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Original Article

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Serum Total Sialic Acid and Lipid-linked Sialic Acid May Be the New Potential Biomarkers in Paracetamol Nephrotoxicity

Ersoy Öksüz[1], Muhammet Serdar Buğday[2], Feyza Demir[3], Suat Ekin[4], Okan Arıhan[5], Gökhan Oto[1]

[1]Department of Medical Pharmacology, Van Yüzüncü Yıl University School of Medicine, Van, Turkey
[2]Department of Urology, Malatya Training and Research Hospital, Malatya, Turkey
[3]Department of Medical Pathology, Van Yüzüncü Yıl University School of Medicine, Van, Turkey
[4]Department of Biochemistry, Van Yüzüncü Yıl University School of Science, Van, Turkey
[5]Department of Physiology, Van Yüzüncü Yıl University School of Medicine, Van, Turkey

Abstract

Objective: In recent years, paracetamol has been shown to have toxic effects on the kidneys. Sialic acid (SA), an important component of the cell membranes, increases in many pathological conditions. This study aimed to investigate the effects of different doses of paracetamol on the kidney tissue and serum total SA (TSA) and lipid-bound SA (LSA) levels.
Materials and Methods: A total of 5 different groups were formed, with 8 rats in each group; 20 and 500 mg/kg/intraperitoneal paracetamol was applied to the groups once daily for 1 and 3 days, respectively. Renal pathology was evaluated with hematoxylin and eosin. TSA/LSA levels and urea/creatinine levels were measured from the blood samples taken from the rats.
Results: TSA levels were significantly higher in the groups in which paracetamol was administered in a single dose and 500 mg/kg dose for 3 days than control ($p<0.05$ and $p<0.001$). LSA levels were significantly higher in the groups that received 1 and 3 doses of 500 mg/kg/day and 3 doses of 20 mg/kg than control ($p<0.05$, $p<0.001$, and $p<0.05$).
Conclusion: SA levels may be a specific marker for kidney damage because of the increase in the SA levels in direct proportion to this level of renal degeneration.
Keywords: Paracetamol, nephropathy, sialic acid, acetaminophen, kidney injury

Corresponding Author: Ersoy Öksüz ✉ drugoksuz@hotmail.com
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INTRODUCTION

Paracetamol is widely used as an analgesic-antipyretic throughout the world. Unlike the nonsteroidal anti-inflammatory drugs (NSAIDs), there are fewer side effects of paracetamol; the most important side effect is that it causes hepatotoxicity, especially in high doses. Paracetamol is primarily metabolized by glucuronic acid and sulfate in the liver (63%, 34%) (1, 2). A very small percentage (<5%) is transformed into N-acetyl-p-benzoquinone imine (NAPQI) by oxidative metabolism with cytochrome P450 (CYP450) enzyme systems. This metabolite, which is formed under normal conditions, is converted to cysteine and mercaptopurine by glutathione. However, if paracetamol is taken in high doses, the amount of NAPQI increases and glutathione depots in the hepatocytes are reduced (3). NAPQI, which is not metabolized, binds to cellular proteins, disrupts hemostasis, causes caspase activation and cellular apoptosis, and ultimately results in the liver failure (2).

In many studies conducted in recent years, paracetamol has been shown to have toxic effects on the kidney (4, 5). In this toxicity, in addition to the role of the liver CYP450 enzyme system, prostaglandin synthase and N-deacetylase enzymes are also involved (6). The CYP450 enzyme system of the kidney is CYP2E1. Paracetamol metabolized by this enzyme in the kidney as a result of metabolism causes direct toxic effects. In addition, kidney damage also occurs owing to decreased liver glutathione. Paracetamol is converted into toxic metabolite such as NAPQI-like molecules in the liver and p-aminophenol via prostaglandin endoperoxidase synthase and

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N-deacetylase enzymes in the kidney. Metabolites formed by these mechanisms bind to cellular proteins in the kidney and cause cell death and tissue necrosis. This damage occurs in the medulla of the kidney and plays a role in acute toxicity, whereas toxicity from the CYP450 system occurs in the cortex and causes more chronic toxicity (7, 8).

