Levels of renalase and advanced oxidation protein products with regard to catecholamines in haemodialysed patients

Marcin Dziedzic¹, Ewelina Orłowska², Beata Petkowicz³, Anna Bednarek-Skublęwska², Janusz Solski¹, Małgorzata Goździewska⁴

1 Department of Laboratory Diagnostic, Medical University of Lublin, Poland
2 Department of Nephrology, Medical University of Lublin, Poland
3 Department of Oral Medicine, Medical University of Lublin, Poland
4 Institute of Rural Health, Lublin, Poland

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INTRODUCTION

The main mediators of the sympathetic nervous system in the effectors part are catecholamines (CA). An increased sympathetic nerve activity observed in chronic kidney disease (CKD), is due to a raised level of CA in plasma. Renalase is a protein secreted by the kidneys, composed of 342 amino acids, which is able to metabolize the circulating CA and possibly play an important role in the regulation of sympathetic tone and blood pressure. Also, oxidative stress, defined as a disruption of the equilibrium between the generation of oxidants, is a crucial factor in the development of the inflammatory syndrome associated with CKD. The advanced oxidation protein products (AOPP) represent exquisite markers of phagocyte-derived oxidative stress.

Objective. The aim of the study was to investigate the concentration of renalase and explore the associations between AOPP with regards to CA in haemodialysis (HD) patients.

Materials and Method. The study was conducted among 50 residents of the municipality and neighbouring villages in the province of Lublin, central-eastern Poland.

Results. In the studied patients, it was found that an average concentration of renalase was 44.8 ± 6.5 µg/mL, whereas of AOPP plasma levels – 57.5 ± 21.5 µmol/L. The results demonstrated the correlation between levels of renalase and AOPP in the HD patients. Indeed, elevated levels of renalase and AOPP in HD may be due to the presence of uremic toxins in blood. The concentration of urea affects the plasma concentrations of AOPP and renalase causing a direct relationship between renalase and AOPP. However, there is no clear relationship between renalase and circulating catecholamines in HD patients.

Key words
renalase, advanced oxidation protein products, catecholamines, haemodialysis

Renalase is a protein composed of 342 amino acids. Recently discovered as a new renal hormone, renalase – flavin adenine dinucleotide (FAD) – dependent amine oxidase [3, 4, 5], is secreted by the kidneys and can metabolize the circulating CA and possibly play an important role in the regulation of sympathetic tone and blood pressure. The concept that renalase might be involved in the regulation of blood pressure is supported by the fact that the inactivation of the RNLS gene in mice by homologous recombination is associated with an elevated blood pressure, and a sympathetic activity in the absence of other measurable changes in renal function [6, 7, 8]. The relationship between renalase and catecholamines has been intensively studied since their discovery. However, the possible role of renalase in the pathogenesis of hypertension in haemodialysis (HD) patients is still not fully understood.

Oxidative stress, defined as a disruption of the equilibrium between the generation of oxidants and the activity of antioxidant systems, plays a significant role in the development of the inflammatory syndrome associated with CKD and hemodialysis [9]. The advanced oxidation protein products (AOPP) represent exquisite markers of phagocyte-derived oxidative stress, and their role in the pathophysiology of CKD and dialysis-related complications might be of great importance. The significance of AOPP has been analysed in numerous diseases as they are widely regarded as easily...
measurable markers of oxidative stress. Moreover, the AOPP accumulation is an independent risk factor for cardiovascular events (CVDs) in CKD. Only in HD patients, the AOPP levels exhibit an association with ischaemic heart disease. Thus, there is a need for simple and cheap biomarkers to assess the oxidative stress levels in these patients. Furthermore, the mechanism of accumulation of AOPP, which is affected by the dialysis modality, remains unclear.

