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PROGRESS STUDY: Longitudinal Analysis of Antioxidant Status and Its Relationship with Heat Shock Proteins in Children with Chronic Kidney Disease.

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Abstract

The progression of chronic kidney disease (CKD) occurs through complex mechanisms and eventually results in renal fibrosis. Oxidative stress is one of these pathological pathways and impaired antioxidant defense mechanisms have been implicated in CKD. Our aim was to investigate changes in serum and urine levels of superoxide dismutase (SOD), catalase, and glutathione over time as markers of antioxidant defense in children with CKD. Additionally, we evaluated the relationship between these antioxidant markers and heat shock proteins (HSPs). A total of 117 children with CKD and 56 healthy children were enrolled in the study. The CKD group was followed prospectively for 24 months. Serum and urine levels of creatinine (Cr), protein, glutathione, catalase, and superoxide dismutase (SOD) were measured using ELISA at baseline, 12 months and 24 months. Serum catalase and SOD levels, as well as urinary catalase, SOD, glutathione, and their ratios to creatinine, were higher in the CKD group than in the control group. Serum and urine levels of SOD and catalase, also urine SOD and catalase ratio to creatinine were steadily decreased over time, similarly to urinary HSPs (HSP27, HSP40, HSP47, HSP60 and HSP72). Serum glutathione, SOD and catalase levels were positively correlated with each other. Urine catalase levels were negatively correlated with urine SOD levels, while urine SOD and glutathione levels were positively correlated to each other. Serum catalase and serum SOD levels were positively correlated to their urine levels. However, according to univariate and multivariate regression model baseline urine antioxidant levels could not predict CKD progression. In conclusion, glutathione, catalase and SOD levels (except serum glutathione) were increased in CKD to counteract to oxidative stress however the antioxidant defense mechanism may be insufficient to overcome oxidative stress in the uremic milieu and their levels decrease as CKD progresses.

INTRODUCTION

Chronic kidney disease (CKD) in children can arise from various congenital and acquired diseases. CKD is a devastating condition that leads to progressive and irreversible renal damage, ultimately resulting in the need for renal replacement therapy, regardless of the underlying cause. The progression of CKD disease eventually results in fibrosis in both the glomeruli and the tubulointerstitial areas of the kidneys. Multiple molecular and cellular mechanisms contribute to renal fibrosis, such as oxidative stress, inflammation, damage to endothelial cells, and apoptosis [1].

The disruption of the balance between the formation of reactive oxygen species and antioxidant defense mechanisms leads to an oxidative stress environment. Superoxide dismutase (SOD) is one of the major components of the antioxidant defense system. SOD catalyzes the conversion of superoxide anions to hydrogen peroxide and oxygen. Hydrogen peroxide is then converted to water and oxygen via catalase [2]. Glutathione peroxidases cooperate with catalase to decompose hydrogen peroxide into water and oxidized glutathione. The oxidized glutathione is then reduced by glutathione reductase. As a member of the non-enzymatic antioxidant defense system, glutathione contains a thiol group that provides a source of electrons for neutralizing free radicals. Therefore, SOD, catalase, and glutathione are important components of the antioxidant defense system [2, 3].

Heat shock proteins (HSPs) are continuously expressed under normal conditions and play an important role in regulating the turnover of intracellular proteins as well as maintaining cellular integrity. HSP expression increases under stress conditions such as oxidative stress, inflammation, and ischemia. They serve as cytoprotective chaperones by assisting with polypeptide folding, assembly, translocation, refolding, repair or degradation of denatured proteins [4]. Additionally, they play an important role in apoptosis regulation, suppression of pro-inflammatory cytokines, and protection from oxidative stress [4].

It has been stated that oxidative stress is one of the main mechanisms in the pathogenesis of CKD progression [5, 6]. Additionally, HSPs have been reported to work together with the antioxidant defense system in an oxidative stress milieu [7]. The data on antioxidant mechanisms and their relationship with HSPs in CKD, especially in children, are quite limited. Previously we demonstrated that serum and urine HSPs alteration over time in patients with CKD [8]. Therefore, in this study, we aimed to evaluate serum and urine levels of SOD, catalase, and glutathione, as well as their changes over time, and to investigate their relationship with HSP levels in children with CKD.

MATERIALS AND METHODS

Approval from the local ethics committee was obtained for this study (Project No: 2015/487). Written informed consent was obtained from the parents of all participants.

