Frontiers in Health Informatics www.healthinformaticsjournal.com
ISSN-Online: 2676-7104
Open Access
2024; Vol 13: Issue 5

Oxidative Stress And Antioxidant Dysfunction In Hypertension: Mechanisms And Clinical Insights

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Cite this paper as: Dr. Sanchit Tiwari, Oxidative Stress And Antioxidant Dysfunction In Hypertension: Mechanisms And Clinical Insights. *Frontiers in Health Informatics*, 13 (5s), 01-09

ABSTRACT

Background: Hypertension (HTN) is a leading risk factor for cardiovascular and cerebrovascular diseases. Oxidative stress, an imbalance between reactive oxygen species (ROS) and antioxidants defences, has been implicated in the pathogenesis of HTN. This study investigates the association between oxidative stress markers, anthropometric indices, lipid profiles, and HTN.

Material and Methods: A case-control study was conducted with 120 hypertensive subjects and 120 normotensive subjects (ages 30–60) at Index Medical College, Indore. Anthropometric measures, blood pressure (BP), lipid profiles, and oxidative stress markers (CAT, SOD, GPx, and LPO) were assessed. Statistical analysis was performed using IBM-SPSS ($p < 0.05$).

Results: Hypertensive subjects exhibited significantly higher BMI, waist-to-hip ratio (WHR), and lipid profile parameters, including cholesterol and triglycerides ($p < 0.001$), compared to normotensive subjects. Oxidative stress markers showed significant differences: CAT, SOD, and GPx levels were lower, while LPO levels were elevated in hypertensive subjects ($p < 0.001$). Correlation analysis revealed a positive association between BMI, WHR, lipid parameters, and BP, while antioxidant enzyme levels were negatively correlated with systolic (SBP) and diastolic blood pressure (DBP).

Conclusion: The study highlights the significant role of oxidative stress in the pathophysiology of HTN. Reduced antioxidant activity and increased lipid peroxidation suggest redox imbalance. Additionally, the positive correlation between anthropometric indices, lipid profiles, and BP emphasizes the interplay of metabolic and oxidative factors in HTN. These findings underscore the potential of targeting oxidative stress and metabolic dysregulation for therapeutic interventions in hypertensive subjects.

Key words: Hypertension, BMI, WHR, Lipid Profile and Oxidative Stress.

INTRODUCTION:

Hypertension (HTN), or elevated blood pressure (BP), is the most prevalent noncommunicable disease and a primary risk factor for cardiovascular diseases(CVD). The risk of cardiovascular and cerebrovascular events, as well as mortality, increases progressively with each millimeter of mercury rise in BP [1]. HTN is characterized by sustained elevation in arterial BP, defined as a systolic blood pressure (SBP) of ≥140 mm

Hg and/or a diastolic blood pressure (DBP) of ≥90 mm Hg, based on repeated measurements under standardized conditions [2].

Oxidative stress, characterized by an imbalance between cellular antioxidants and prooxidants like reactive oxygen species (ROS) and reactive nitrogen species (RNS), is a central mechanism in HTN pathogenesis. This imbalance results from either excessive ROS/RNS production or diminished antioxidant defenses [3]. ROS, while essential for vascular homeostasis, contribute to HTN development. Elevated ROS levels, coupled with reduced nitric oxide (NO) availability and antioxidant defenses, are common in both experimental and clinical HTN cases[4]. ROS play a key role in endothelial-dependent vascular functions, including smooth muscle and endothelial cell growth, survival, and remodeling. However, dysregulation of these processes promotes vascular dysfunction, contributing to CVD progression [5]. Oxidative stress is linked to endothelial dysfunction, vascular hypertrophy, remodeling, and tissue damage in HTN [6].

