Renalase and lupus nephritis: disease activity and histopathological classification

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Aim
To measure the level of serum renalase and to clarify its relation to lupus nephritis (LN) activity and histopathological classification.
Patients and methods
This study was carried out on 40 patients with systemic lupus erythematosus (SLE), diagnosed according to systemic lupus international collaborating clinics classification criteria (SLICC) criteria, and 20 healthy controls. They were 20 patients without nephritis and 20 patients with LN (17 active and three inactive LN). Venous blood samples were taken from all participants for complete blood count, erythrocyte sedimentation rate, kidney function, anti-double-stranded DNA, C3, C4, and renalase level. The serum renalase levels were determined by enzyme-linked immunosorbent assay. Assessments of protein in 24-h urine collection and protein/creatinine (P/C) ratio were done. Renal biopsies were obtained from patients with LN, with staging and activity and chronicity indices assessment. SLE disease activity was measured by Systemic Lupus Erythematosus Disease Activity Index, and LN activity was estimated by renal Systemic Lupus Erythematosus Disease Activity Index.
Results
Renalase levels were higher in patients with LN than both patients with SLE without LN and control group. The serum renalase levels of patients with LN were positively correlated with P/C ratio, 24-h proteinuria and C3, but negatively correlated with Systemic Lupus Erythematosus Disease Activity Index. For patients with active LN, there was no significant correlation between their serum renalase levels and the indicators of renal activity, including erythrocyte sedimentation rate, proteinuria, P/C ratio, anti-double-stranded DNA, C3, C4, and activity index of renal biopsy. The median of renalase as a marker for diagnosis of LN was 134.65, with a cutoff value of 100 μg/ml.
Conclusion
Serum renalase may be involved in LN pathogenesis but was not a good predictor for either LN activity or various stages of LN histopathology.

Keywords:
lupus nephritis, renalase, histopathogenesisxx

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that can affect virtually any organ of the body. Clinical features in individual patients can be quite variable, ranging from mild joint and skin involvement to severe life-threatening internal organ disease. The pathogenesis of SLE, which involves the various facets of the immune system, is complex and perplexing [1].

The kidney is the signature organ affected in SLE, and almost all studies of prognosis have identified lupus nephritis (LN) as a significant predictor of poor outcome [2].

LN has varying clinical presentations and consequences. It is diagnosed by the presence of urine protein/creatinine (P/C; or 24-h urine protein) representing 500 mg of protein/24 h or cell casts, and more definitely by biopsy [3]. Usually, an elevated erythrocyte sedimentation rate (ESR) and anti-double-stranded DNA (anti-dsDNA) and low C3 and C4 levels are associated with active nephritis, especially focal proliferative and diffuse proliferative LN. Clinically relevant LN is associated with a 30% decrease in creatinine clearance, proteinuria of greater than 1000 mg/d, and renal biopsy findings indicating active LN [4]. Kidney involvement is a great predictor of poor outcome in SLE, with 5–10% progression to

end-stage renal disease (ESRD) despite immunosuppressive therapy [5].

The principal goal of therapy in LN is to normalize renal function or, at least, to prevent the progressive loss of renal function. So early detection of LN or its activity is considered an essential step for proper treatment and better prognosis.

Renalase (amine oxidase), which is capable of metabolizing catecholamines, is mostly secreted by the kidney into the blood. Recently, reduced plasma renalase concentration was detected in patients with ESRD [6]. Up to our knowledge, there was only one published data about the potential role of renalase in LN pathogenesis and activity [7]. Therefore, this study was conducted to study the possibility of correlation of the serum renalase levels to the histopathogenesis and the activity of LN.

Patients and methods

This study was carried out on 40 patients with SLE, diagnosed according to systemic lupus international collaborating clinics classification criteria (SLICC) criteria [8], and 20 healthy controls. They were recruited from the inpatients and the outpatients' clinic of Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospitals. All participants were females, and their ages ranging between 20 and 49 years. The patient group included 20 patients without nephritis and 20 patients with LN, with 17 active LN and three inactive LN, grouped according to renal Systemic Lupus Erythematosus Disease Activity Index (rSLEDAI). The control group consists of 20 apparently healthy individuals with matched age and sex. All patients and controls provided an informed consent before participation. This work was approved by the ethical committee of faculty of medicine, Benha University.

