# THE IMPLICATIONS OF INFLAMMATORY MARKERS AND LACTIC ACID IN ELDERLY PATIENTS WITH DEPRESSION

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THE IMPLICATIONS OF INFLAMMATORY MARKERS AND LACTIC ACID IN ELDERLY PATIENTS WITH DEPRESSION (Abstract): Depression can be defined as the nosological entity that includes both mood swings and psychotic symptoms, accompanied by emotional changes and a significant decrease in cognitive and psychomotor functions. The hypothesis of membrane theories of depression and its pathophysiology is based on the existence of a change in the structure and physiology of the cell membrane regarding receivers and loci for different substances. Tissue lesions are present in the cerebral atherosclerotic process with manifestations in the arterial endothelium whose dysfunction occurs as a result of a chronic inflammatory process caused by the atherosclerotic plaque. **Material and methods:** The study took place between January and June 2015 at the 5th Medical Clinic of the "CFR" Clinical Hospital in Iași, Romania. The study was conducted on 98 patients divided into two groups according to cardiovascular disease and the presence of depression and cognitive deficit**.** The objective of the study is the evaluation of depression and anxiety in correlation with the inflammatory profile in patients with cardiovascular disease. **Results:** Statistical analysis of intergroup differences for inflammatory markers, lactic acid and markers of subclinical atherosclerosis revealed that there are statistically significant differences between the average of said parameters between the two study groups. **Conclusions:** In the control group (patients with only cardiovascular disease) there were statistically significant correlations between the inflammatory markers, subclinical atherosclerosis, lactic acid and the assessment of depression and cognitive deficit. **Keywords:** DEPRESSION, ANXIETY, INFLAMMATORY MARKERS, LACTIC ACID, SUBCLINICAL ATHERO-SCLEROSIS.

Depression is considered an independent cardiovascular risk factor for future coronary events in healthy subjects. The most studied association between anxiety symptoms and somatic symptoms is that of cardiovascular and respiratory diseases, which can trigger states of fear, anxiety, and anxious waiting. Anxiety caused by the

presence of severe heart disease is worsened by the awareness of cardiac dysfunctions (tachycardia, extrasystoles, arrhythmias), the occurrence of retrosternal pain, breathing difficulties or fatigue (1-4).

A study carried out by the University of Iowa showed statistically significant correlations of lactic acid levels with anxiety levels. The results of the Iowa study suggest that one of the triggers for spontaneous panic attacks in patients with anxiety disorders could be increased lactic acid concentration in acid-sensitive fear circuits. Determination of lactic acid in the blood is known to play an important role in monitoring patients with tissue hypoxia (5). Clinical studies show the importance of determining blood lactate especially in patients in critical condition or at high risk of decompensation. The role of lactate in biochemistry and physiology is confirmed by clinical and experimental research. Clinically, the increase of blood level lactate indicates an exacerbation of tissue disorders and an increased risk of death. However, research has shown that the concentration of lactic acid <1 mmol/L has diagnostic significance. Lactic acid is one of the intermediates of glucose metabolism, a process that occurs in all organs and systems (6, 7). The largest production of lactate is in erythrocytes and muscle tissue, from which it enters the blood. Lactic acid is used in cardiomyocytes and hepatocytes in energy metabolism and glucose synthesis (gluconeogenesis). Sufficient perfusion of tissues with oxygen reduces glucose to $CO_2$ and $H_2O$ with energy release.

Insufficient perfusion of oxygen in the tissues can greatly accelerate anaerobic processes, which are known to be accompanied by the production of a much higher amount of lactic acid, which accumulates in the tissues and blood with the development of lactic acidosis. One such disorder that the elderly is more prone to and can lead to lactic acidosis is chronic venous disease (8). The determination of this metabolic product is a necessary method of monitoring patients with hypoxia and whose clinical condition changes rapidly (9). The concentration of lactic acid, according to the data of different studies, should be in the range of1.8-2.0/1.85-2.2/2.2-2.7 mmol/L.

The increase of lactic acid production in the myocyte leads to the decrease of the intracellular pH and implicitly the inhibition of glycolysis, the use of fatty acids and the overall process of protein synthesis, which ultimately leads to the necrosis of cardiomyocytes. In ischemia, it is known that increased lactic acid levels are one of the major causes of angina (10). Another effect high lactic acid can have on the body is the influence on bone density over time and future prosthetic interventions, which may, in turn, exacerbate the overall functional status of elderly patients, thus leading to depression (11).