Superoxide radicals (O_2^-) are particularly important in modulating vascular tone and BP. These radicals, although less reactive, can interact with intracellular targets to form cytotoxic species like peroxynitrite ($ONOO^-$), generated through reactions between O_2^- and NO. The inactivation of NO by O_2^- plays a key role in the association between ROS, superoxide overproduction, and elevated BP [7]. Regulation of ROS involves enzymes like superoxide dismutases (SOD), catalase (CAT), and glutathione peroxidase (GPx). SOD converts O_2^- into hydrogen peroxide (H_2O_2), reducing NO inactivation and peroxynitrite formation [8]. CAT helps mitigate oxidative stress by breaking down H_2O_2 into water and oxygen [9]. HTN is also associated with altered glutathione (GSH) metabolism, with lower reduced GSH levels and higher oxidized GSH ratios observed in hypertensive subjects. (Red blood cells)RBC-GSH levels are negatively correlated with SBP in hypertensive subjects [10]. GPx plays a vital role in reducing peroxides that deactivate NO and break down S-nitrosoglutathione (GSNO), essential for vascular homeostasis [11]. GPx activity is compromised by oxidative stress, as O_2^- anions inhibit its function, further contributing to vascular dysfunction in HTN [12].

MATERIAL AND METHODS:

Study Design:

This case-control observational study was conducted at the outpatient department (OPD) of the Department of Medicine, Index Medical College, Hospital and Research Centre, Indore, with institutional ethical approval. Informed written consent was obtained from all subjects.

Subjects:

The study included 240 subjects (120 hypertensive subjects and 120 normotrnsive subjects), aged 30–60 years. Inclusion criteria: Hypertensive subjects (defined as average BP ≥140/90 mmHg according to JNC 7th report) [13]. Exclusion criteria: Age <30 or >60 years, renal failure, nephropathy, diabetes, cardiac disease, pregnancy, and use of antihypertensive medications.

Anthropometric Measurements:

Height, weight, and BMI (kg/m²) were measured. Waist circumference (WC) and hip circumference (HC) were assessed, and the waist-to-hip ratio (WHR) was calculated.

Blood Pressure Measurement:

BP was recorded three times in the sitting position on the right arm using a standard aneroid sphygmomanometer.

Sample Collection and Storage:

5 ml of whole blood was collected; 1 ml was used for lipid profile analysis and 4 ml for oxidative stress parameters. Samples were processed within 1 hour, stored at −20°C, and analyzed within 1 month.

Biochemical Measurements:

- **Fasting Lipid Profile (FLP)**: Analyzed using the Erba Mannheim kit and XL system on the Erba EM 360 analyzer.
- **Catalase (CAT)**: Measured by Aebi (1974) method [14].
- **Superoxide Dismutase (SOD)**: Measured by McCord and Fridovich (1969) method [15].

- **Lipid Peroxide (LPO)**: Measured by Ohkawa et al. (1979) method [16].
- **Glutathione Peroxidase (GPx)**: Measured by Pagila and Valentine (1967) method [17].

Statistical Analysis:
Data were analyzed using Microsoft Excel and IBM-SPSS (version 20). Results were expressed as mean ± SD, with significance set at $p < 0.05$.

RESULTS:
A total of 240 participants were enrolled in the study, consisting of 120 hypertensive subjects and 120 normotensive subjects. Biochemical parameters were assessed following a 12-hour fasting period. Anthropometric analysis revealed significantly higher BMI and WHR in the hypertensive subjects compared to controls ($p < 0.001$). Furthermore, both SBP and DBP were significantly elevated in hypertensive subjects relative to the normotensive subjects ($p < 0.001$) (Table 1).

Table 1: Comparison of Physiological and Biochemical Parameters between Normotensive and Hypertensive Subjects.

Parameters	**Normotensive subjects (n=120)**	**Hypertensive subjects (n=120)**
BMI (Kg/m^2)	24.15 ± 2.44	32.69 ± 3.88***
WHR	0.94 ± 0.07	1.02 ± 0.01***
Systolic (mmHg)	124.92 ± 8.91	157.75 ± 16.17***
Diastolic (mmHg)	82.66 ± 8.49	109.86 ± 16.05***
Cholesterol (mg/dl)	175.61 ± 16.43	281.76 ± 28.78***
TG (mg/dl)	136.02 ± 15.13	312.29 ± 43.13**
LDL (mg/dl)	72.05 ± 12.53	125.61 ± 10.82***
CAT (Unit/mg protein)	12.59 ± 5.53	10.48 ± 2.29***
SOD (Unit/mg protein)	7.11 ± 2.94	3.67 ± 1.5 ***
LPO (nmol MDA/ml)	2.01 ± 0.89	4.56 ± 1.16 ***
GPx (unit/min/mg protein)	49.61 ± 8.64	25.35 ± 3.45***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

In the normotensive subjects, all circulatory parameters were within the normal range. When comparing the lipid profile between hypertensive subjects and normotensive subjects, serum cholesterol and low-density lipoprotein (LDL) levels were significantly higher in hypertensive subjects ($p < 0.001$), while triglyceride (TG) levels also showed a statistically significant difference ($p < 0.01$) (Table 1).