Clinical histories and blood samples were collected from all patients and controls, and also renal biopsies were obtained from patients with LN on the same day of blood sampling. SLE disease activity was assessed according to the SLEDAI score to mild (score, 0–10), moderate (score, 11–20), severe (score, 21–45), and very severe (score >45), with rSLEDAI consisted of four kidney-related items of the total SLEDAI: hematuria, pyuria, proteinuria, and urinary casts/high power field (HPF), and ranges from 0 (inactive renal disease) to a maximum score of 16 [9].

Venous blood samples were obtained from all participants, and the following parameters were measured: complete blood count, serum creatinine, creatinine clearance, antinuclear antibody by immunofluorescence technique, anti-dsDNA antibody, complement C3 and C4, C-reactive protein, and ESR. The 24-h urine and spot urine sample was collected to estimate urinary protein excretion. Serum renalase was determined by blood coagulation at room temperature for 10–20 min, and then centrifugation for 20 min at a speed of 2000–3000 rpm for separation of the serum, which was then kept at −20°C until used. Serum renalase levels were carried out using a sandwich monoclonal enzymelinked immunosorbent assay kit for renalase in human urine and serum (EIAab Science Inc., Wuhan, China).

Renal biopsies of patients with LN enrolled in this study were obtained by ultrasound-guided procedure and evaluated using the International Society of Nephrology/Renal Pathology Society classification [10].

Results

Our participants were grouped to group Ⅱ, which included 20 patients with SLE without renal manifestation, and their ages ranged from 20 to 49 years (mean±SD, 28.90±6.55); group ⅡI, which included 20 patients with SLE with renal manifestation, and their ages ranged from 25 to 44 years (mean±SD, 29.60±4.92), which was subdivided to subgroup IIa that included 17 (85%) patients with LN showing active disease and subgroup IIb that included three (15%) patients with LN showing inactive disease; and finally, group III, the control group, and their ages ranged from 20 to 48 years (mean±SD, 29.90±7.11).

Focusing on our aim, renalase levels were higher in patients with LN than both patients with SLE without LN and control group (Table 1). The cutoff value of

Table 1 Serum renalase level comparison among the studied groups

Serum renalase (ng/ml)	Group I SLE without LN (*N*=20)	Group II SLE with LN (*N*=20)	Group III control (*N*=20)
Interquartile range	54.23–122.6	72.63–892.98	54.28–153.78
Median	69	134.65	63.3
$^{KW}\chi^2$		4.541	
P value		0.014*	
	Group I and group II	Group I and group III	Group II and group III
Z_{MW}	0.012*	0.714	0.032*

$^{KW}\chi^2$, χ^2 for Kruskal–Wallis test; LN, lupus nephritis; SLE, systemic lupus erythematosis; Z_{MW}, Mann–Whitney test. $P>0.05$, significant. $P<0.05$, nonsignificant. *Significant.

Table 2 Cutoff curve of serum renalase

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Serum renalase	100	72	89	78	85	81

NPV, negative predictive value of a test; PPV, positive predictive value of a test.

serum levels of renalase was 100 ng/ml with sensitivity 72% and specificity 89% of the test. The positive predictive value of the test is 78% and the negative predictive value of the test is 85%. The accuracy of the test is 81% (Table 2 and Fig. 1).

We reported that serum renalase levels of patients with LN were statistically positively correlated with P/C ratio, 24-h proteinuria and C3, but negatively correlated with SLEDAI. However, patients with SLE without LN had no statistically significant correlation between their serum renalase and all the clinical and laboratory parameters as shown in Table 3.

