

Association of Pre- and Post- dialysis Uric Acid Difference to Left Ventricular Structural and Functional Disorders in Maintenance Hemodialysis Patients

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Abstract:

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Background: The hallmark of gout is hyperuricemia. This substance has ties to cardiovascular disease's pathophysiology, which is the main killer of dialysis patients. Diabetes, insulin resistance, and other cardiovascular diseases as well as hypertension are all linked to hyperuricemia. Death from any cause is prevented by high SUA levels. Smaller studies found J-shaped relationships between SUA and all-cause mortality. In line with its function in protein metabolism, a recent study suggests that SUA could be used as a nutritional status indicator in hemodialysis patients. Rather than a high SUA, a superior nutritional state may explain survival connections. In HD patients, LVH with diverse etiologies is predictive of CV mortality and morbidity. **Aim:** to investigate the relationship between left ventricular morphological and functional problems and pre- and post-dialysis uric acid differences in individuals receiving maintenance hemodialysis. **Subject and Methods:** This study was carried out on ESRD patients in Internal Medicine Department of Benha University in the hemodialysis unit, where 100 patients were selected.

Results: There were high statistically significant differences between the studied patients systolic and diastolic blood pressure before and after hemodialysis. There were high statistically significant differences between the studied patient's serum level of uric acid, creatinine and urea before and after hemodialysis. **Conclusion:** This study found a strong relationship between uric acid and both LV parameters and ejection fraction. We discovered through regression analysis that serum uric acid was an important indicator of LV ejection fraction.

Key words: uric acid pre- and-post dialysis, Heart failure, hemo-dialysis.

Introduction

The last product of purine metabolism is uric acid, which is excreted through the

kidneys (60–70%) and the intestines (30–40%). As a result, increasing serum

uric acid levels are linked to diminishing renal function, and 40% to 80% of people with end-stage renal disease (ESRD) have hyperuricemia, which is often indicated by SUA levels below 7 mg/dl (416 mmol/L). (1) Due to its sieving coefficient (1.01) and clearance +7/pattern, SUA is effectively removed from blood in patients receiving hemodialysis; as a result, 1 g of uric acid is typically cleared after one hemodialysis session (1) Hyperuricemia is often a defining characteristic of gout. The leading cause of death in dialysis patients, cardiovascular disease, has also been linked to this substance's genesis, and it has been suggested that it has deleterious pathophysiological effects (2) The NACHT, LRR, and PYD domains (NALP3) inflammasome, which causes the production of interleukin-1b and reactive oxygen species, as well as having antioxidant properties, have been demonstrated to trigger inflammatory pathways in the body. Additionally, uric acid activates the renin-angiotensin-aldosterone pathway, damages the endothelium, affects artery function, and encourages the growth of vascular smooth muscle cells (3,4).

This is due to the fact that hyperuricemia has been linked to a variety of illnesses,

including those connected to cardiovascular disease, such as hypertension, diabetes mellitus, and insulin resistance (1,5). Despite studies investigating the role of SUA in the context of high risk of mortality and cardiovascular disease in ESRD patients being inconclusive and reporting direct, inverse, or different forms of associations, there is consensus regarding the relationship between high SUA levels and the risk of all-cause mortality as well as cardiovascular related mortality in the general population (6, 7). High SUA levels were found to be associated with a lower risk of death in the four largest cohort studies, which included data from the Dialysis Outcomes and Practice Patterns Study (DOPPS; n5827) (8), DaVita Inc. (n4298) (9), Korean Society of Nephrology registry (n7333) (10), and Taiwan Society of Nephro A U-shaped link between SUA and all-cause mortality was discovered by another sizable Asian cohort study with 1738 participants (11); nevertheless, smaller studies discovered J-shaped interactions(12,13).

Differences in cohort characteristics, a lack of statistical power, and the possibility of residual confounding could all be factors in the inconsistent results

of the study. Regarding the latter, new research has identified SUA as a marker of nutritional status among hemodialysis patients (9,14) and has hypothesised that a superior nutritional status, rather than a high SUA, is likely to explain survival relationships. This is consistent with SUA's role in protein metabolism. Target SUA levels for individuals undergoing hemodialysis can be defined by better understanding the underlying processes of these unexpected findings. In HD patients, left ventricular hypertrophy (LVH), which has a complicated aetiology, is a reliable indicator of CV mortality and morbidity.