In terms of oxidative stress, circulatory levels of antioxidant enzymes, including CAT, SOD, and GPx, were significantly lower in hypertensive subjects compared to normotensive subjects ($p < 0.001$). Conversely, circulatory levels of the oxidant enzyme LPO were significantly higher in hypertensive subjects ($p < 0.001$) (Table 1).

Table 2: Pearson's Correlation of hypertension with clinical characteristics of the hypertensive subjects:

Parameters	SBP (mmHg)		DBP (mmHg)	
	Pearson (r)	***p* - value**	**Pearson (r)**	***p* - value**
BMI (Kg/m^2)	0.3437	**0.001****	0.3371	**0.001*****
WHR	0.2937	**0.0006*****	0.3150	**0.0002*****
Cholesterol (mg/dl)	0.5236	< **0.0001*****	0.5296	< **0.0001*****
TG (mg/dl)	0.6626	< **0.0001*****	0.6509	< **0.0001*****
LDL (mg/dl)	-0.1209	0.0942	-0.1617	**0.0388***
CAT (Unit/mg protein)	-0.2168	**0.0087****	-0.1925	**0.0176***
SOD (Unit/mg protein)	-0.05765	0.2658	-0.05524	0.2745
LPO (nmol MDA/ml)	0.07643	0.2033	0.1078	0.1207
GPx (unit/min/mg protein)	-0.1725	**0.0298***	-0.1536	**0.0470***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2 presents the correlation matrix, illustrating the relationship between SBP and DBP with various clinical characteristics. Anthropometric indices, including BMI (r = 0.3437, $p = 0.001$) and WHR (r = 0.2937, $p = 0.0006$), showed a significant positive correlation with SBP in hypertensive subjects. Similarly, DBP was positively correlated with both BMI (r = 0.3371, $p = 0.001$) and WHR (r = 0.3150, $p = 0.0006$) (Figure 1).

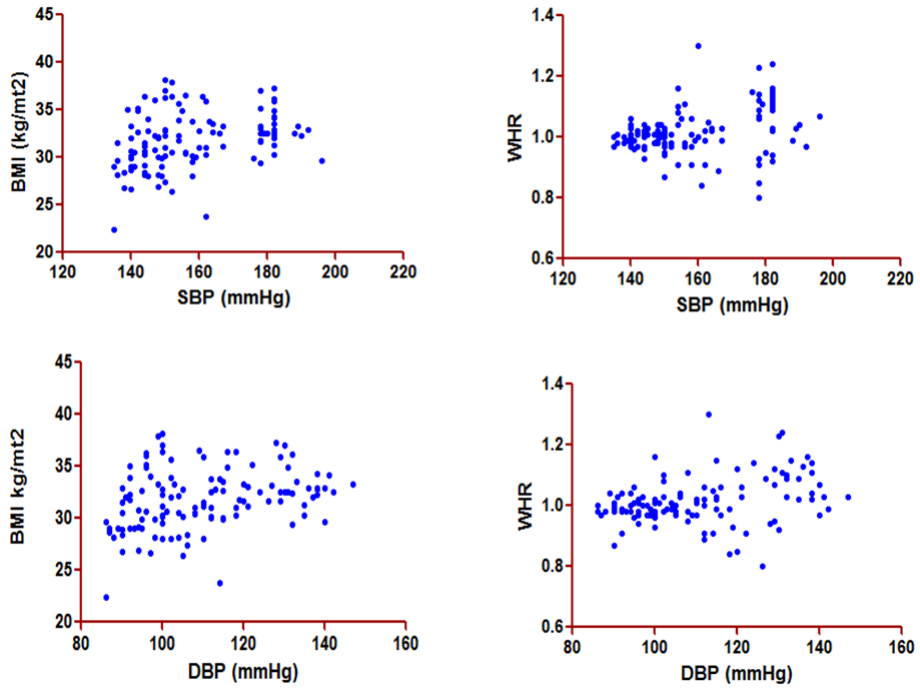

Figure 1: Correlation between anthropometric parameters and blood pressure.