For patients with active LN, there was no significant correlation between their serum renalase levels and the indicators of renal activity including ESR, proteinuria, P/C ratio, anti-dsDNA, C3, C4, and activity index of renal biopsy (Table 4). The median of renalase as a marker for diagnosis of LN was 134.65 with a cutoff value of 100 μg/ml.

A renal biopsy from each patient with LN had been obtained on the same day of blood sampling. International Society of Nephrology/Renal Pathology Society classification system was used for grading LN [11].

A total of 20 patients had evidence of LN. Four (20%) patients had LN grade II, 10 (50%) patients had LN grade III, four (20%) patients had LN grade IV-G, and two (10%) patients had LN grade IV-S.

Regarding serum renalase levels, there was no statistically significant difference between the stages of renal biopsy ($P<0.05$) (Fig. 2).

Statistical analysis

Statistical presentation and analysis of the present study was conducted, using the mean, SD and χ^2 test by statistical package for the social sciences, version 20. The Student's t test is used to compare the variables between two groups when necessary. Analysis of variance was done by analysis of variance tests (f). The comparison of all categorical variables such as frequency or percentage (%) was performed using the χ^2 test. The correlation between two variables was determined through linear correlation coefficient (r). The receiver operating characteristic curve was performed by plotting sensitivity and specificity of serum renalase values according to Youden's index. The results were expressed as P value, where less than 0.05 was considered statistically significant.

Discussion

SLE is a chronic autoimmune inflammatory disease that targets the kidneys, being pathologically evident in ~90% and clinically in ~50% of patients. LN is a foremost risk factor for overall morbidity and mortality in SLE, and even with potent anti-inflammatory and immunosuppressive therapies, it still ends in chronic kidney disease (CKD) or ESRD for many patients [12]. So, an early diagnosis of LN has an imperative clinical implication in administrative treatments of patients with SLE [13].

Antibodies to dsDNA and the reduction of complements C3 and C4, which are considered indicators for renal affection and activity, were also found in patients without LN and patients with clinically inactive SLE with a relatively high percentage [14]. Such a lack of specificity led to search for other reliable biomarkers for identifying patients with SLE with active nephritis [15].