## MATERIAL AND METHODS

The study took place between January and June 2015 at the 5$^{th}$ Medical Clinic of the "CFR" University Clinical Hospital in Iasi, Romania. The study was conducted on a number of 98 patients divided into two groups according to cardiovascular disease and the presence of depression and cognitive deficit.

- Group I: Normal cognition, which includes subjects with cardiovascular disease and normal psychological ageing without cognitive impairment or clinical depression - control group.
- Group II: Normal cognition, which in-

cludes subjects with cardiovascular disease and normal psychological ageing without cognitive impairment but with clinical depression.

Exclusion criteria included: history of substance use disorders, cognitive impairment, psychotic disorders, history of allergy to antihypertensive drugs, heart failure class III or IV NYHA, hepatitis B, C and/or HIV positive.

*The aim of the study.* To investigate the interaction of fibrinogen, C-reactive protein (CRP) as an inflammatory marker and lactic acid as a factor relating to depressive disorders. The study aims to explore whether determining the values of C-reactive protein, lactic acid and subclinical atherosclerosis have a predictive role in the occurrence of mixed depression/anxiety events in coronary patients.

*The objectives of the study*. Assessment of depression and anxiety in correlation with the inflammatory profile in patients with cardiovascular disease. Assessment of the clinical and biological correlations of depression-anxiety- subclinical atherosclerosis in the geriatric patient.

## RESULTS

*Group I*

*Assessment of anxiety and depression*

The average value of the Hamilton scale scores for depression was 2.43 points, 85% of the patients had the values of the Hamilton scale scores for depression within the range of 0-5 points (fig. 1).

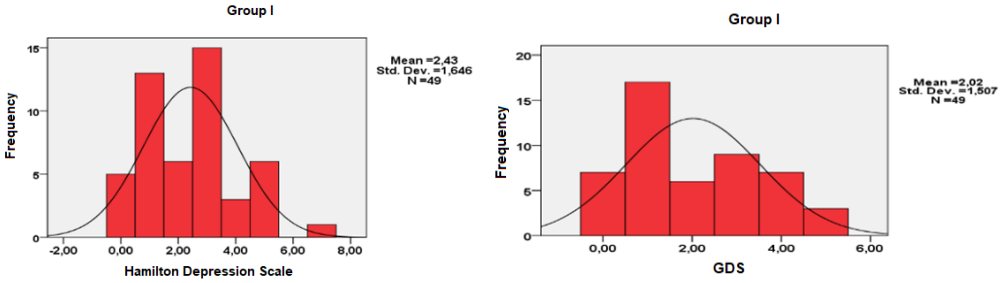


**Fig. 1**. Histogram of the distribution of the average values of the Hamilton scale in group I

The average value of the Geriatric Depression Scale scores was 2.02 points in group I. (fig. 1). Statistical analysis of the differences in the mean scales for assessing depression for the patients in group I by gender did not reveal statistically significant differences for both scales used (tab. I).

The average value of the Geriatric Depression Scale scores was 22.46 points, 69% of the patients had the values of the Geriatric Depression Scale scores within the range of 25-30 points (fig. 2). The average value of the Hamilton scale scores for depression was 24.06 points, 87% of the patients had the values of the Hamilton scale scores for depression within the range of 22-24 points (fig. 2).

TABLE I

**Mann-Whitney test in group I**

| test | HDRS | GDRS |
|---|---|---|
| Mann-Whitney U | 237,000 | 265,000 |
| Wilcoxon W | 562,000 | 590,000 |
| Z | - 1.274 | -0.707 |
| p | 0.49 | -0.28 |