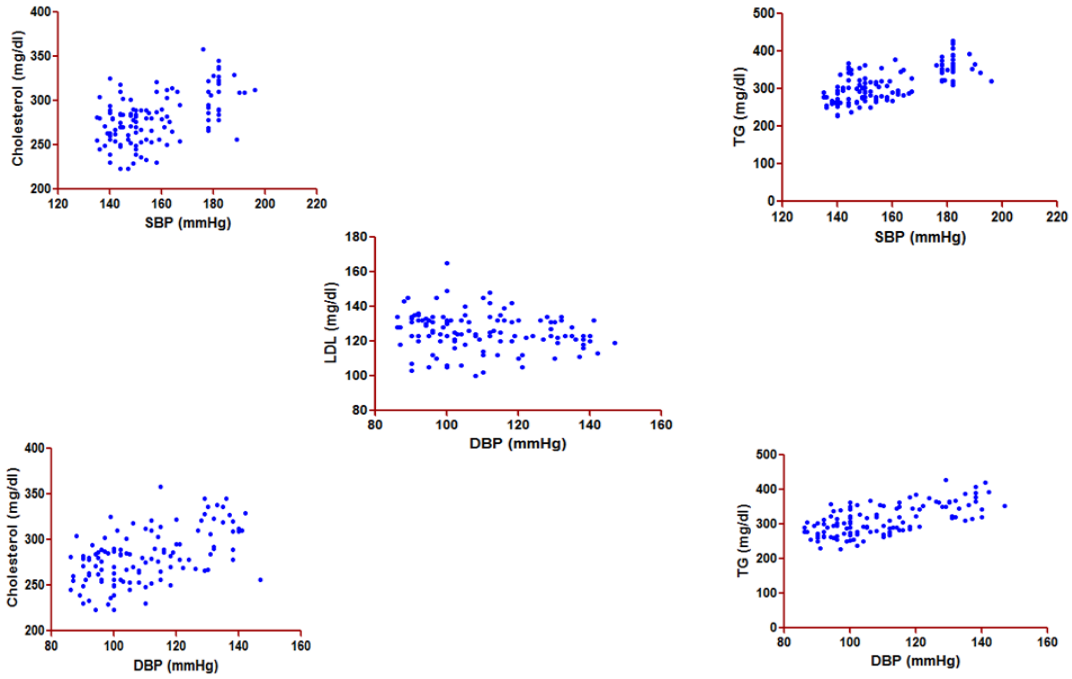

Figure 2: Correlation between lipid profile parameters and blood pressure.

In the lipid profile, serum cholesterol (r = 0.5236, $p < 0.0001$) and TG (r = 0.6626, $p < 0.0001$) exhibited a strong positive correlation with SBP in hypertensive subjects. Both cholesterol (r = 0.5296, $p < 0.0001$) and TG (r = 0.6509, $p < 0.0001$) were also positively correlated with DBP, while LDL (r = -0.1617, $p = 0.0388$) showed a negative correlation with DBP (Figure 2).