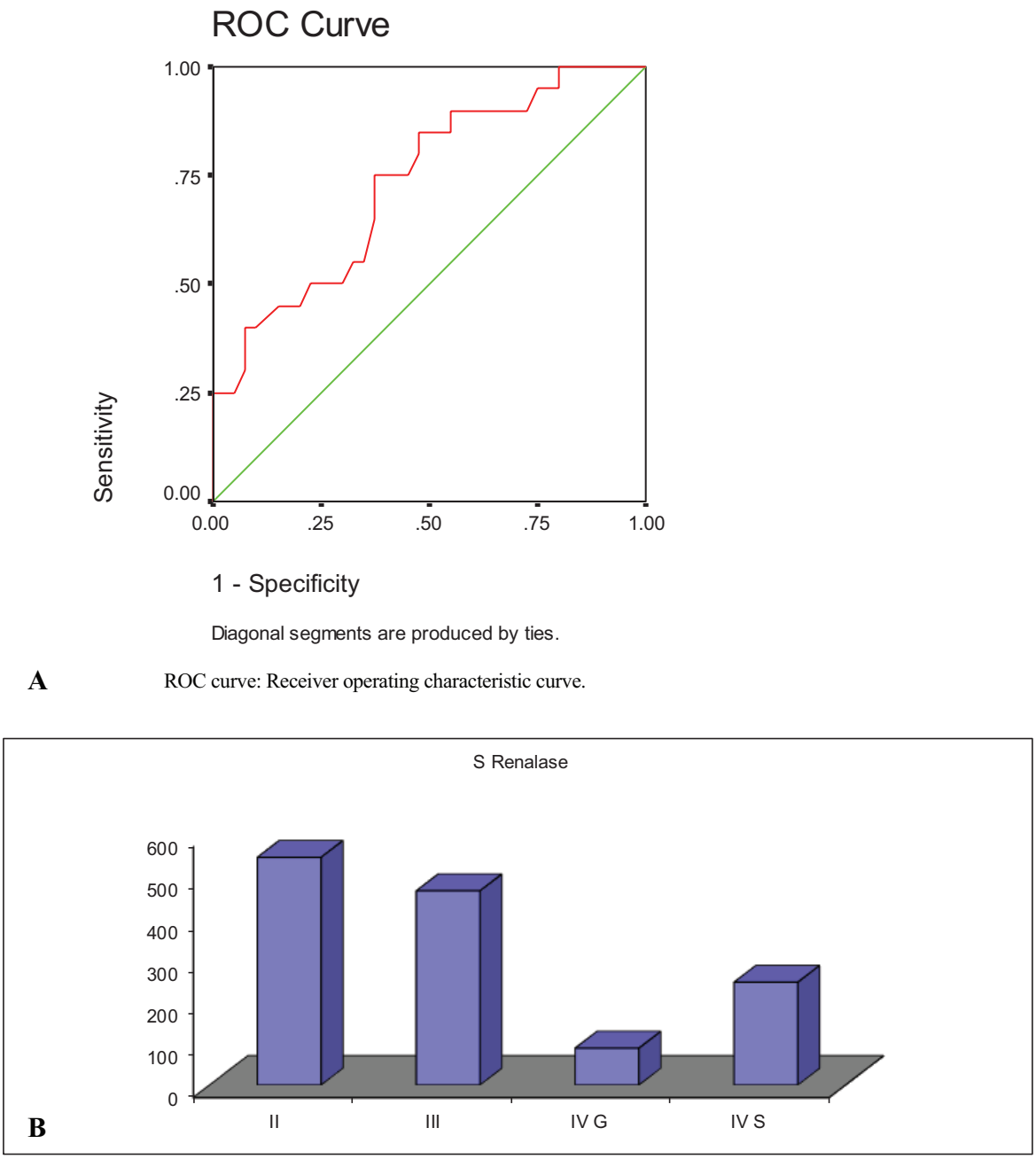
Recently renalase (monoamine oxidase) was implicated in the pathogenesis of LN and its flare; therefore, our study aimed at evaluation of the serum level of renalase in patients with SLE with and without LN.

This control–case study was carried out on 40 patients with SLE, where 50% had LN and 100% were female, and their ages ranged between 20 and 50 years. Overall, 85% of the patients with LN with active disease belonged to II, III, and IV grades.

Serum renalase was elevated in patients with LN than nonrenal patients and normal group. On the contrary, there was no statistically significant difference in its level between patients with active LN and those with inactive LN.

The previous studies showed that SLE was more predominated in female with a ratio of 9 : 1 (female : male). In this study, 100% of the patients diagnosed as

Figure 1



Cutoff curve of serum renalase. ROC curve, receiver operating characteristic curve.

having SLE were female. This difference may be caused by the small sample number in our study. Our patients' ages ranged between 20 and 50 years old, which is in agreement with the same age range in the patient sample obtained by Somers *et al.* [16].

Our results showed that 20% had LN grade II, 50% had LN grade III and 30% had LN grade IV. The higher frequency of grades III and IV LN in this study might be owing to late presentation and the significant association between symptoms and signs with these grades at presentation. Our percentages were close to those of Somers *et al.* [16], which reported 14% class I, 22% class II, 10%, class III, 35% class IV, and 20% class V of their studied patients.