Over the previous ten years, a number of cross-sectional clinical investigations have investigated the relationship between UA and LVH in the general population, hypertensive cohorts, and patients with diabetes and renal failure (15 & 16). The first study to demonstrate UA as a predictor of long-term echocardiographic alterations from normal left ventricular mass index (LVMI) to LVH in a population sample was the Pressioni Arteriose Monitorate E Loro Associazioni 10-year follow-up study (17). This is the first clinical study to examine the association between serum UA level and LVH in HD patients since, to our knowledge, there is no information in the literature on the

clinical effect of longitudinal changes in blood UA levels on LVH in HD patients.

Patients and Methods

Patients:

This prospective study was carried out on ESRD Patients in internal medicine department of Benha university in the hemodialysis unit, where 100 patients was selected from the beginning of dialysis and follow up according to their serum uric acid difference pre- and post-dialysis and left ventricular parameters after approval of ethical committee and taking consents from the studied group of patients.

Methods:

This prospective study was carried on ESRD patient who began dialysis in our hemodialysis unit and follow up every six months for about one year from June 2021 to July 2022 according to serum uric acid difference pre and post dialysis sessions with left ventricular structural and functional parameter by monitoring next laboratory and radiological investigations.

Regression analysis was conducted to study the correlation between FA- SUA (Follow up- Averaged Serum Uric Acid) and LV parameters and MACEs (Major Adverse Cardiovascular Events including ACS, CVS and Cardiovascular mortality).

□ Inclusion criteria:

Patients with ESRD started dialysis and became on regular hemodialysis.

□ Exclusion criteria:

Age less than 18-years-old, patients with tumor lysis syndrome or on chemotherapy, pregnancy, and patients with thyroid diseases, were excluded

All of them were subjected to the following procedures after taking their written consents.

- History taking included:
- Age (years)
- Gender
- Duration of hemodialysis (months)
- Clinical examination:
- Blood pressure: systolic and diastolic blood pressure pre- and post-dialysis (mmHg).
- Body mass index (BMI).
- The blood tests considered in our plan:
 - Serum Uric acid (mg/dL) pre- and post-dialysis
 - Pre- and post- dialysis uric acid difference= pre-dialysis serum uric acid level minus post-dialysis serum uric acid level
 - Hemoglobin (g/dl)
 - Serum albumin (g/dl)
 - Serum Creatinine (mg/dL)

- Serum urea (mg/dL)
- Serum sodium (mEq/L)
- Serum potassium (mEq/L)
- Serum calcium(mg/dL)
- Serum phosphorus(mg/dL)
- Parathyroid hormone(ng/dL)
- Lipid profile
- C-Reactive protein (CRP) (mg/L)

➤ Imaging:

• Electrocardiography: Twelve lead surfaces ECG was done for each patient.

• Echocardiography:

A) Conventional transthoracic echocardiography (TTE);

Two-dimensional echocardiography and Doppler examination were performed with a commercially available ultrasound system (Philips, Epic 7c, equipped with a 5.5 X transducer). LA and left ventricular (LV) measurements were taken using the two-dimensionally guided M-mode, (2D), conventional Doppler on mitral inflow.

A two-dimensional echocardiographic study was used to assess:

□ LV ejection fraction by modified Simpson biplane method, fractional shortening (FS) and LV diameters (both end-systolic and end-diastolic diameters), were used

□ Left ventricular mass and left ventricular mass indexed to body surface

area estimated by LV cavity dimension and wall thickness at end diastole (19).

LV Mass (g) = $0.8\{1.04(((LVEDD + IVSd + PWd)^3 - LVEDD^3))\} + 0.6$

Pulsed Doppler transmitral flow:

Pulsating wave patterns of mitral inflow Doppler imaging shows early diastole (E wave) passive ventricular filling and late 7 active filling phases during atrial contraction. In the apical four-chamber view, the sample volume is positioned near the tips of the mitral leaflets.

B) Tissue Doppler Imaging:

Using traditional two-dimensional echocardiography while holding your breath and recording a stable ECG, pictures of the apical four chambers and two-chamber view will be obtained for examination of the TDI derived strain of the LA chamber.