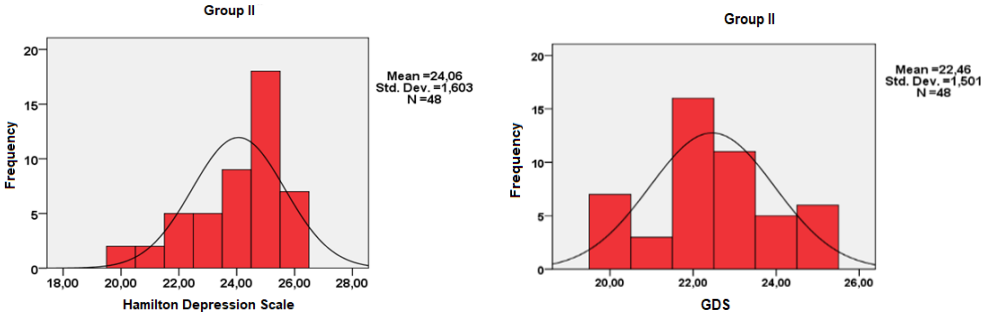


**Fig. 2.** Histogram of the distribution of the average values of the MMSE scores in group II.

Statistical analysis of the differences in the mean scales for the depression assessment for the patients in group II by gender did not reveal any statistically significant differences for both scales used (tab. II).

TABLE II

**Mann-Whitney test in group II**

| test | HDRS | GDRS |
|---|---|---|
| Mann-Whitney U | 267,500 | 158,500 |
| Wilcoxon W | 543,500 | 483,500 |
| Z | -0.419 | - 2.756 |
| p | 0.66 | -0.64 |

*Hamilton Anxiety Scale*

The mean value of the Hamilton Anxiety Scale was 8.31 points, 56% of the patients had the values of the Hamilton Anxiety Scale scores in the range of 4-6 points (fig. 3).

Statistical analysis of the differences in the means of the Hamilton Anxiety Scale for the patients in Group I by gender did not show statistically significant differences (U=298.0; z=-0.041; p =0.96).

The mean value of the Hamilton Anxiety Scale scores was 18.02 points, 81% of the patients had the values of the Hamilton Anxiety Scale scores within the range of 17-20 points.

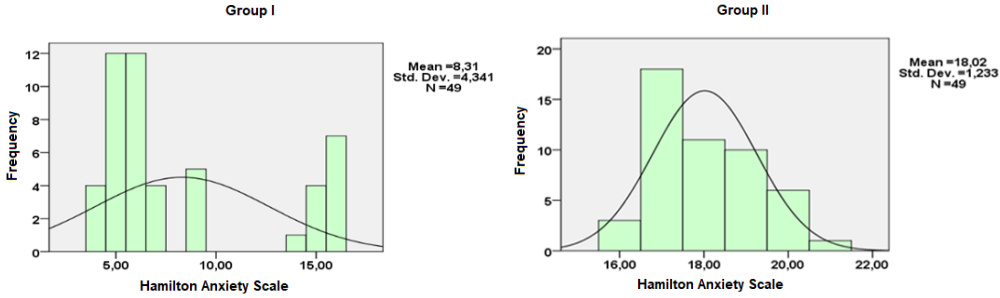


**Fig. 3.** Histogram of the distribution of the mean values of the Hamilton Scale for Anxiety in Group I and Group II

Statistical analysis of the differences in the means of the Hamilton Anxiety Scale for the patients in Group II by gender showed no statistically significant differences (U=287.0; z=-0.49; p =0.80).

*Inflammatory markers*

The mean fibrinogen value was close to 2.57 mg/dL, 59% of patients had mean fi-

brinogen values in the range of 2.5-3.0 mg/dL. The mean CRP value was 3.46 mg/dL, 89% of patients had mean CRP values in the range of 3.0-4.0 mg/dL (fig. 4).