This study is a part of progress study therefore study design and population was described in detail previously [8]. Briefly, from four pediatric nephrology centers, a cohort of 117 children (37 females and 80 males) with CKD stage 2–5 was recruited during routine follow-up appointments [9]. The control group comprised 56 healthy children (27 females and 29 males) who had no chronic diseases and no acute illnesses or surgeries within the three months prior to or during the sampling period.

The CKD group was monitored prospectively for a duration of 24 months. Upon enrollment, both the patients and the control group underwent standard physical examinations. Annual assessments of hemoglobin (Hb), serum parathyroid hormone (PTH), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), and ferritin levels, all tested on the same day as sampling, were obtained from their medical records. The estimated glomerular filtration rate (eGFR) was calculated using the Schwartz formula [10]. Rapid progression of CKD was defined as the necessity for dialysis or kidney transplantation, and/or a 25% decrease in eGFR from baseline levels. By the end of the 24-month period, twelve patients had withdrawn from the study, either due to loss to follow-up (n = 5) or the need for dialysis or kidney transplant (n = 7). Patients' characteristic's and diagnosis were given in supplementary Table.

Blood and urine samples

Samples were collected from patients at baseline, 12 months, and 24 months, while controls provided samples once at baseline. At the time of sampling, patients had no history of infection, surgery, or

hospitalization in the preceding three months. Urinary tract infections were ruled out through urinalysis and urine culture. Urine and blood samples were centrifuged for 10 minutes at 2,000 g. Aliquots of the serum and urine supernatant were stored at -80°C until analysis.

Serum and urine concentrations of human catalase, glutathione, and superoxide dismutase (SOD) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (YH Biosearch, Shanghai, China; Cat. Nos. HB0636Hu, YHB1373Hu, and YHB2870Hu, respectively). All samples were analyzed in duplicate in accordance with the manufacturer's instructions. Concentrations were determined based on standard curves generated from optical density (OD) values, and the arithmetic mean of the duplicates was used as the final result. The levels of glutathione, catalase, and SOD were expressed as ng/mL, KU/L, and U/L, respectively.

Serum and urine creatinine (Cr) levels, along with urine protein concentrations, were measured using the Architect c16000 analyzer (Abbott Laboratories, Abbott Park, IL, USA). The results are reported in mg/dl, while urine protein-to-creatinine ratios are presented in mg/mg.

Serum and urine levels of HSP27, HSP40, HSP47, HSP60, HSP70, HSP72, and HSP90, as well as serum levels of anti-HSP60 and anti-HSP70, were analyzed using ELISA, as previously described. The results are presented in the earlier study [8].

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics software (version 22.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Descriptive statistics were presented as either median values with interquartile ranges. Categorical variables were analyzed using the Chi-square test. As none of the variables showed a normal distribution, nonparametric methods were applied for group comparisons. The Mann–Whitney U test was used for two-group comparisons, including between CKD and control groups and between patients with and without rapid CKD progression. Longitudinal changes over time (baseline, 12 months, and 24 months) were analyzed using the Friedman test, while pairwise comparisons were performed using the Wilcoxon signed-rank test with Bonferroni correction for multiple testing. Associations between continuous variables in CKD patients were evaluated using Spearman's rank correlation coefficient. Additionally, both univariate and multivariate logistic regression analyses were conducted to investigate the predictive value of antioxidant biomarkers for disease progression. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of the baseline results of CKD and control group

Serum catalase and serum SOD levels were higher in CKD group than in control group (p=0.008, p<0.0001, respectively). However, serum glutathione levels were not different between CKD and control

group ($p>0.05$). Urine catalase, SOD and glutathione and their ratio to creatinine levels were higher in CKD group than in controls ($p<0.0001$) (Table 1).

Comparison of the three consecutive years results of CKD group

Serum and urine glutathione and glutathione/Cr levels were not different between consecutive three years results ($p>0.05$). However, serum SOD and catalase levels were steadily decreased over the years and eventually reached the comparable to control group levels at 24th month. Also urine SOD, catalase and their ratio to creatinine levels were steadily decreased over the years, however their levels were still higher than controls at the 24th month (Table 1).

Comparison of the groups with and without rapid CKD progression

We evaluated whether baseline antioxidant biomarker levels predicted rapid CKD progression. Patients with rapid CKD progression had lower urine catalase and higher urine SOD (Table 2). According to univariate and multivariate regression model baseline urine antioxidant levels cannot predict CKD progression.