It is worth pointing out that patients with advanced chronic kidney disease under hemodialysis treatment have a high prevalence of protein-energy malnutrition and inflammation. As these three conditions often occur concomitantly in HD patients, they have been referred together as 'Malnutrition-Inflammation-Atherosclerosis' (MIA) syndrome to emphasize its important association with atherosclerotic cardiovascular disease. Possible causes of MIA syndrome include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, decreased clearance of inflammatory cytokines, volume overload, and dialysis-related factors. MIA syndrome is believed to be the main cause of erythropoietin hyporesponsiveness, high rate of cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients. Regarding atherosclerosis, the kidney can be victim or villain. On the one hand, both kidney disease per se and renal insufficiency can induce vascular damage, thereby increasing cardiovascular risk. Moreover, the kidney can be the victim of atherosclerosis. Ischemic nephropathy, caused by atherosclerotic renal artery disease and atheroembolism from the abdominal aorta, are two examples. Finally, it is important to consider that the kidney, being an organ with a wide vasculature, could be a sophisticated sensor of subclinical cardiovascular damage.

Therefore, there are many mechanisms underpinning the increased cardiovascular disorders. Recent studies have explored association between variants in the reninase gene and an increased risk of cardiovascular disorders [10]. Renalase gene RNLS resides on chromosome 10 (10q23.31). Stec et al. [11] investigate the association between rs10887800 and rs2576178 renalase gene polymorphisms and risk of coronary artery disease (CAD) in HD patients. The authors [11] observed that rs10887800 renalase gene polymorphism significantly increased the risk of CAD in HD. Moreover, the rs10887800 polymorphism affected the CAD risk independently of age, gender and other CAD risk factors, including smoking, BMI, hyperlipidemia, arterial hypertension and diabetes mellitus. Besides, Buraczynska et al. [10] demonstrate that renalase gene polymorphism rs2296545 is associated with hypertension in type 2 diabetes patients. Also, authors reported a strong association of the rs10887800 polymorphism with stroke in diabetes patients with hypertension, and also in stroke patients without diabetes.

The aim of the study was to investigate the renalase concentration and explore the associations between AOPP with regards to CA in hemodialysis patients. The effects of hemodialysis sessions on CA levels were also assessed.

**MATERIALS AND METHODS**

The study was conducted among residents of the municipality and neighbouring villages in the province of Lublin, central-eastern Poland. Fifty subjects (25 males and 25 females) on haemodialysis, aged 68.5 ± 16.1 years, median time on HD: 45.5 months, were investigated.

The study protocol was approved by the local Ethics Committee at the Medical University in Lublin. All patients qualified to participate in the study were informed about the aim and were asked to sign a written consent.

All patients underwent a clinical examination in the Department of Nephrology of the Medical University in Lublin. All observed subjects underwent HD 3 times a week. Each procedure lasted from 3.5–4.5 hours. Low-flux dialyzers were used; bicarbonate dialysate contained a calcium concentration of 1.5 mmol/L. A dialyzer blood flow rate ranged between 230–400 ml/min, while the dialysate flow rate was 500 ml/min.

Blood samples were obtained from the venous part of the vascular access prior to HD. Standard phlebotomy techniques were used to obtain the samples. The blood samples were later stored in chilled tubes (EDTA) at 4°C. Plasma was then separated and stored at −80°C until analysis. The concentration of AOPP and renalase were measured prior to HD from the plasma. Similarly, the haematological testing was carried out using the collected blood. Also, several scores and parameters were calculated for each patient, such as comorbidity score (CS) according to the scale published by Charlson et al. [12]. HD adequacy was expressed by Kt/V parameter [13], normalized protein catabolic rate [14], body mass index (BMI), and mean arterial pressure (MAP). MAP was calculated on the basis of blood pressure measurement taken prior to HD in a horizontal position. The following formula was used: MAP = diastolic pressure + ⅓ (systolic pressure-diastolic pressure). The well-controlled blood pressure was assessed according to KDIGO guidelines as lower then 140/90 mmHg in HD patients before haemodialysis session, and lower than 130/80 mmHg after the session [15]. The following biochemical parameters were measured using an enzyme-linked immunosorbent assay (ELISA): AOPP (R&D Systems Inc.) and renalase (USCN Life Science, Inc.) assays (sensitivity; the minimum detectable dose less than 0.57 ng/mL). The analysis of CA levels in biological fluids has necessitated the use of highly sensitive analytical techniques. Therefore, the extraction of catecholamines from plasma was carried out with a ChromSystems Reagent kit for HPLC analysis. Plasma concentration of catecholamines was measured prior to and following haemodialysis by the method of high performance liquid chromatography with electrochemical detection (HPLC-ED), limit of quantification: NA 15 ng/L, A 15 ng/L, DA 30 ng/L.