In our current study, we found that the level of renalase was significantly higher in patients with LN compared with patients without LN and healthy controls. Moreover, in the correlation studies, we demonstrated a positive correlation between serum renalase and proteinuria, P/C ratio and complement 3 and a negative correlation between it and SLEDAI score, which suggests the relation of renalase to the pathogenesis of LN. The receiver operating

Table 3 Correlation between serum renalase level and some clinical and laboratory findings between group I and group II

	Serum renalase			
	Group I SLE without LN (*N*=20)		Group II SLE with LN (*N*=20)	
	R	*P*	*r*	*P*
Age	−0.096	0.687	−0.408	0.074
Duration	−0.074	0.757	0.488	0.029*
RBCs	−0.017	0.942	0.562	0.010*
WBCs	0.166	0.484	−0.659	0.002*
PLT	−0.352	0.128	0.793	0.001*
Hb	0.002	0.994	−0.256	0.275
ESR	−0.066	0.782	0.113	0.635
CRP	0.089	0.709	−0.363	0.055
Proteinuria	−0.152	0.522	0.624	0.004*
P/C ratio	−0.090	0.704	0.726	0.001*
Creatinine clearance	−0.160	0.500	−0.028	0.905
Anti-dsDNA	0.192	0.419	−0.226	0.338
ANA	0.193	0.416	−0.144	0.546
C3	−0.097	0.683	0.462	0.040*
C4	−0.095	0.690	0.289	0.217
SLEDAI	−0.299	0.200	−0.466	0.038*

ANA, antinuclear antibody; anti-dsDNA, antibodies to double-stranded deoxyribonucleic acid; C3, complement 3 level; C4, complement 4 level; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; LN, lupus nephritis; P/C ratio, protein-to-creatinine ratio; PLT, platelet blood test; *r*, Pearson's correlation; RBCs, red blood cells; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosis disease activity index (maximum score=105); WBCs, white blood cells. $P>0.05$, significant. $P=0.001$, high significant. $P<0.05$, nonsignificant. *Significant.

Table 4 Correlation between serum renalase and some clinical, laboratory findings, and renal biopsy in subgroup IIa

	Serum renalase	
	Subgroup IIa (*N*=17)	
	r	*P*
Age	−0.298	0.246
Duration	0.516	0.034*
RBCs	0.520	0.032*
WBCs	−0.751	0.001*
PLT	0.891	0.001*
Hb	−0.333	0.192
ESR	0.256	0.321
CRP	−0.473	0.055
Proteinuria	0.142	0.586
P/C ratio	0.182	0.485
Creatinine clearance	0.095	0.716
Anti-dsDNA	−0.126	0.631
ANA	0.151	0.562
C3	0.310	0.226
C4	−0.142	0.587
rSLEDAI	−0.438	0.079
Activity index	−0.298	0.246
Chronicity index	0.365	0.149

ANA, antinuclear antibody; anti-dsDNA, antibodies to double-stranded deoxyribonucleic acid; C3, complement 3 level; C4, complement 4 level; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; P/C ratio, protein-to-creatinine ratio; PLT, platelet blood test; *r*, Pearson's correlation; RBCs, red blood cells; rSLEDAI, renal systemic lupus erythematosis disease activity index (maximum score=16); WBCs, white blood cells. $P>0.05$, significant. $P=0.001$, high significant. $P<0.05$, nonsignificant. *Significant.

characteristic curve also showed that serum renalase could be a good predictor for LN. The results obtained by Qi *et al.* [8] support our findings as they reported that the level of renalase was significantly higher in patients with LN compared with healthy controls, especially in patients with proliferative LN.

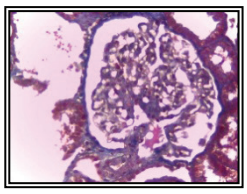
On the contrary, we found that there was no significant relation between renalase level and the activity of LN, as our data for patients with LN with active renal disease established no significant correlation between their serum renalase levels and the indicators of renal activity, including ESR, proteinuria, P/C ratio, anti-dsDNA, C3, C4, and activity index of renal biopsy.

Contrary to our data, the results by Qi *et al.* [8] revealed higher renalase levels in patients with active LN compared with patients with inactive LN, especially in proliferative grade. They proved their findings by descending serum renalase levels following immunosuppressive therapy along with the anti-dsDNA antibodies, C3, and SLEDAI score. Furthermore, renalase expression was upregulated in the glomeruli of proliferative LN patients, suggesting that renalase expression and signaling may play a role in the pathogenesis of active LN.