In the apical four- and two-chamber views, the pulsed wave TDI sample volume will be positioned on the mitral annulus. In order to get mitral annular velocities, pulsed wave tissue Doppler imaging (TDI) was carried out in the apical views. The early diastolic (E') and systolic (S) measurements were made.

Six months and one year follow up:

A. Major adverse cardiovascular events:

- Coronary artery disease.
- Heart failure.

- Stroke
- Arrhythmia
- DM and metabolic syndrome.
- Hypertension.
- Other cause mortality

B. Electrocardiography.

C. Echocardiography:

The previous echocardiographic parameters were reassessed again.

Data management and statistical analysis: -

The collected data was recorded then presented, and statistically analyzed by computer using Statistical Package for the Social Sciences (SPSS) 22.0 for windows (SPSS Inc., Chicago, IL, USA) as follow:

- Editing and coding.
- Data entry in computer.
- Data were summarized and presented in tables and graph.
- The normality of distribution for the
- The Kolmogorov-Smirnov test was used to test the investigated variables. As applicable, the mean and Standard Deviation (SD) for parametric data, the median and Inter Quartile Range (IQR) for nonparametric data, and the number and percentage for qualitative data were used to summarise the collected data. The paired t-test and repeated measurements were used to compare the various study participants. To find

differences between patients, Wilcoxon test and Friedman ANOVA test to compare nonparametric quantitative data (median & IQR), ANOVA test to examine parametric quantitative data (mean and SD), and post HOC test were used. Spearman correlation between nonparametric quantitative data was done.

- Linear regression for predictors of quantitative data was done.
- All tests were two sided. The accepted level of significance in this work was ($p < 0.05$), $p \leq 0.001$ was considered highly statistically Significant (HS), and $p > 0.05$ was considered Non statistically Significant (NS).

Results

Table (1) shows that there were high statistically significant differences

between the studied patients serum level of uric acid, creatinine and urea before and after hemodialysis ($p < 0.001$). the mean \pm SD of uric acid, creatinine and urea level had significantly decreased after hemodialysis (7.7 ± 2.6 mg/dl), (5.04 ± 0.87 mg/dl) and (92.4 ± 15.1 mg/dl) respectively.

Table (2) shows that there were high statistically significant differences between the studied patients LV ejection fraction before and after 6 and 12 months of hemodialysis ($p < 0.001$). LV ejection fraction has significantly increased on 6 and 12 months follow up after hemodialysis. the mean \pm SD of LV ejection fraction before and after 6 and 12 months of hemodialysis were (44.2 ± 5.5 %), (44.6 ± 5.5 %), (45.2 ± 5.4 %) respectively.

Table (1): Serum uric acid, creatinine, and urea levels before and after hemodialysis among studied patients:

All patients (n= 100)		Mean \pm SD	Paired t test	P value
Serum Uric acid (mg/dL)	Pre-dialysis	8.1 \pm 2.8	6.567	< 0.001 (HS)
	Post- dialysis	7.7 \pm 2.6		
Serum Creatinine (mg/dL)	Pre-dialysis	11.7 \pm 1.5	40.565	0.000 (HS)
	Post- dialysis	5.04 \pm 0.87		
Serum urea (mg/dL)	Pre-dialysis	281.6 \pm 53.2	33.629	0.000 (HS)
	Post- dialysis	92.4 \pm 15.1		

Table (2): LV ejection fraction pre-and post-dialysis among studied patients:

LV ejection fraction (%)	Mean \pm SD	Repeated measure ANOVA Test	P-value
Pre-dialysis (%)	44.2 \pm 5.5	7.291	
6 months post dialysis (%)	44.6 \pm 5.5		< 0.001
12 months post dialysis (%)	45.2 \pm 5.4		(HS)

Table (3): Correlation between pre-dialysis serum uric acid pre-dialysis LV ejection fraction:

Normal level of serum uric acid	Spearman correlation Coefficient	P value
LV ejection fraction	.628	.012(S)
Increased level of serum uric acid	Spearman correlation Coefficient	P value
LV ejection fraction	-.981	.000(HS)

Table (3) shows that there was significant positive correlation between baseline serum uric acid at normal level ($p < 0.05$) and LV ejection fraction. There was significant negative correlation between baseline serum uric acid at high level (hyperuricemia) and LV ejection fraction ($p < 0.05$).