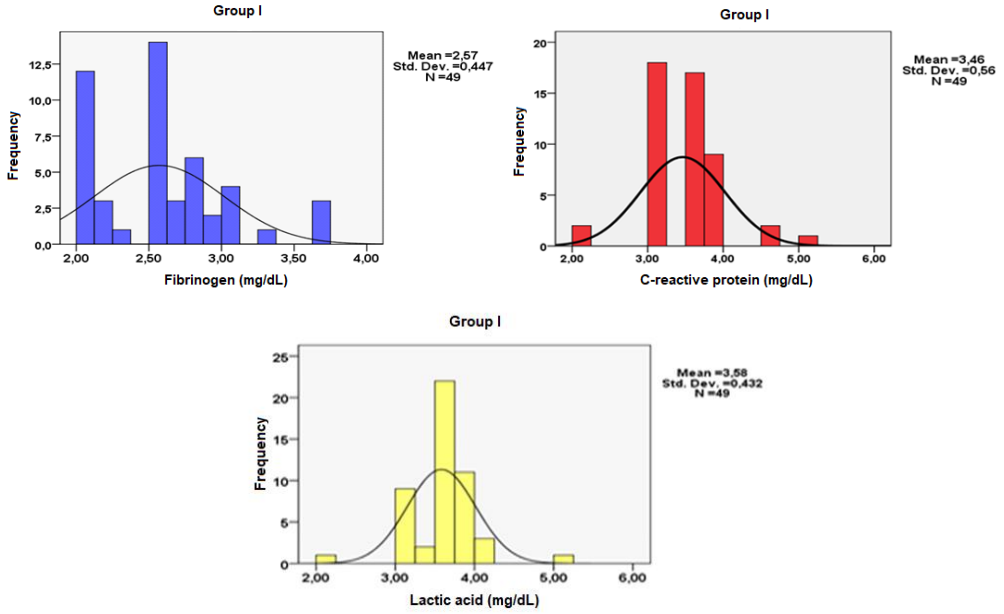


**Fig. 4.** Histogram of the distribution of fibrinogen means values in group I.

The mean lactic acid value was 3,68 mg/dL, 96% of patients had mean lactic acid values in the range of 3-4 mg/dL (fig. 4).

*Group II*

The mean fibrinogen value was 2.88 mg/dL, 67% of patients had the mean fibrinogen value in the range of 2.5-2.9 mg/dL. The mean CRP value was 3.86 mg/dL, 61% of patients had mean CRP values in the range of 3.3-3.8 mg/dL. The mean lactic acid value was 4.65 mg/dL, 69% of patients had mean lactic acid values in the range of 4.5-4.8 mg/dL (fig. 5).

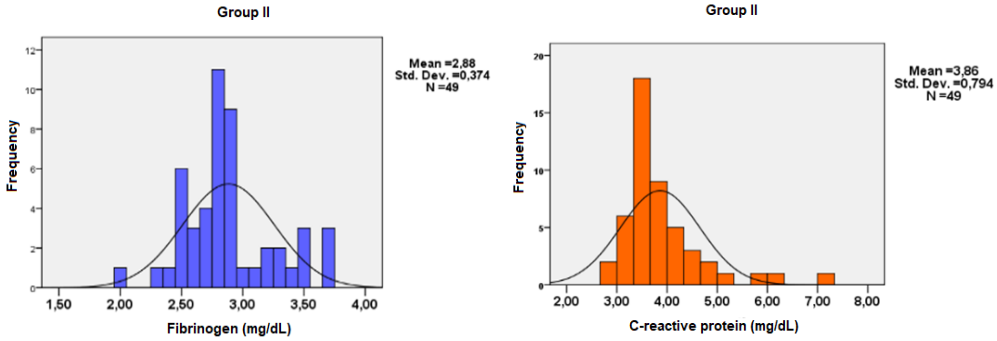


**Fig. 5.** Histogram of the distribution of the average fibrinogen values in group II

*The markers of subclinical atherosclerosis*

The literature suggests that the identification of subclinical atherosclerosis by noninvasive techniques such as ankle-brachial index (ABI), carotid intimal thickness (CIT), cardiac calcium scoring, arterial stiffness index, in asymptomatic individuals could be a useful method for both long-term predictions, where there is still no prediction tool, as well as for improving short-term prediction.

Subclinical atherosclerosis is strongly correlated with future cardiovascular events, independent of conventional cardiovascular risk factors. Its detection would be important because it would indicate an extremely aggressive intervention on risk factors, both by optimizing lifestyle and statin therapy, independent of the overall cardiovascular risk, highlighting subclinical atherosclerosis in a vascular territory being constantly accompanied by other locations.

The mean value of the ABI scores was 0.77. 94% of the patients had the ABI values in the range of 0.7-0.8 (fig. 6).

The mean value of the CIT scores was close between men (0.74±0.71 SD) and women (0.74±0.72 SD) of group I. (0.74±0.71 SD). 88% of the patients had the CIT values in the range of 0.7-0.8 (fig. 6).