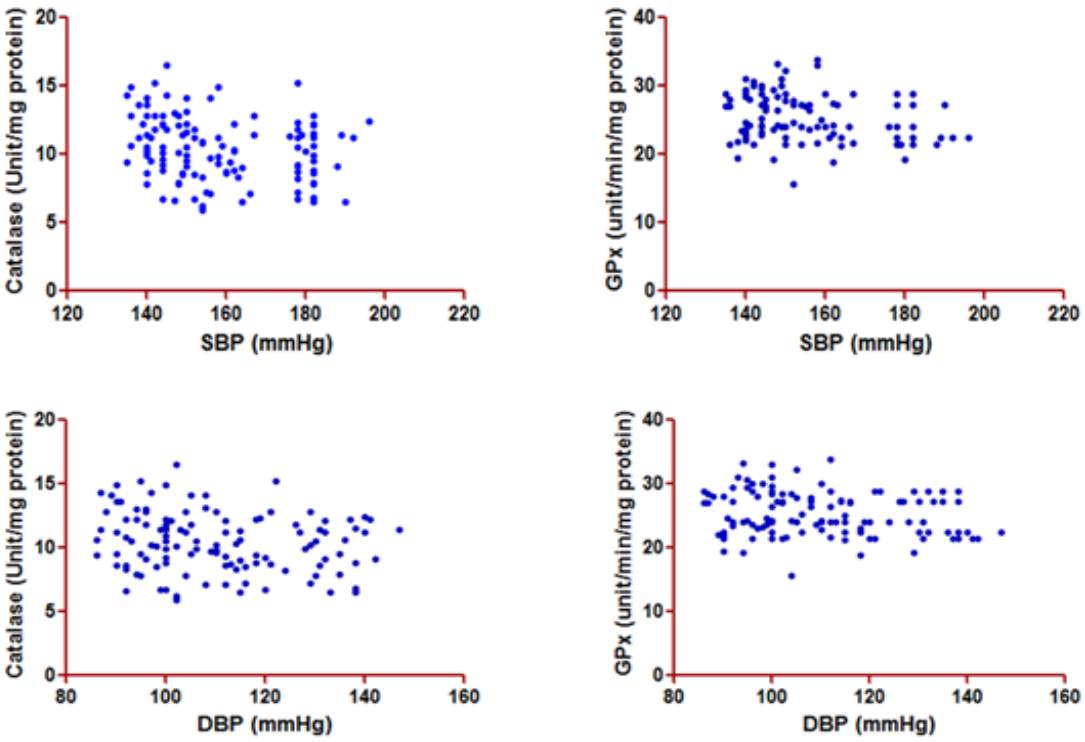

Figure 3: Correlation between oxidative stress parameters and blood pressure.

Regarding oxidative stress, CAT (r = -0.2168, p = 0.0087) and GPx (r = -0.1725, p = 0.0298) were negatively correlated with SBP in hypertensive subjects. Similarly, DBP showed a negative correlation with CAT (r = -0.1925, p = 0.0176) and GPx (r = -0.1536, p = 0.0470) (Figure 3).

DISCUSSION:

The present study found significant differences in anthropometric indices, with BMI and WHR being significantly higher ($p < 0.001$) in hypertensive subjects compared to normotensive subjects. A statistically significant positive correlation was observed between both BMI and WHR with SBP and DBP. These findings are consistent with those of Adegoke et al. (2021) [18]. Similarly, Naval K. Vikram et al. (2016) [19] identified BMI and WHR as significant risk factors for HTN. A meta-analysis by Yusni Y et al. (2024) [20] further supports that higher BMI is consistently associated with HTN. Increased body fat, particularly visceral fat, contributes to insulin resistance, which in turn raises BP.

While BMI is commonly used to assess obesity, it has limitations, such as its inability to differentiate between fat and lean mass or consider fat distribution. Growing evidence suggests that fat distribution, especially in the abdominal region, may pose a greater health risk than the total amount of body fat [21]. Research has shown that WHR is a strong predictor of cardiovascular risk and myocardial infarction across different populations [22].

This study examined the relationship between lipid profiles, HTN and atherosclerotic indices, with a particular focus on dyslipidemia. The results demonstrated that hypertensive subjects had significantly higher levels of cholesterol, TG, and LDL compared to normotensive subjects. Chen et al. (2022) [23] found that elevated cholesterol and LDL levels were strongly associated with HTN, while TG levels did not show a significant correlation. The positive correlation observed between SBP, DBP and cholesterol, TG, as well as the relationship between LDL and DBP, aligns with the findings of Otsuka et al. (2016) [24]. One proposed mechanism for this association is the impairment of endothelial function due to dyslipidemia, which disrupts the balance between endothelium-derived relaxing and contracting factors, ultimately reducing NO production [25]. This endothelial dysfunction negatively impacts vasomotor activity, leading to dysregulated vasoconstriction and elevated BP, thus creating a self-perpetuating cycle [26]. Furthermore, endothelial damage exacerbates vascular stiffness and atherosclerosis, which further contributes to the development and progression of HTN.