Correlations among antioxidant biomarkers

Serum glutathione, SOD and catalase levels were positively correlated each other. Urine catalase levels were negatively correlated to urine SOD levels. Urine SOD and glutathione levels were positively correlated to each other. Additionally, serum catalase levels showed positive correlations with urine catalase, but were negatively correlated with urine SOD levels. Serum SOD levels were positively correlated with urine glutathione and SOD levels. Urine glutathione/Cr, catalase/Cr, SOD/Cr levels were correlated to each other (Table 3).

Correlation of antioxidant biomarkers and heat shock proteins (HSPs)

Serum catalase levels were positively correlated with all serum HSP levels. Serum glutathione and SOD levels also showed positive correlations with serum HSPs. Additionally, serum SOD levels were correlated with anti-HSP60 levels, while glutathione levels were correlated with anti-HSP70 levels (Table 4). Serum catalase and SOD levels tended to decrease over the years, similar to serum HSP47 and 60 (Figure 1).

Urine glutathione and SOD levels were positively correlated with urine HSP27, HSP60, and HSP72, while negatively correlated with HSP90 levels. Urine catalase levels showed positive correlations with urine HSP27, HSP40, HSP47, and HSP90 levels, but were negatively correlated with HSP60 levels (Table5). Urine antioxidant biomarkers/Cr ratios were correlated urine HSPs/Cr ratios except urine SOD/Cr showed did not correlation to HSP90/Cr (Table 6). Additionally, urine SOD and catalase levels tended to decrease over the years, similar to urinary HSPs (HSP27, HSP40, HSP47, HSP60 and HSP72) (Figure 2). Data on HSPs have been reported in detail in our previous publication [8].

DISCUSSION

Oxidant molecules such as reactive oxygen species (ROS) former continuously and removed by the antioxidant defense system under normal physiological conditions. At moderate levels, ROS serve as a second messengers and have a physiological role in signal transduction pathways [11]. However, overproduction of ROS or decreased degradation by the antioxidant system can lead increase in oxidation end products and eventually resulting in oxidative cell damage [3, 11]. Kidney is one of the organs vulnerable to oxidative stress due to high oxidative activity of its mitochondria [12]. There is increasing evidence that oxidative stress impairs kidney function and significant contributes to CKD progression [3, 11].

Studies on adult CKD were primarily evaluated oxidant and antioxidant status in serum, plasma, erythrocytes, monocytes or polymorphonuclear leukocytes. In addition, they included different characteristics of patient groups, such as primary diagnoses, stage of the disease, dialysis status and dialysis type. They also evaluated oxidant and antioxidant status using different molecules and enzymes by employing various methods. These studies have reported conflicting results for antioxidant enzyme activities or levels, indicating that they may be increased, decreased, or unchanged [13–31]. In terms of glutathione, SOD and catalase, most studies reported that glutathione levels were lower or unchanged, however SOD and catalase levels were increased, decreased or unchanged in CKD patients [15, 17, 20, 23, 24, 28]. Kuo et al differently evaluated urine extracellular SOD (SOD3) in patients with diabetes alone, diabetes with CKD and early CKD and they found that urine and serum SOD3 levels were higher in patients with CKD and diabetes [30].

Among limited pediatric studies, Garcio Belo et al. found that glutathione levels were higher in predialysis patients than dialysis patients and patients with abnormal carotid intima media thickness demonstrated lower levels of glutathione [32]. Kotur-Stevuljević et al. reported that CKD patients demonstrated lower levels of SOD activity, total antioxidant capacity and paraoxanase 1 [16]. Zwolinska et al. demonstrated lower plasma and erythrocyte SOD, catalase and GPX activity levels in pediatric patients with end stage renal disease (ESRD) [33]. Conversely, Asayama et al. showed that both manganese and copper-zinc SOD in lymphocytes and monocytes of HD and CAPD patients, as well as manganese SOD in polymorphs of HD patients, were elevated compared to the controls. However, the levels of copper-zinc SOD, glutathione peroxidase, and catalase in erythrocytes remained unchanged [13].