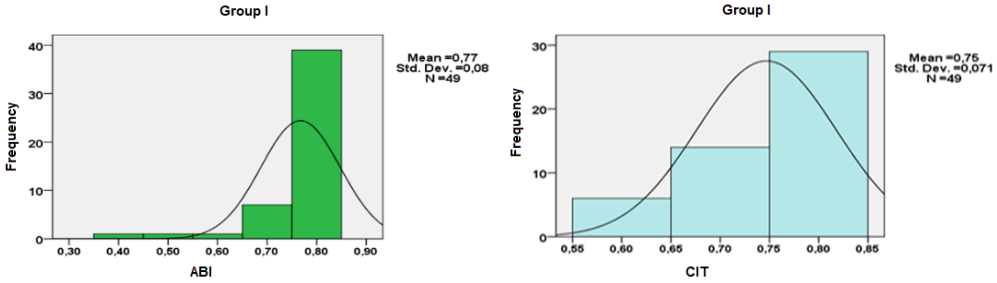


**Fig. 6.** Histogram of the distribution of the mean values of ABI, CIT in group I.

The mean value of the ABI scores was 0.81, 94% of the patients had the ABI values in the range of 0.7-0.8 (fig. 7).

The mean value of the CIT scores was 0.80, 88% of the patients had the CIT values in the range of 0.8-0.9 (fig. 7).

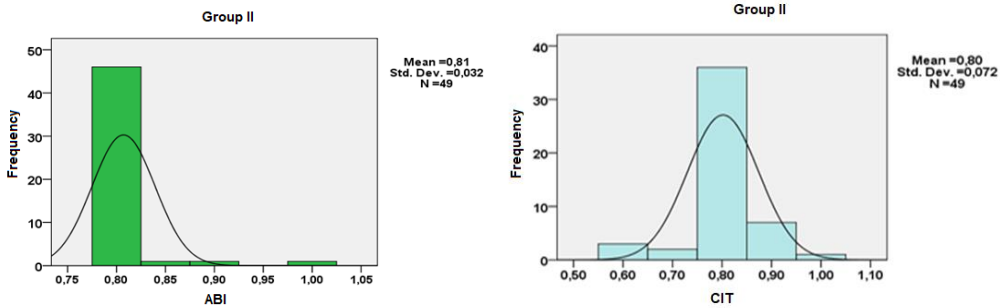


**Fig. 7.** Histogram of the distribution of the mean values of ABI, CIT in group II

*Correlation analysis*

The study of the correlations between the markers of subclinical atherosclerosis and cognitive status, depression, and anxiety in the patients of group I highlighted the following significant correlations:

- *Fibrinogen* was significantly correlated with lactic acid (p =0357. r=0.012), Hamilton Anxiety Scale (p=0.283. r=0.049), Hamilton Depression Scale (p=0.386. r=0.006), Geriatric Depression Scale (p=0.309. r=0.031), ABI (p=0.529. r ≤ 0.001), GIN (p =0.623. r ≤0.001).

- *CRP* was significantly correlated with lactic acid (p =-0.05. r ≤0.001), Hamilton Anxiety Scale (p =0.492. r ≤0.001). Hamilton Depression Scale (p =0.49. r ≤0.001).

- *Lactic acid* was significantly correlated with CRP (p =-0.5. r ≤0.001), fibrinogen (p = 0.357. r=0.012), Hamilton Depression Scale (p =0.792. r ≤0.001), Hamilton Anxiety Scale (p = 0.439. r ≤0.001), Geriatric Depression Scale (p =0.372. r=0.008), CIT (p =0.368. r=0.009).

The study of the correlations between the markers of subclinical atherosclerosis and cognitive status. depression and anxiety in the patients of group II highlighted the following significant correlations:

- *Fibrinogen* was significantly correlated with MMSE (p =0.521. r ≤0.001), Hamilton Anxiety Scale (p =0.286. r=0.046), Hamilton Depression Scale (p =0.357. r=0.012), CRP (p =-0.49. r ≤0.001)

- *CRP* was significantly correlated with lactic acid (p =-0.48. r ≤0.001), MMSE (p = 0.75. r ≤0.001), Hamilton Anxiety Scale (p =-0.349. r=0.014), Hamilton Depression Scale (p =-0.48. r ≤0.001).