Sialic acid (SA), an important component of the cell membranes, is an acetylated neuraminic acid derivative. It is vital to the protection, integrity, permeability, and survival of the cell structure. Nevertheless, it has a role in the transport of positively charged molecules and negativity of the cell (9). Total sialic acid (TSA) is found in 2 different forms in the body: lipid-bound SA (LSA) and protein-bound SA. TSA levels have been shown to be increased in pathological conditions, particularly in cancer and cardiovascular system diseases (10). Serum TSA levels are also increased owing to the renal damage. It has been shown in different studies that it is higher in patients with diabetic nephropathy and chronic glomerulonephritis than in normal individuals (11, 12).

This study aimed to investigate the toxic effects of low- and high-dose paracetamol on the kidney tissue and to determine the relationship between this toxicity and serum TSA-LSA, urea, and creatinine levels.

MATERIALS AND METHODS

Experimental Protocol

The study was approved by the Animal Experiments Local Ethics Committee of Van Yüzüncü Yıl University (Approval Date: July 06, 2017; Approval Number: 2017/06). In this study, adult male Wistar-albino rats weighing 200-250 g were used. The rats were fed with standard feed and tap water. They were kept for 12 h in the light and 12 h in the dark. Moreover, 5 different groups were formed, with 8 rats in each group, and paracetamol (Paracerol 10 mg/mL intravenous, Polifarma; Turkey) was administered to the groups as follows: control group, saline intraperitoneal (i.p); group 1, 20 mg/kg/i.p 1 day (low dose 1 day [L1D]); group 2, daily 20 mg/kg/i.p. 3 days (low dose 3 days [L3D); group 3, 500 mg/kg/i.p. 1 day (high dose 1 day [H1D]); group 4, daily 500 mg/kg/i.p. 3 days (high dose 3 days [H3D]); group 5 (7). The blood samples and kidney tissues were obtained 24 h after the application of single dose of paracetamol. In other groups, the samples were obtained 24 h after the administration on the third day. The kidney and blood samples were obtained by sacrificing the rats under with 80 mg/kg ketamine anesthesia.

Main Points

- This study is very important because it is the first study in which serum sialic acid has been shown to be elevated in analgesic nephropathy.
- Urinary creatinine level did not increase although kidney toxicity was shown pathologically, indicating that sialic acid could be a more specific marker.
- Our study is also important to show that paracetamol, which has been known as a safe analgesic for many years, can cause kidney toxicity.

Histopathological Evaluation

The kidney samples were fixed in paraffin blocks after fixation with 10% formalin. Furthermore, 4-mm sections were taken from the blocks; hematoxylin-eosin staining was performed, and the slides were observed under a light microscope. Renal damage was assessed by scoring, as indicated in Table 1 (13).

TSA-LSA Analysis

Serum analyses

Serum TSA concentration was determined using the method described by Sydow (14). Briefly, a mixture of 0.2 mL serum and 1.5 mL of 5% perchloric acid was incubated for 5 min at 100°C, cooled down, and centrifuged at 500 g for 4 min. Thereafter, 0.2 mL Ehrlich's reagent was added to 1 mL of the clear supernatant and heated for 15 min at 100°C. After cooling, 1 mL distilled water was added to this mixture, and the optical density was measured at 525 nm in a spectrophotometer. The amount of TSA was determined using a standard curve developed from a standard sample of n-acetyl neuraminic acid. Serum LSA concentration was determined using the method described previously (15). Briefly, 44.7 µL of serum was transferred with a capillary pipette to 150 µL distilled water. The contents were vortexed for 5 s. The tube was transferred to crushed ice; 3 mL of cold (4 C-5 C) 2:1 (v/v) chloroform:methanol was added to the tube, and the mixture was vortexed for 30 s. To this mixture, 0.5 mL cold distilled water was added, and the tube was capped. The contents were then mixed by repeatedly inverting the tube for 30 s. After centrifuging the tube for 5 min at room temperature at 500 g, 1 mL of the upper layer was transferred into another tube. Furthermore, 50 mL of phosphotungstic acid solution (1 g/mL) was added, and after mixing, the tube was kept at room temperature for 5 min. The tube was centrifuged for 5 min at 500 g, and the supernatant was removed by suction; 1 mL of distilled water was added, and the tube was vortexed until the precipitate was in suspension without grossly visible particles. Then, 1 mL of the resorcinol reagent was added, and the tube was mixed and placed in boiling water for exactly 15 min. Immediately after 15 min, the tube was transferred to an ice and water bath and left for 10 min. To the ice-cold tube, 2 mL of 85:15 (v/v) butyl acetate:n-butyl alcohol was added at room temperature, and the tube was vortexed and centrifuged for 5 min at 500 g. The extracted blue color was evaluated at 580 nm. The amount of LSA was determined using a standard curve developed from a standard sample of n-acetyl neuraminic acid.

