.2±8.7, but only 23% were smokers. Hyperuricemia was higher in males, it was associated with advancing age, and higher BMI.

The prevalence of hypertension was 60% versus 68% in the control group. As regards DM the percentage was 96% versus 52% among the controls. Regarding dyslipidemia, the prevalence was 76% vs 44% in the control group. The percentage of hyperuricemia was 40% (vs. 10% in the control group P- value=0.001). It was higher in hypertensives 7.70 ± 3.81, in patients with dyslipidemia 6.51± 3.25) & in diabetics (6.45 ± 2.95). Uric acid was significantly higher in the patient's group 6.33 ± 2.94 (vs. 4.89 ± 1.61 in the controls P value= 0.003). It showed a significant negative linear correlation with ABI (P-value =0.003). After further subdividing UA levels among subjects into tertiles the negative relation with ABI remained highly significant, the highest tertile of UA showed the lowest ABI (P-value =0.006).

Logistic regression analysis showed uric acid levels weresignificantly associated with PAD (OR= 1.3, P-value= 0.006). However, after adjustment of confounding risk factors, that correlation became non-significant (OR = 2.165 P-value=0.227 CI 95%) & remained significant only for BMI, DM & dyslipidemia.

This came in parallel with **Langlois *et al.*** [(6)] who found that DM, dyslipidemia and uric acid were higher in hypertensive patients with PAD than in those without PAD.

Concordantly to our work **Di Stolfo *et al.*** [(7)] revealed that the population with higher uric acid levels had a higher prevalence of DM, HTN, dyslipidemia, and lower ABI. Disconcordantly, **Sotoda *et al.*** [(8)]**,** studied the correlation between serum uric acid and decreased ABI and the percent of the decrease in ABI after exercise in patients with the peripheral arterial disease who received revascularization treatment. The percent of DM was only 44%, most of them had well-controlled HTN and lipid profiles, and most of them had UA<5mg/dl.

A randomized controlled study evaluated 283 cases of PAD. The serum uric acid levels among these patients were compared with those who did not develop PAD during the study period. Multivariate logistic regression analyses measured the risk of developing PAD associated with higher levels of serum uric acid after adjusting for the effect of traditional vascular risk factors. Age and smoking are independently associated with the development of PAD, with odds ratios of 1.08 (95% confidence interval [CI], 1.06-1.09) and 3.83 (95% CI, 2.49-5.91) per year, respectively. Hyperuricemia (serum uric acid level, >7.0 mg/dL) was an independent risk factor, with an odds ratio of 1.23, but the confidence interval of the estimate is wide (95% CI, 0.98-1.54). Serum uric acid level was independently associated with a higher (but statistically non-significant) risk of PAD[(9)].

A cross-sectional study was piloted among 3987 patients in the National Health and Nutrition Examination Survey between 1999-2002 in participants without clinical history of cardiovascular disease. Main

consequence-of-interest was PAD defined as ankle-brachial index <0.9 (n=229). Higher serum uric acid levels were positively associated with PAD, independent of smoking, body mass index (BMI), hypertension, diabetes, serum total cholesterol, serum creatinine, and other confounders. Multivariable odds ratio (OR) [95 percent confidence intervals (CI)] comparing serum uric acid levels > or =75th percentile (> or =380.8 micromol/L) to uric acid levels <50th percentile (<315.6 micromol/L) was 1.62 (1.08-2.44), p-trend=0.015. This correlation persisted in a separate analysis among men and women. Further, the results were constant in subgroup analyses by categories of age, current smoking, BMI, and diabetes mellitus[10].

Regarding UA relation to lower limb (LL) atherosclerosis, low ABI in our study showed a significant correlation with male gender, uric acid, & HTN, also a non-significant negative correlation with smoking, DM, BMI, dyslipidemia& advancing age. That correlation remained significant with UA tertiles, however, it lost its significance in the adjusted model.

Concordantly to our study, **Ishizaka *et al.*[11],** studied the relationship between brachial-ankle pulse wave velocity (baPWV), (as an indicator of arterial stiffness), ABI, uric acid, and carotid intima-media thickness (CIMT). He found that the highest quartile of uric acid was associated with the highest baPWV in subjects with & without metabolic syndrome (Odds Ratios= 4 & 2.5 respectively). Uric acid was higher among males& currently smokers, significantly higher in hypertensives and dyslipidemias. Also, **Zhan *et al.*[12]** who studied UA correlation with ABI in patients with high cardiovascular risk & found that higher uric acid levels were significantly associated with low ABI & after adjusting the confounding factors, participants in the highest quartile of UA showed higher Odds Ratio of decreased ABI than those in the lowest quartile, however after further adjusting for the renal functions that association was only significant in women.

Sotoda *et al.*[8], found a linear correlation between serum uric acid & decreased ABI. Moreover, UA was correlated to the percent of the decrease in ABI after exercise, that correlation remained significant after adjustment of other risk factors. In parallel to our study, the Asymptomatic Polyvascular Abnormalities (APAC) study that was done by **Song *et al.*[13],** conveyed that serum uric acid & every 1mg/dl increase was significantly associated with low ABI (Odds Ratio 1.75 P-value= 0.0001).

Concordantly to our results, the BEST (Beijing Vascular disease patients Evaluation Study) conducted by **Liu *et al.*[14],**found a negative linear correlation between hyperuricemia & ABI. Also, all vascular parameters & hyperuricemia were higher thanin males & older population.

Kang *et al.*[15], studied the relation between UA & arterial stiffness as indicated by baPWV in healthy Korean individuals as an indicator of subclinical PAD & there was a significant linear correlation between UA quartiles, age, systolic BP & increased baPWV (P-value=< 0.001), this came in line with the results of the current study.

Moreover, **Shin *et al.*[16],** studied the correlation between serum uric acid (SUA) & ABI in healthy Korean men (free from established CV disease, controlled on medications for HTN &DM). They reported a significant negative linear correlation (P-value= <0.001) & it remained significant after further adjustment for confounding factors.

LIMITATIONS of our study were:

- No, follow-up for both groups.
- Lack of drug intervention to evaluate whether hypouricemic drugs have a role in the improvement of limb function, walking distance, or increment of ABI, despite the presence of multiple risk factors for PAD in the same patient.
- Also, we didn't correlate UA with levels of limb obstruction.
- Single-center study and a small population.
- It is a Case-control study so it can be used to establish a correlation between exposure and outcome, but cannot establish causation.
- The potential for having confounding variables or exposures, introducing the possibility of confounding bias, which might affect the results.

CONCLUSION

Low ABI was significantly associated with UA among the patient's group denoting a probable relation of UA with lower limb atherosclerosis as it showed a significant negative linear correlation with ABI. Moreover, UA might act as a predictor for PAD as indicated by ABI.

RECOMMENDATIONS

Further larger multicenter studies are needed to verify that uric acid is an independent risk factor for PAD preferably combining values of ABI with data from imaging tools such as lower limb duplex, CT angiography, or MRA to evaluate whether UA is correlated with the site and severity of obstruction. Prospective validation of UA levels as a predictor of low ABI in hyperuricemic subjects without clinical or subclinical atherosclerotic PAD. Also, a large interventional trial is needed to validate the effect of hypouricemic drugs on decreasing the incidence of PAD.

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Author contribution: Authors contributed equally to the study.

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