**Statistical analysis.** All values were expressed as mean and standard deviations. Distributions of the analyzed variables were tested using the Shapiro-Wilk test. For normally distributed variables, comparison of the obtained results was analyzed by the Student t-test. For variables that did not demonstrate any compliance with the normal distribution, the non-parametric U Mann-Whitney test was applied. Statistical relationship between the 2 variables was investigated using Spearman’s test for correlation. In all tests, p-value < 0.05 was considered as statistically significant.
RESULTS

The main demographic and clinical characteristics of the patients included in the study are listed in the Table 1. As a result of the conducted study, it was found that the concentration of renalse was 44.8 ± 6.5 µg/mL, whereas the plasma levels of advanced oxidation protein products were 57.5 ± 21.5 µmol/L. After taking into consideration the patients gender, no significant differences were found in the plasma concentration of renalse or AOPP (p>0.05). CA concentration before and after HD treatment are presented in Table 1. The results indicated that NA before HD (633.4 ± 333.0 pg/mL) in plasma had a significantly lower concentration after haemodialysis treatment (451.0 ± 249.8 at p<0.001). Univariate correlations of circulating renalse and AOPP concentrations are presented in Tables 2 and 3. According to the correlation analysis, plasma levels of renalse were directly proportional to the concentration of

Table 1. Demographic and biochemical characteristics of patients on long-term dialysis

| Parameter                      | Whole study group | Males | Females |
|-------------------------------|-------------------|-------|---------|
| Age (years)                   | Mean ± Standard deviation | N = 50 | N = 25 |
| Time on HD (months)           | 68.6 ± 16.2       | 63.8 ± 18.1 |
| BMI (kg/m²)                   | 26.7 ± 6.6        | 20.0 ± 8.5  |
| Kt/V                          | 1.6 ± 0.2         | 1.5 ± 0.2  |
| Haemoglobin (g/dL)            | 10.4 ± 1.1        | 10.6 ± 1.0 |
| Ferritin (ng/mL)              | 258.4 ± 177.8     | 281.5 ± 196.2 |
| EPO dose (µL/kg)              | 66.9 ± 37.3       | 62.4 ± 38.6 |
| CRP (µg/mL)                   | 6.9 ± 4.7         | 5.3 ± 4.5  |
| Total Calcium (mmol/L)        | 2.2 ± 0.2         | 2.2 ± 0.2  |
| Phosphorus (mg/dL)            | 1.6 ± 0.4         | 1.7 ± 0.5  |
| PTH (pg/mL)                   | 632.9 ± 510.3     | 738.8 ± 627.0 |
| Urea (mg/dL) Before HD        | 110.2 ± 25.5      | 107.1 ± 27.8 |
| Urea (mg/dL) After HD         | 29.6 ± 8.4        | 27.3 ± 9.3 |
| Comorbidity Score             | 7.0 ± 2.9         | 6.5 ± 3.2  |
| Renalse (µg/mL)               | 44.8 ± 6.5        | 46.2 ± 5.5 |
| Noradrenaline (µg/mL) Before HD | 633.4 ± 333.0  | 551.5 ± 327.7 |
| Adrenaline (µg/mL) Before HD  | 71.5 ± 63.9       | 77.4 ± 75.3 |
| Dopamine (µg/mL) Before HD    | 13.7 ± 7.9        | 13.3 ± 7.0 |
| Noradrenaline (µg/mL) After HD | 451.0 ± 249.8   | 416.2 ± 232.0 |
| Adrenaline (µg/mL) After HD   | 49.6 ± 32.0       | 45.7 ± 28.7 |
| Dopamine (µg/mL) After HD     | 7.2 ± 4.8         | 6.3 ± 3.0  |
| AOPP (µmol/L)                 | 575.5 ± 21.5      | 60.6 ± 19.4 |
| Diastolic blood pressure (mm/Hg) | 70.9 ± 13.0   | 68.3 ± 13.1 |
| Systolic blood pressure (mm/Hg) | 125.6 ± 41.8  | 121.6 ± 23.6 |
| MAP (mmHg)                    | 86.9 ± 12.7       | 86.0 ± 13.9 |