Table (4) shows that there was significant positive correlation between serum uric acid at normal

level after dialysis ($p < 0.05$) and LV ejection fraction after dialysis. There was significant negative correlation between serum uric acid at high level after dialysis (hyperuricemia) and LV ejection fraction after dialysis ($p = 0.000$). There was significant positive correlation between serum uric acid at low level after dialysis ($p < 0.05$) and LV ejection fraction after dialysis.

Table (4): correlation between serum uric acid and LV ejection fraction post-dialysis:

Normal level of serum uric acid (mg/dl)	Spearman correlation Coefficient	P value
LV ejection fraction (%)	0.57	.026(S)
Decreased level of serum uric acid (mg/dl)	Spearman correlation Coefficient	P value
LV ejection fraction (%)	.637	.03 (S)
Increased level of serum uric acid	Spearman correlation Coefficient	P value
LV ejection fraction	-0.549	0.000 (HS)

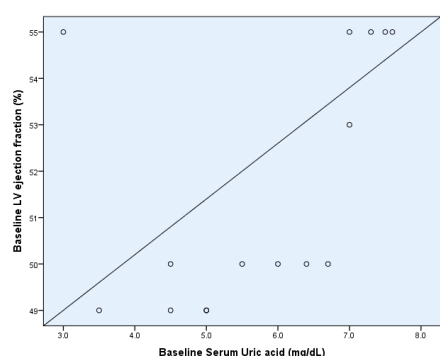


Figure (1): Correlation between baseline serum uric acid at normal level and baseline LV ejection fraction

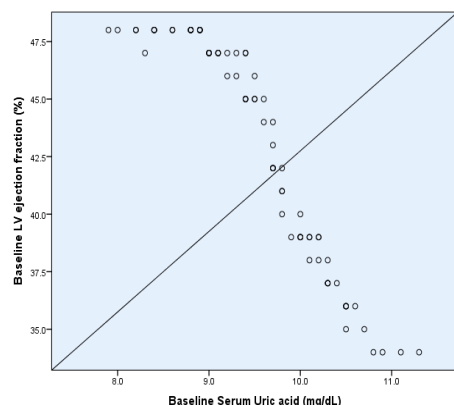


Figure (2): Correlation between hyperuricemia and baseline LV ejection fraction

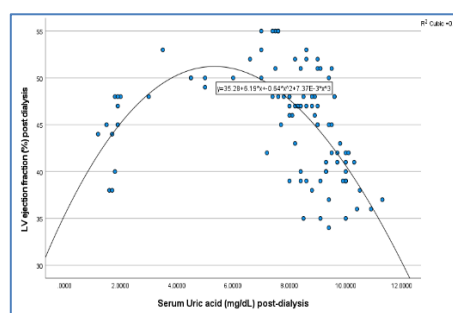


Figure (3): Correlation between serum uric acid and LV ejection fraction after dialysis

Table (5) shows that there was significant positive correlation between serum uric acid level after dialysis and E & S waves after dialysis among the studied patients ($p = 0.013$). There were significant negative correlations between baseline serum uric acid and E' wave among the studied patients ($p = 0.014$). Table (6) shows that there was significant correlation between change of uric acid pre- and post-dialysis and left ventricular ejection fraction and there were no significant correlations between uric acid change

pre- and post-dialysis and A, S, E, E'

Waves, LV mass and LV mass index.

Table (5) Correlation between post-dialysis serum uric acid and LV tissue doppler parameters:

Serum uric acid	Spearman correlation	P value
Left ventricular mass	.140	.164
E wave	.237	.018 (S)
A wave	.014	.889
S wave	.247	.013 (S)
E' wave	-.246	.014 (S)

Table (6) Correlation between pre- and post-uric acid difference and all LV parameters:

Pre- and post-Serum uric acid difference (Mean \pm SD= 0.45 \pm 0.69)	Pearson correlation	P value
LV EF %	.223	.026 (S)
Left ventricular mass (g)	.021	.837
LVMI (g/m ²)	-.026	.795
E wave (ms)	-.003	.980
A wave (ms/s)	.063	.530
S wave (cm/sec)	.118	.241
E' wave (cm/sec)	-.079	.432

Discussion

Despite being a significant antioxidant in human plasma, uric acid is the end product of purine metabolism in humans, and both correlate with and predict the onset of diseases linked to oxidative stress. Therefore, it has been demonstrated that an increase in serum UA is linked to an increased risk of hypertension (18), diabetes mellitus (19), coronary heart disease (20),

cardiovascular disease (21), stroke (22), and all-cause and CV mortality in the general population (23).