In this study, we observed decreased erythrocyte levels of CAT, SOD, and GPx in hypertensive subjects, alongside increased levels of LPO. These findings highlight the intricate relationship between oxidative stress and HTN. CAT is a critical antioxidant enzyme that reduces oxidative stress by catalyzing the breakdown of H_2O_2 into water and oxygen. However, CAT can also inhibit endothelial-dependent dysfunction of arteries, which may contribute to HTN [27]. Our results align with those of Ahmad et al. (2013), who reported a significant downregulation of circulatory CAT levels in hypertensive subjects in an Indian population [28]. Additionally, our correlation analysis revealed a significant inverse relationship between CAT activity and both SBP and DBP in hypertensive subjects, suggesting the potential role of CAT in the pathophysiology of HTN. This is consistent with the findings of Guo et al. (2018), who also reported a significant negative correlation between CAT activity and HTN [29], further supporting the hypothesis that reduced CAT activity is associated with elevated BP.

SOD is a key antioxidant enzyme responsible for dismutating superoxide radicals into H_2O_2, thereby mitigating oxidative stress. In the present study, we observed significantly lower SOD activity in hypertensive subjects (3.67 ± 1.5 U/mg protein) compared to normotensive subjects (7.11 ± 2.94 U/mg protein). This finding is consistent with Awasthi et al. (2003), who reported a reduction in SOD activity in hypertensive subjects, attributing this decline to the enzyme's compensatory response to chronic oxidative stress [30]. Furthermore, Xiaoqian Yu et al. (2022) demonstrated a significant negative correlation between SOD activity and early renal damage in hypertensive subjects, suggesting a protective role for SOD in preserving renal function in HTN [31]. Research by Gomez-Marcos et al. (2015) highlighted the potential of SOD as a marker for cardiovascular changes in hypertensive and diabetic subjects, linking variations in SOD levels to alterations in vascular structure and function, and suggesting that SOD may serve as a biomarker for vascular and renal complications in HTN [32].

GPx levels were significantly lower in hypertensive subjects (25.35 ± 3.45 vs. 49.61 ± 8.64 U/min/mg protein), indicating a compromised antioxidant defense system. Our correlation analysis revealed a significant negative correlation between GPx activity and both SBP and DBP in hypertensive subjects. This

finding is consistent with Ahmad et al. (2013), who also reported a significant negative correlation between GPx activity and HTN [28]. CAT, SOD, and GPx are essential components of the antioxidant defense system, where SOD converts superoxide radicals to H_2O_2, which is then metabolized by CAT and GPx. The interplay among these enzymes is critical for mitigating oxidative stress and maintaining vascular health [33]. Malondialdehyde (MDA), a product of LPO, is a well-established marker of oxidative stress and has been shown to impair mitochondrial function by disrupting the electron transport chain and oxidizing sulfhydryl groups in proteins. These alterations can interfere with various cellular processes, including signal transduction [34]. In the present study, we observed significantly elevated LPO levels in hypertensive subjects (4.56 ± 1.16 nmol MDA/ml) compared to normotensive subjects (2.01 ± 0.89 nmol MDA/ml), which further supports the role of oxidative damage in HTN. Increased LPO levels are commonly associated with HTN, indicating an underlying oxidative stress component in the pathophysiology of the disease [35].

CONCLUSION:

This study elucidates the complex relationship between HTN, oxidative stress, and metabolic abnormalities. Hypertensive subjects exhibited significant alterations in anthropometric parameters, lipid profiles, and oxidative stress biomarkers. Increased BMI and WHR were strongly associated with elevated BP, highlighting the role of obesity, particularly visceral fat, in the pathogenesis of HTN. Dyslipidemia, characterized by elevated cholesterol, TG, and LDL-C, exacerbated endothelial dysfunction and vascular damage.

Reduced activity of antioxidant enzymes (CAT, SOD, GPx) and elevated LPO levels in hypertensive subjects underscore the contribution of oxidative stress to HTN development. The negative correlation between antioxidant enzyme activity and BP suggests oxidative stress as a potential therapeutic target.

Management strategies for HTN should prioritize addressing oxidative stress, dyslipidemia, and obesity. Further research should focus on interventions aimed at enhancing antioxidant capacity and improving metabolic health to mitigate cardiovascular risk in hypertensive subjects.

Acknowledgment: We would like to acknowledge all the participants who took part in the study.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

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