- *Lactic Acid* was significantly correlated with CRP (p =-0.48. r ≤0.001), MMSE (p =-0.45. r=0.001), Hamilton Anxiety Scale (p =0.595. r ≤0.001), Hamilton Depression Scale (p =0.44. r≤0.001), Geriatric Depression Scale (p =0.296. r=0.039), CIT (p =-0.28. r=0.046).

## DISCUSSION

In most degenerative processes specific to cardiovascular ageing, but also in cardiovascular diseases, adaptive structural and functional tissue changes occur at both macrovascular and microvascular levels (12). The significant increase in the carotid intimal thickness and the rarefaction of the conjunctival microcirculation (a phenomenon characterized by a decreased density of arterioles and capillaries) are examples of such changes. The carotid intimal thickness is used as a predictive index of future cardiovascular and cerebrovascular events (13). The association of the change of the carotid intimal thickness with cerebrovascular diseases, symptomatic strokes but also with cerebral lacunes was confirmed by clinical studies. An association between asymmetric cerebrovascular pathology and left cerebral pathology was also observed. High blood pressure has also been described as an independent risk factor, possibly a predictor of cerebral lacunes and cerebral white matter lesions, which in turn, are predictive factors for the development of cognitive impairments over time (14).

Oxidative stress amplifies the movement of proinflammatory cells, increases the expression of some adhesion molecules to the surface of endothelial cells and causes lipid oxidation at the blood-brain barrier (10, 15-17). Similar to our results, it was found that erythrocyte sedimentation rate and total serum proteins could be used as a predictive biomarker for high or low levels of anxiety in patients with chronic obstructive pulmonary disease, indicating that routine blood panels could serve as objective indicators of psychiatric symptoms in chronically ill patients (18).

The pathophysiology of Alzheimer's disease is described microscopically by the presence of senile plaques and neurofibrillary tangles along with the decrease in the

number of synapses and macroscopically by cerebral atrophy. Tests on oxidative damage were performed in the brains of patients with Alzheimer's disease by post-mortem harvesting. The main element of senile plaques is β-amyloid. Although this is not a defining characteristic, it is associated with Alzheimer's disease and old age. The relation of the β-amyloid with oxidative stress is controversial. Some studies give it as a source of free radicals and give it a prooxidative role (19) and as an inducer of neuronal apoptosis.

The boundaries between degenerative dementia and vascular dementia are now less clear and both types include several risk factors, clinical and/or pathological features of the same kind. Cerebrovascular disease is thought to play an important role in the presence and severity of Alzheimer's disease (9). A meta-analysis of randomized controlled research shows that cholinesterase inhibitors used in the treatment of degenerative dementia led to only minor cognitive improvements, causing uncertain clinical significance in patients with early to moderate vascular dementia.

Differences in the calibration of depression, research design and presentation of results, determined the heterogeneous nature of the findings. Risk factors for post-stroke dementia are female gender, physical disability, a history of depression and a history of mental and emotional vulnerability after stroke. The diagnosis of post-stroke depression can be masked by symptoms such as aphasia, agnosia, apraxia, and memory disorders. Although there is encouraging data on the prophylactic use of antidepressants in stroke patients, there is still insufficient evidence to implement this approach in therapeutic protocols after a stroke (1, 20).

Territorial increase of cardiac noradrenergic activity may be the condition by which desipramine (a possible noradrenaline reuptake inhibitor) leads to increased blood pressure values (1).

Another theory shows that the central serotonin system could be responsible for regulating blood pressure. Inhibition of serotonin reuptake causes a cascade of changes in central neurotransmission, accentuating the tone of the vegetative nervous system. Fluoxetine and sertraline lead to increasing and altered blood pressure in patients with orthostatic hypotension and can be used to treat recurrences of hypotension.

## CONCLUSIONS

Within the control group (patients with only cardiovascular disease) there were significant statistical correlations between the inflammatory markers, subclinical atherosclerosis, lactic acid and the assessment of depression.

There were no statistically significant differences between the means of the studied parameter values based on the gender of the patient in the overall study group.

Inflammatory markers were significantly correlated with the scores obtained when assessing depression and anxiety.

Lactic acid as a substrate for anxiety has been correlated with depression.

ABI and CIT as indirect determinants of subclinical atherosclerosis were statistically significantly correlated with depression.

## CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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