Although greater blood UA levels were linked to increased all-cause and CV mortality in CKD patients, the exact role of UA in the development of CKD is still unknown (24 - 27). Patients with CKD typically exhibit an increased UA level. However, it is still unknown and debatable how the UA level affects the

morbidity and mortality of hemodialysis (HD) patients. The variation of serum UA levels in HD patients is substantial. Studies show that serum UA levels in 40–80% of all HD patients are less than 7 mg/dL. (1, 12).

However, several research (7,28) have shown either increased or no difference in mortality. There is an inverse relationship between serum UA and CV and/or all-cause mortality, according to numerous studies that included HD patients (1,12).

Throughout recent years, various cross-sectional clinical examinations have explored the relationship among UA and LVH in everybody, hypertensive accomplices, and patients with diabetes and renal disappointment (16). The 10-year follow-up study was quick to show UA as an indicator of long-haul echocardiographic changes from ordinary LVMI to LVH in a populace test (17).

The primary goal of this study was to investigate the relationship between left ventricular structural and functional problems in maintenance hemodialysis patients and differences in uric acid levels between pre- and post-dialysis. The hemodialysis unit at Benha University served as the site of this prospective observational study. The

subjects of this study were 100 ESRD patients.

The main results of this study were as follows:

According to the current study's findings about differences between serum uric acid, creatinine, and urea levels before and after hemodialysis among studied patients, our research revealed that the examined patients' serum levels of uric acid, creatinine, and urea were significantly different before and after hemo-dialysis ($p < 0.001$). After hemo-dialysis, the mean \pm SD serum levels of uric acid, creatinine, and urea of the patients who were being investigated dramatically decreased. (7.7 ± 2.6 , 5 ± 0.8 and 92.4 ± 15.1 mg/dl respectively).

Patients with renal failure have elevated uric acid levels because of reduced clearance (5). Uric acid can be partially removed from blood via dialysis (29). Higher uric acid levels have been linked to higher mortality in hemodialysis patients, according to research. (30).

Hyperuricemia is common in patient with end-stage renal disease, which has been reported in up to 50% of subjects, probably due to deficiency in UA excretion (31).

In agreement with our results, it was reported that (32) mean pre-dialysis

serum uric acid was 6.56 ± 1.85 mg/dl while the post dialysis serum uric acid was mean 3.2 ± 2.24 mg/dl. There was a significant reduction in serum uric acid after hemodialysis.

Also, in agreement with our results (33) reported that Kidney function blood tests demonstrated significant decrease in creatinine, uric acid and urea levels in post-dialysis samples in comparison with pre-dialysis samples ($p < 0.001$) with a percent reduction of 57.62 ± 9.85 , 64.14 ± 18.8 and 67.03 ± 11.4 , respectively.

Regarding the differences between LV ejection fraction pre and post dialysis among studied patients, we found that there were high statistically significant differences between the studied patients LV ejection fraction before and after 6 and 12 months of hemodialysis ($p < 0.001$). LV ejection fraction has significantly increased on 6 and 12 months follow up after hemodialysis. The mean \pm SD of LV ejection fraction before and after 6 and 12 months of hemodialysis were (44.2 ± 5.5 %), (44.6 ± 5.5 %) and (45.2 ± 5.4 %) respectively.

In agreement with our results (34) reported that there were high statistically significant differences between the studied patients LV ejection fraction before and after hemodialysis ($p = 0.049$).

Also, in agreement with our results (35) reported that there were high statistically significant differences between the studied patients LV ejection fraction before and after hemodialysis ($p < 0.001$).

However, (36) revealed that there was no significant difference between pre- and post-dialysis LV ejection fraction. The same results were reported by (37).

According to the results of the current investigation, uric acid and LVEF have an inverted U-shaped association. However, other studies have found a U-shaped connection between uric acid and all causes of mortality (38,39).