Biochemical Parameters

In the serum samples, urea and creatinine levels were analyzed using a commercial kit (Roche, Mannheim, Germany) on the Hitachi/P800 modular auto analyzer (Roche; Mannheim, Germany).

Table 1. Kidney tissue damage scoring

Evaluation	Histopathology
Grade 0	No significant changes in diagnosis
Grade 1	Loss of brushed margins in the tubule epithelial cells, occasional nuclear loss owing to cellular condensation and extension of the tubular epithelial cells to contain no more than one-third of the tubular epithelium
Grade 2	In addition to alterations in grade 1 level, loss of nuclear loss in two-third of tubules
Grade 3	Loss of nuclear loss in more than two-third of tubular structures

Statistical Analysis

Descriptive statistics of the results of histopathological evaluation were presented as median, mean, standard deviation, and minimum and maximum values and as count and percentage for the categorical variables. The Kruskal-Wallis test was used to compare the groups. The chi-square test was performed to determine the relationship between the categorical variables. Statistical significance levels were considered as 5%, and the IBM Statistical Package for the Social Sciences version 21 software (IBM SPSS Corp.; Armonk, NY, USA) was used for all statistical computations. The results of TSA-LSA are expressed as the arithmetic means±the standard error of the mean ($\bar{X}$±SEM). The analysis of variance was used for statistical analysis, and Tukey's test was used for post-hoc comparison of the means. The statistical analysis was carried out using the IBM Statistical Package for the Social Sciences version 22 software (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

In the control group, the kidney tissues of rats showed normal histology. In the L1D applied group, mild epithelial changes were observed in less than one-third of the tubules, and renal microscopy findings were considered to be close to normal. In the L3D group, in addition to the histological changes of single-dose group, mild cellularity was increased in some glomeruli. However, in the H1D applied group, there were tubular necrosis with hydropic degeneration reaching two-third of the tubules; small cavity formation in some tubules and focal losses in the Bowman's capsule in the glomeruli were observed. Partial Bowman's membrane losses in the glomeruli, hypercellularity, and atrophy in some areas were observed in the H3D group, and tubular necrosis was observed in the tubules, which showed more severe vacuolar changes in the tubules, more than two-third of the tubule area in this group (Figure 1).

Nephrotoxicity Score

Scores of all the rats were 0 in the control group. In the L1D group, 4 rats were evaluated as grade 0 and the remaining 4 rats as grade 1. These values were similar for low dose administered for 3 days (2 samples, grade 0; 6 samples, grade 1). In the H1D group, 2 rats were evaluated as grade 1 and the remaining 6 rats were as grade 2. In the H3D group, 6 rats were evaluated as grade 2 and 2 rats were as grade 3. Grade average of the H3D group was statistically higher than that of all the groups ($p<0.001$). Grade average of H1D group was only statistically higher than the control group ($p<0.001$). There was no significant difference between the L1D and L3D groups and the control group ($p>0.05$) (Table 2).

TSA levels were higher in the H3D and H1D groups than the control group ($p<0.001$ and $p<0.05$, respectively). In addition, the TSA level in the H1D group was significantly higher than the L1D group, and the TSA level of the H3D group was significantly higher than that of L1D and L3D groups ($p<0.05$, $p<0.001$, and $p<0.05$, respectively). There was no significant difference between the other groups ($p>0.05$) (Table 3).