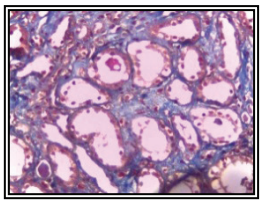
Our findings may be supported by the fact that LN pathogenesis takes place in the glomeruli and the main source of renalase secretion from the kidney is the proximal tubules. Lee *et al.* [17] confirmed the selective expression of renalase in proximal tubular cells.

We also reported that all our patients had normal renal functions represented in creatinine clearance, serum creatinine, and blood urea, with no significant relation between renalase levels. On the contrary, Malyszko *et al.* [18] found a relation of renalase levels to kidney function tests, as they observed that in patients with estimated glomerular filtration rate over 60 ml/min, renalase was significantly lower than in patients with estimated glomerular filtration rate below 60 ml/min. In addition, renalase was related in the univariate analysis to kidney function, age, time after transplantation, and markers of endothelial dysfunction. They observed that renalase levels were predicted by kidney function. It results from the fact that as kidney function deteriorates, endothelial damage increases, which is reflected by the rise in thrombomodulin, cytokines, and renalase.

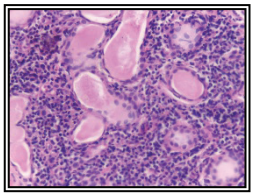
Figure 2



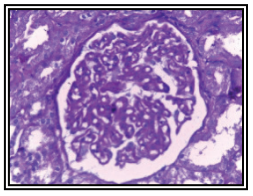
Lupus nephritis class III ISN/RPS Showing glomeruli with focal glomerulosclerosis (MT X400).



Lupus nephritis class III ISN/RPS Showing mild tubular fibrosis (MT X400



Lupus nephritis class IVG ISN/R Showing glomerulosclerosis (PAS X400).



Lupus nephritis class IVs ISN/RPS Showing glomeruli with wireloop (PASs400).

Comparison between various stages of renal biopsy regarding serum renalase levels.

Another finding was documented by many previous studies that renalase level decreased in the CRD and ESRD, suggesting that renal blood flow may affect renalase production, with reflection on their blood pressure as renalase was accused in metabolizing catecholamines and resulting in hypertension in those patients [19,7,20].

However, West and Marnett [21] reported differing results and explained that the significant increase in renalase levels detected in CKD and ESRD, possible, is primarily a reflection of accumulated renalase breakdown products. Moreover, it suggested that the increase level is owing to the existence of extrarenal sites for renalase secretion.

In our current study, we could not prove the relation between serum renalase levels and CKD and ESRD, and this may be owing to the small sample number of patients with inactive LN (three patients) in our study, being unsuitable for statistical analysis.

Regarding hypertension affected by renalase levels, Wang *et al.* [22] and Schlaich *et al.* [23] in their studies reported that decreased serum renalase level led to increase in blood pressure in their patients. Moreover, studies in animal models by Xu *et al.* [7], Wu *et al.* [20], Desir *et al.* [24], and Fedchenko *et al.* [25] support this finding. However, Zbroch *et al.* [26] reported no association between serum renalase and blood pressure in hemodialysis or peritoneal dialysis patients. We unfortunately could not relate renalase levels to hypertension in our patients for the same obstacle of having a small number of patients having hypertension (four patients).

Our study's limitations were as follows: the small sample number of patients, as they were recruited from one area, Benha University Hospitals, which also led to devoid of our study of male patients; the numbers of patients with inactive renal disease and hypertensive patients were small, which made us unable to obtain the statistical relation between them and the renalase levels; and finally, we did not scope on the effect of the immunosuppressive therapies on renalase levels in patients with renal disease. Therefore, the findings of this study need to be confirmed in a larger cohort of patients with LN and should include various ethnic groups. Our conclusion is that serum renalase may be involved in LN pathogenesis but is not a good predictor for either LN activity or various stages of LN histopathology.

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Nil.

Conflicts of interest
There are no conflicts of interest..

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