* p<0.05; **p<0.01; ***p<0.001
† p<0.001 – Compared ‘Before HD’ vs. ‘After HD’

Table 2. Correlations between concentration of renalse (µg/mL) and analyzed parameters

| Parameter                      | Whole study group | Males | Females |
|-------------------------------|-------------------|-------|---------|
| Age (years)                   |−0.08             |−0.08 |−0.15   |
| Time on HD (months)           | 0.1               |−0.06 | 0.18    |
| Haemoglobin (g/dL)            |−0.14             |−0.1  |−0.17   |
| Ferritin (ng/mL)              |−0.17             | 0.06  |−0.32   |
| CRP (µg/mL)                   |−0.01             | −0.48 | 0.41   ***|
| Total Calcium (mmol/L)        |−0.11             |−0.1  |−0.09   |
| Phosphorus (µg/mL)            | 0.5 *            | 0.5 * |0.45 ** |
| PTH (pg/mL)                   | 0.09             | −0.10 | 0.16   |
| Urea (mg/dL) Before HD        | 0.22             | 0.51 ** | 0.001 |
| Urea (mg/dL) After HD         | 0.24             | 0.65 * | 0    |
| Renalse (µg/mL)               | 0.46 *           | 0.56 * | 0.35   |
| Noradrenaline (µg/mL) Before HD | 0.09             | 0.27  | 0.04   |
| Adrenaline (µg/mL) Before HD  |−0.18             |−0.21 |−0.19   |
| Dopamine (µg/mL) Before HD    |−0.01             |−0.08 | 0.07   |
| Noradrenaline (µg/mL) After HD | 0.07             | 0.23  | 0     |
| Adrenaline (µg/mL) After HD   | 0.05             | 0.45 ** |−0.30 |
| Dopamine (µg/mL) After HD     | 0.25             | 0.27  | 0.29   |
| Diastolic blood pressure (mm/Hg) |−0.09             | 0.01  |−0.13   |
| Systolic blood pressure (mm/Hg) |−0.06             | 0.2   |−0.14   |
| MAP (mmHg)                    |−0.09             | 0.001 |−0.16   |

* p<0.001; ** p<0.01; *** p<0.05
† p<0.001 – Compared ‘Before HD’ vs. ‘After HD’

Table 3. Correlations between advanced oxidation protein products and analyzed parameters

| Parameter                      | Whole study group | Males | Females |
|-------------------------------|-------------------|-------|---------|
| Age (years)                   |−0.05             |−0.03 | 0.07   |
| Time on HD (months)           | 0.22             | 0.06  | 0.26   |
| Haemoglobin (g/dL)            | 0.04             | 0.20  |−0.08   |
| Ferritin (ng/mL)              |−0.12             |−0.32 |−0.19   |
| CRP (µg/mL)                   | 0.03             |−0.42 | 0.40   |
| Total Calcium (mmol/L)        |−0.07             |−0.06 | 0.08   |
| Phosphorus (µg/mL)            | 0.23             | 0.24  | 0.20   |
| PTH (pg/mL)                   | 0.36             | 0.25  | 0.56 ** |
| Urea (mg/dL) Before HD        | 0.19             | 0.21  | 0.19   |
| Urea (mg/dL) After HD         | 0.24             | 0.5 ** | 0.17   |
| Noradrenaline (µg/mL) Before HD | 0.19             | 0.18  | 0.37   |
| Adrenaline (µg/mL) Before HD  |−0.05             |−0.05  | 0.006  |
| Dopamine (µg/mL) Before HD    |−0.05             |−0.02  |−0.01   |
| Noradrenaline (µg/mL) After HD | 0.32 **          | 0.45 ** | 0.25 |
| Adrenaline (µg/mL) After HD   |−0.05             | 0.24  | 0.25   |
| Dopamine (µg/mL) After HD     | 0.03             |−0.02  |−0.05   |
| AOPP (µmol/L)                 | 0.46 *           | 0.56 * | 0.35   |
| Diastolic blood pressure (mm/Hg) |−0.09             |−0.04 |−0.09   |
| Systolic blood pressure (mm/Hg) |−0.13             |−0.25 | 0.01   |
| MAP (mmHg)                    |−0.09             |−0.12 |−0.03   |