LSA levels in the H3D, H1D, and L3D groups were significantly higher than those in the control group ($p<0.001$, $p<0.001$, and $p<0.05$, respectively). The LSA level in the H3D group was statistically significant compared with the L1D group ($p<0.001$). There was no significant difference between the other groups ($p>0.05$) (Table 3).

No significant difference was found between the groups in terms of urea and creatinine values ($p>0.05$) (Table 4).

DISCUSSION

In this study, we investigated the effect of paracetamol on the renal tissue and serum TSA-LSA levels. We found that paracetamol has a toxic effect on the kidney in high doses, and serum SA levels increased in direct proportion to this toxicity. In addition, a statistically significant difference ($p<0.05$) was observed according to the increasing dosage (H1D and H3D).

Paracetamol causes severe damage as a result of acute tubular necrosis that can result in kidney failure especially when used in prolonged or high doses, such as other NSAIDs. In many studies, high-dose paracetamol administration has been shown to lead to nephrotoxicity, in which several pathological changes, such as necrosis, vacuolar degeneration, and epithelial desquamation in the tubular kidneys, are at the forefront (16-19). In addition to the well-known mechanisms, such as that of the cytochrome enzyme system, paracetamol has been shown to induce renal damage by increasing the parameters of oxidative stress (4, 5, 20). In our study, similar to the previous