Regarding the differences between LV mass pre and post dialysis among studied patients, we found that there were high statistically significant differences between the studied patients left ventricular mass before and after 6 and 12 months of hemodialysis ($p < 0.001$). Left ventricular mass has significantly decreased on 6 and 12 months follow up after hemodialysis. The mean \pm SD of left ventricular mass before and after 6 and 12 months of hemodialysis were (42.5 ± 6.9 g), (40.9 ± 7.2 g) and (40.2 ± 6.6 g) respectively. A previous study stated that increased LVM has been well described as a frequent component of ESRD (40).

In agreement with our findings, it was reported that pre-dialysis systolic blood pressure reductions are significantly linked with significant reductions in both LV mass and volumes (41).

Regarding the differences between LV mass index before and after dialysis among studied patients, we found that there were high statistically significant differences between the studied patients left ventricular mass index before and after 6 and 12 months of HD ($p < 0.001$). LVMI has significantly decreased on 6 and 12 months follow up after HD. the mean \pm SD of LVMI were (26.9 \pm 6.88 g/m²), (24.8 \pm 5.3 g/m²) and (24.3 \pm 5.1g/m²) respectively.

In agreement with our findings, it was stated that increased uric acid associated with high LVMI and LVMI decline with efficient sessions of dialysis and decrease volume overload (42).

Following 1 year of dialysis, we observed that there was huge positive relationship between serum uric corrosive at ordinary level after dialysis ($p < 0.05$) and LV ejection fraction after dialysis. There was critical negative relationship between serum uric level at high level after dialysis (hyperuricemia) and LV ejection fraction after dialysis ($p = 0.000$). There was huge positive relationship between serum uric level at

low level after dialysis ($p < 0.05$) and LV ejection fraction after dialysis.

After 1 year of dialysis, our outcomes showed that there was critical positive correlation between serum uric acid level after dialysis and E and S waves after dialysis among the studied patients ($p = 0.13$). There were critical negative connections between pre-dialysis serum uric level and E' wave among the studied patients ($p = 0.14$) (43).

In agreement with our results a group of researchers reported that a direct relationship between the level of serum uric acid and the ejection fraction was established ($p = 0.03$); patients with higher uric acid had an increased risk of having a lower ejection fraction. Also, concluded that higher serum uric acid levels are significantly correlated with the severity of congestive heart failure and left ventricular ejection fraction (44).

Our findings were corroborated by the study done by the group of researchers in 2019 that found a significant relationship between greater blood uric acid levels and the severity of congestive heart failure and left ventricular ejection fraction (44). Additionally, there was a strong connection between the FA UA group and LVH and CV mortality in patients receiving dialysis (44). As

opposed to our findings (45), it was shown that there was a substantial correlation between uric acid and left ventricular ejection fraction in CKD prior to dialysis, they claimed that serum uric acid was linked to left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction (LVDD). The discrepancy resulted from different inclusion criteria. The metabolic anomalies that result from the on-going decline in ejection fraction are possible contributory factors in these individuals' hyperuricemia. According to new evidence, uric acid, a result of purine metabolism, has a role in the development of heart failure along with other prognostic variables for the condition (46,47).

Serum uric acid was found to be a significant predictor of baseline LV ejection fraction in a linear regression study of predictors. Previous authors proved that a high blood uric acid is a direct risk factor for cardiac dysfunction validated this (48). Additionally, previous studies came to the conclusion that serum uric acid levels were a reliable indicator of LVD and LVDD in CKD patients, indicating that serum uric acid might serve as a biomarker for these conditions (45). In addition, others came to the conclusion that left ventricular hypertrophy occurs in HD patients who

experience chronic hypouricemia (46). The sole explanation for this counterintuitive connection is the idea that uremic milieu in HD patients alters the impact of uric acid.

Conclusion

In ESRD patients, hemodialysis was associated with significant reduction of SBP, DBP, uric acid, creatinine and urea, it was also associated with significant reduction in E & S waves, significant reduction Left ventricular mass while there was significant increase in E' wave and LV ejection fraction.

According to the current study, there is a strong relationship between uric acid and both LV ejection fraction and LV characteristics. We discovered through regression analysis that serum uric acid was an important indicator of LV ejection fraction.

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