* p<0.05; ** p<0.01; *** p<0.001
† p<0.001 – Compared ‘Before HD’ vs. ‘After HD’

for differences or correlations. All statistical analyses were conducted using Statistica 10.0 software.
Patients with advanced CKD undergoing HD have an increased risk of cardiovascular morbidity and mortality. Endothelial dysfunction is one of the mechanisms that exacerbate atherosclerosis and lead to CVDs. The factors induced in pathogenesis of endothelial dysfunction in haemodialysis patients are still unclear. The accumulation of AOPP has been recognized in patients with CKD. In the presented study, in HD patients, it was noticed that the plasma concentrations of AOPP were elevated. These results were in agreement with Zadrazil et al. [16] who stated that plasma concentrations of AOPP increased with the progression of CKD and were closely related to the advanced glycation end products (AGEs). In addition, Witko-Sarsat et al. [17] provided information on AOPP, claiming that they are able to trigger the synthesis of inflammatory cytokines in neutrophil leukocytes and monocytes, and seem to act as inflammatory mediators in CKD patients. Focusing on the AOPP, it has been recognized that the HD process may lead to a generation of reactive oxygen species, impairing the antioxidant capacity of the organism [18]. However, detailed pathways for oxidative stress in HD patients are still poorly understood. Increased levels of AOPP observed in the presented study can be explained by the fact that the cumulative iron loading used for treatment of anaemia might be a resource of reactive oxygen species. Also, other consequences are coming in line with the presented finding: elevated AOPP concentration may also be affected by high levels of uremic toxins and disturbances of the calcium-phosphate homeostasis regulation. According to the authors’ best knowledge, uremic toxins, hypothyroidism, hypersplenism and ongoing infection can reduce the erythrocyte life span, contributing to a renal anaemia. Anaemia has been shown to be significantly associated with left ventricular hypertrophy in dialysis patients [19] connected with an endothelial dysfunction, cardiovascular risk and the progression of renal damage.

In the presented study, it was observed that renalase expression correlated with AOPP. Thus, the obtained results may constitute an explanation for the high renalase activity reduced by the inhibition of circulating enzyme in CKD patients. No clear relations between circulating renalase and CA in plasma have been observed. Recently, much research performed on the metabolism of circulating CA has focused on renalase. This recently discovered compound, flavinadenin dinucleotide (FAD) containing hormone, is secreted by the kidneys, circulates in the blood, and may play a key role in the metabolism of CA [20,21,22]. However, the role of renalase as a catalyzer of aminochromes production remains unconfirmed.

The current study shows elevated levels of renalase and CA in HD patients. In addition, no significant correlations between CA and renalase were observed. These findings are in agreement with the studies by Zbroch and Malyzko [23] who did not observe any correlation between DA, NA and renalase levels. The elevated concentrations of CA in end-stage renal disease (ESRD) patients are the results not only of the inhibition of nitric oxide (NO), followed by an increased angiotensin II level and a rise in sympathetic afferent outflow from the diseased kidney, but also from a reduced CA clearance [24]. Also, the abnormalities in the renalase pathway are discussed in the case of these patients [25, 26]. Nevertheless, it should be emphasized that renalase is secreted not only by the kidney, but also by cardiomyocytes, liver, adipose tissue, skeletal muscles, endothelium, and by the Central Nervous System [27]. Previously, Gu et al. [28] reported an increased renalase concentration in HD patients. They hypothesized that in this condition a more activated renalase was synthesized to cope with the increased NA levels. Recently, renalase was induced in pathogenesis of endothelial dysfunction in...
suggested to preferentially metabolize the circulating A, and its capacity to decrease blood pressure is directly correlated to this particular enzymatic activity [29, 30]. However, to metabolize A, renalase uses a mechanism that is different from that exhibited by the monoamine oxidase (MAO). Indeed, unlike MAOs, renalase uses nicotinamide adenine dinucleotide (NADH) as a cofactor and reacts with oxygen to generate superoxide anion [31, 32]. This reaction scheme is similar to that of flavoprotein monoxygenases, a diverse class of enzymes that can catalyze a wide variety of oxidation reactions, including amine oxidation. Malyszko et al. [33], reported that renalase is secreted by the kidneys, and to a much lesser extent it is also removed by dialysis. The same authors claimed that there is no clear relationship between renalase and blood pressure, at least in patients with CKD, and could not confirm that renalase was a monoamine oxidase, or even an oxidase at all [34]. In contrast to the study by Beaupre et al. [35], who reported that renalase does not consume catecholamines, renalase is not kinetically regulated by CA and renalase is not isolated in an inhibited form and cannot be activated by blood plasma or CA. In addition, Beaupre et al. [35] suggested that blood has very little active renalase. This observation is consistent with its newly-identified activity and suggest that renalase has an exclusively intracellular/molecular role. Other authors [36] have also raised serious doubts regarding the putative catecholamine-degrading activity of renalase, suggesting that although renalase may have an important physiological role in the context of hypertension and cardio-renal disease, it appears unlikely to be mediating the degradation of catecholamines. Wang et al. [37] showed that renalase promoted cell survival and protected against renal ischaemia reperfusion injury in mice through the activation of intracellular signalling cascades, independent of its ability to degrade catecholamines. More recently, Moran et al. [38] found that, in fact, renalase does bind to A and performs no catalytic transformation of A [39]. Quelhas-Santos et al. [40] reported that renalase degrades catecholamines catalyzing the formation of aminochromes.