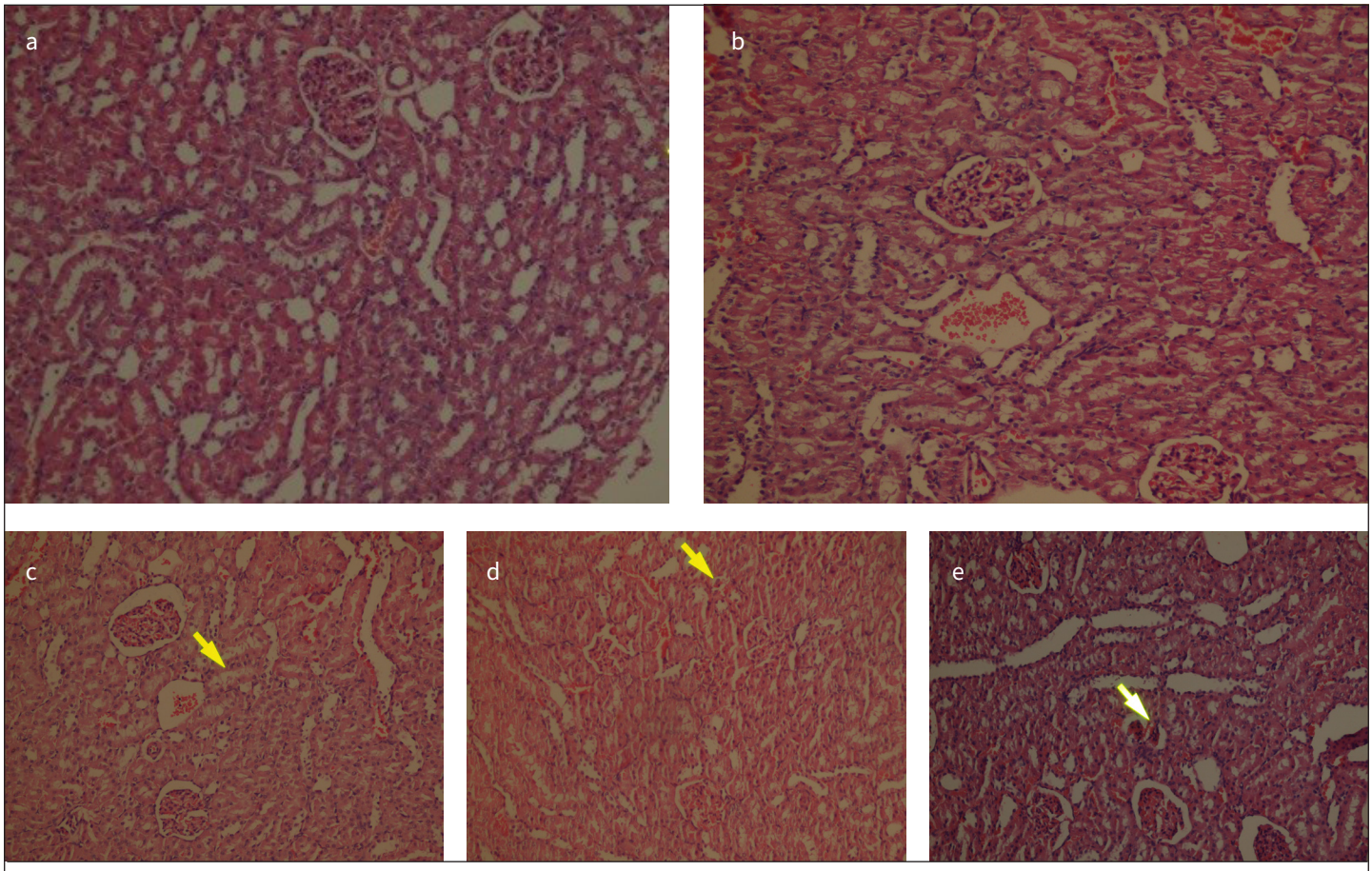

Figure 1. a-e. Hematoxylin-eosin (magnification X200). a) Control group. b) Near-normal renal microscopy in the low single dose administered group. c) Low increase in cellularity in the glomeruli in the 3-low dose group and slight epithelial changes in the tubules in a way that does not exceed one-third tubule area (yellow arrow). d) Increased cellularity in the glomeruli and small cavity formation in the tubules (yellow arrow) in group with high single dose. e) Bowman's membrane losses in the glomerulus and atrophy (yellow arrow) in high dose administered in 3 doses

Table 2. Histopathological evaluation of groups

Grade	Control (n)	L1D (n)	L3D (n)	H1D (n)	H3D (n)
0	8	4	2	-	-
1	-	4	6	2	-
2	-	-	-	6	6
3	-	-	-	-	2
Mean (Min-max)	0 ± 0.0^{c} (0-0)	0.5 ± 0.53^{bc} (0-1)	0.75 ± 0.46^{bc} (0-1)	1.75 ± 0.46^{b} (1-2)	2.25 ± 0.46^{a} (2-3)

Groups with different letters are statistically significantly different from each other according to analysis of variance results and Tukey post-hoc test ($p<0.001$)
L1D: low dose 1 day; L3D: low dose 3 days; H1D: high dose 1 day; H3D: high dose 3 days

studies, there were tubular damage, tubular necrosis, epithelial desquamation, and glomerular degenerations, especially in high-dose paracetamol groups. In parallel with the findings of studies indicating that high doses of paracetamol are associated with higher renal toxicity, our pathological findings were significantly higher in the H3D group than the other groups. Although there was no significant difference in the L1D and L3D groups compared with the control group, the kidney damage was higher in both groups than the control group, especially in the L3D group. Our findings, which show that paracetamol leads to kidney damage in high doses, are in accordance with the findings of existing studies in the literature. In addition, our results suggest that paracetamol may cause kidney damage even at the treatment doses when administered for a long term.

Table 3. Total sialic acid and lipid-bound sialic-acid levels of the groups

Parameters	Control $\bar{X}$±SEM	L1D $\bar{X}$±SEM	L3D $\bar{X}$±SEM	H1D $\bar{X}$±SEM	H3D $\bar{X}$±SEM
TSA (mmol/L)	3.703±0.52[a]	3.838±0.79[a]	4.334±0.60[ab]	5.037±0.57[b]	5.466±0.66[c]
LSA (mmol/L)	0.313±0.06[a]	0.329±0.04[ab]	0.415±0.07[bc]	0.430±0.07[bc]	0.479±0.05[c]

Groups with different letters are statistically significantly different from each other according to analysis of variance results and Tukey post-hoc test (a: p<0.001, b: p<0.01, c: p<0.05)
$\bar{X}$±SEM: mean±standard error of the mean; TSA: total sialic acid; LSA: lipid-bound sialic acid; L1D: low dose 1 day; L3D: low dose 3 days; H1D: high dose 1 day; H3D: high dose 3 days