The discrepancy among studies may be related to the methods of determination. The different results in blood levels based on western blots and ELISA need further exploration and raise concerns about the interpretation of renalase levels in patients with kidney disease. The most relevant issue is that the two antibodies used in the commercial sandwich ELISA kit (Uscn Life) have not been fully validated. The identity of the antibodies and the epitopes they recognize, and information on how they behave in native western blots is not available. For example, they may recognize epitopes undetected by the original studies with polyclonal antibodies [41, 42, 43]. Alternatively, increased renalase levels by ELISA in advanced CKD could be due to accumulated renalase breakdown products, or to cross-reaction with an unrelated epitope. The polyclonal antibody predominantly detects the dimeric form of renalase (~75 kDa), with an estimated concentration of 4 μg/mL, while the monoclonal preferentially binds to higher molecular weight species. It is possible that lower GFR could favor the formation and accumulation of higher molecular weight multimers. It is interesting that western blot and ELISA give virtually identical results in subjects with normal renal function. Finally, it is possible that the measurement of plasma renalase activity may be the answer to this issue, as it would provide important insights into the function of renalase in health and disease [43, 44]. Therefore, recombinant renalase exerts powerful and rapid hypotensive effects on rats through including catecholamines degradation. Yin et al. [45] confirmed the beneficial effects of renalase supplementation on functional and histological alterations of kidney and heart, and investigated the underlying mechanism in a rat model with progressive renal injury. Furthermore, the authors [45] have demonstrated that the systemic delivery of renalase, a kidney-derived protein, attenuated both renal and cardiac fibrosis, improved renal function and prevented cardiac remodeling six weeks after renal ablation through its anti-inflammatory and anti-oxidant effects, inhibition of extracellular signal-regulated kinase (ERK) pathway, which indicate that renalase may play a crucial role in the interaction between kidney and heart. Taken together, these findings indicated renalase supplementation might protect renal injury through inhibiting inflammation activation and oxidative stress in remnant kidney. Taking all these new data into consideration, it seems intriguing that these studies yielded contradictory results. The nature of this interaction needs to be evaluated by further experimental and longitudinal clinical studies to clarify whether there really exists a cause-effect relationship.

CONCLUSIONS

The results of the presented study demonstrate the correlation between levels of renalase and advanced oxidation protein products in haemodialysis patients. Indeed, the elevated levels of renalase and AOPP in HD may be due to the presence of uraemic toxins. The concentration of urea affects the plasma concentrations of AOPP and renalase, causing a direct relationship between renalase and AOPP. Of note, lowering plasma AOPP concentration may represent therapeutic target for prevention of cardiovascular events in progressive renal damage. Moreover, there is no clear relationship between renalase and circulating catecholamines in HD patients. Regardless of the mechanism underlying their association, it seems important to study the interaction between CA and renalase levels with respect to the high mortality and cardiovascular morbidity rates for patients with ESRD. Prospective studies are needed to better elucidate the role of renalase and AOPP with regard to catecholamines in haemodialysis patients.

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