Table 4. Creatinine and urea levels of the groups

Biochemistry	Control	L1D	L3D	H1D	H3D	p
Creatinine (mg/dL)	0.42±0.03	0.44±0.04	0.48±0.04	0.39±0.04	0.37±0.05	>0.05
Urea (mg/dL)	53.8±3.9	61.0±3.69	40.6±8.03	53.0±6.23	39.6±5.18	>0.05

$\bar{X}$±SEM significance levels according to analysis of variance test results (p>0.05)
L1D: low dose 1 day; L3D: low dose 3 days; H1D: high dose 1 day; H3D: high dose 3 days

SA has a role in various pathological events, such as sialidosis, tumor formation, autoimmune disorders, and bacterial invasion. Although the serum SA levels have been shown to be increased in different diseases, the cause of this increase is not known (11). Several studies have shown that serum SA levels increase in many tumors, such as brain, leukemia, ovarian, and lung. Similarly, it has been found to increase in various pathological conditions, such as diabetes, inflammatory diseases, toxicity caused by chronic substance exposure, and hereditary metabolic diseases in children (11, 21-23). There are also studies suggesting that SA levels increase in kidney diseases. For example, serum SA levels have increased in patients with chronic renal failure or hemodialysis (9, 24, 25). Similar with the previous studies, in our study, the serum TSA and LSA levels were found to be significantly higher in the H1D and H3D groups, which have high kidney damage, than those of the control and low-dose groups. Although not significant, the TSA level in the L3D group was higher than that of the control and L1D group. In contrast to TSA, LSA levels in the L3D-treated group were significantly higher than those in the control group. The findings of SA in our study support the pathological findings and show that paracetamol increases the SA levels in direct proportion to kidney damage at high doses, and it causes a significant increase in the serum SA levels even in long-term use at low doses.

Excretion of urea and creatinine from the blood to urine is reduced and accumulated in the body owing to the degree of kidney damage. Therefore, serum urea and creatinine levels are the most frequently used hematological parameters to monitor the degree of renal damage and the level of kidney failure. In many studies with experimental animals, serum urea and creatinine levels increased in direct proportion to nephrotoxicity caused by paracetamol, and this increase was found to be directly proportional to renal degeneration (4, 15, 16). However, these markers do not allow for a timely nephrotoxicity diagnosis because they are not induced early or are not sufficiently sensitive. Moreover, they are influenced by several factors, such as gender, body weight, and age, which are independent of the kidney injury. In some toxicity studies, it has been found that serum creatinine levels do not increase secondary to nephrotoxicity or differ according to measurement time (26). In our study, although the renal damage of paracetamol was determined pathologically, there was no significant difference in the serum urea and creatinine levels between the groups. Considering that this may be the result of our blood storage conditions or laboratory analysis methods, the samples were reassessed in different laboratories, and similar results were obtained. Although our results suggest that serum creatinine levels do not change in patients with nephrotoxicity, it may not be taken into consideration that the results may be owing to our time to terminate the study, experimental conditions, and aforementioned several factors. In this sense, new prospective studies are needed to determine the relation of urea/creatinine levels with nephrotoxicity. Different results in urea/creatinine measurement at different time intervals may affect the diagnosis and treatment. In this context, SA levels instead of urea/creatinine can have a potential to give more accurate results about kidney damage. Studies in this area may offer reliable parameters in addition to the urea and creatinine levels in the test protocols for these damages.

Urea/creatinine and SA levels were determined only at the end of this study. Lack of measurement in different time intervals, such as 12 h, 1 day, and 2 days, after the administration of paracetamol is the limitation of our study.

CONCLUSION

The results of our study indicate that paracetamol causes kidney damage, especially in high doses, but it can also cause kidney damage in prolonged use in treatment doses. Nevertheless, the fact that SA levels are increased in proportion to this level of renal degeneration and there is no similar increase in the serum urea and creatinine levels shows that serum SA levels may be a

more specific marker for kidney injury; however, more comprehensive studies are needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Animal Experiments Local Ethics Committee of Van Yüzüncü Yıl University (Approval Date: July 06, 2017; Approval Number: 2017/06).

Informed Consent: Informed consent was not obtained due to the nature of this study.

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