However, none of these studies evaluated changes in antioxidant systems over time in both urine and serum. Since the study designs and methods of the mentioned studies are different, it does not seem appropriate to compare them with our study. Herein, we report disturbances in SOD, catalase, and glutathione levels in patients with CKD and their longitudinal assessment. According to our results, the serum and urine antioxidant biomarkers were higher in the CKD group than in the controls, except for serum glutathione; however, these levels decreased over time, while serum and urine glutathione levels remained unchanged. We speculated that antioxidant systems were activated to counteract systemic or

locally active oxidative stress that already exist in CKD patients. However, their protective increases diminish as CKD progresses.

Our results suggest that SOD, catalase, and glutathione may not be suitable biomarkers for predicting CKD progression. This may be due to the fact that their levels are dynamically regulated, leading to variability.

Another important aim of our study is evaluated the relationship between HSPs and glutathione, SOD and catalase as antioxidant molecules. An imbalance of antioxidants and oxidative stress can activate heat shock factor (HSF) and subsequent HSP synthesis [7, 34, 35]. It has been reported that, the initial expression of HSP is mainly driven by reactive oxygen species (ROS), while subsequent HSP expression is largely activated by protein damage and heat shock factor 1 [7, 36]. Additionally, HSF1 can induce genes that responsible protect the oxidative stress. HSF1 knockout mice demonstrate downregulation of HSPs expression and increased levels of oxidative stress markers and related oxidative damage [34]. Therefore, the role of HSPs in the balance of the oxidative and antioxidative systems appears to be multidirectional [7]. Our results also suggest that antioxidant defense molecules may work in conjunction with HSPs, showing a strong correlation between HSPs and antioxidant defense biomarkers. Serum catalase and SOD levels tended to decrease over the years, similar to serum HSP47 and 60 (Fig. 1). Additionally, urine SOD and catalase levels tended to decrease over the years, similar to urinary HSPs (HSP27, HSP40, HSP47, HSP60 and HSP72).

It has been considered that HSPs, particularly HSP70 family, play a cytoprotective role against DNA breaks causing by ROS [37]. HSP27 and the HSP70/HSP40/HSP110 complex may affect SOD1 function by reducing its misfolding and aggregation [7]. HSP70 family induce free 20S proteasome thus increase oxidized protein degradation [7]. There are some reports suggested that can reduce of ROS generation via increase SOD activity [7, 38]. Baldisera et al reported that extracellular/intracellular HSP70 ratio was related to increase of SOD activity [39]. Glutathione levels were increased with overexpression of HSP27 [40]. Serum SOD levels were strongly correlated all serum HSPs except anti-HSP70 in our study. Additionally, urine SOD levels were positively correlated to urine HSP27, 60 and 72 whereas negatively correlated urine HSP90. Urine SOD/Cr levels were strongly correlated to all urine HSPs/Cr levels except urine HSP/90 Cr. Similar results were obtained for glutathione and HSPs relationship.

These results suggest that the antioxidant mechanism and HSPs work together and counteract to oxidative stress in pediatric CKD. On the other hand, their protective function may be affected and may not work properly in a uremic milieu. Additionally, their increased levels may involve in the progression of CKD pathogenesis.

There is evidence that HSP90 can bind to oxidized phospholipids and prevent their further oxidation, in some cases acting together with HSP70 [7]. Besides this, some studies demonstrated that administration of HSP90 inhibitor prevent further ischemia, reduces oxidative stress and increases SOD1 and catalase levels in myocardia [7, 41]. Also HSP90 inhibition prevents fibrosis in animal models of renal injury [42, 43]. In our study, HSP90 was the only HSP that increased over time and in this respect its

courses over time was also different from that catalase and SOD. Serum HSP90 levels were positively correlated to serum SOD, glutathione and catalase whereas in urine HSP90 were negatively correlated to urine glutathione and urine SOD and positively correlated to urine catalase. This suggests that the effect of HSP90 on the oxidative system may differ both systemically and locally in the kidney.

The limitations of our study are the relatively small sample size and the limited follow-up period. Despite our limitations our study has important results. The strength of our study is that we followed the course of the biomarkers in patients over the years. We demonstrated that elevated catalase, SOD and glutathione levels in children with CKD, tendency to decreases over time. Additionally, the simultaneous decline in antioxidant markers and HSPs, along with their correlations, suggests that they may act together as part of the response to oxidative stress in CKD. Treatments that restore the oxidant-antioxidant balance in CKD may be considered to slow the progression of CKD.

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Tables

Tables 1 to 6 are available in the Supplementary Files section.

Figures

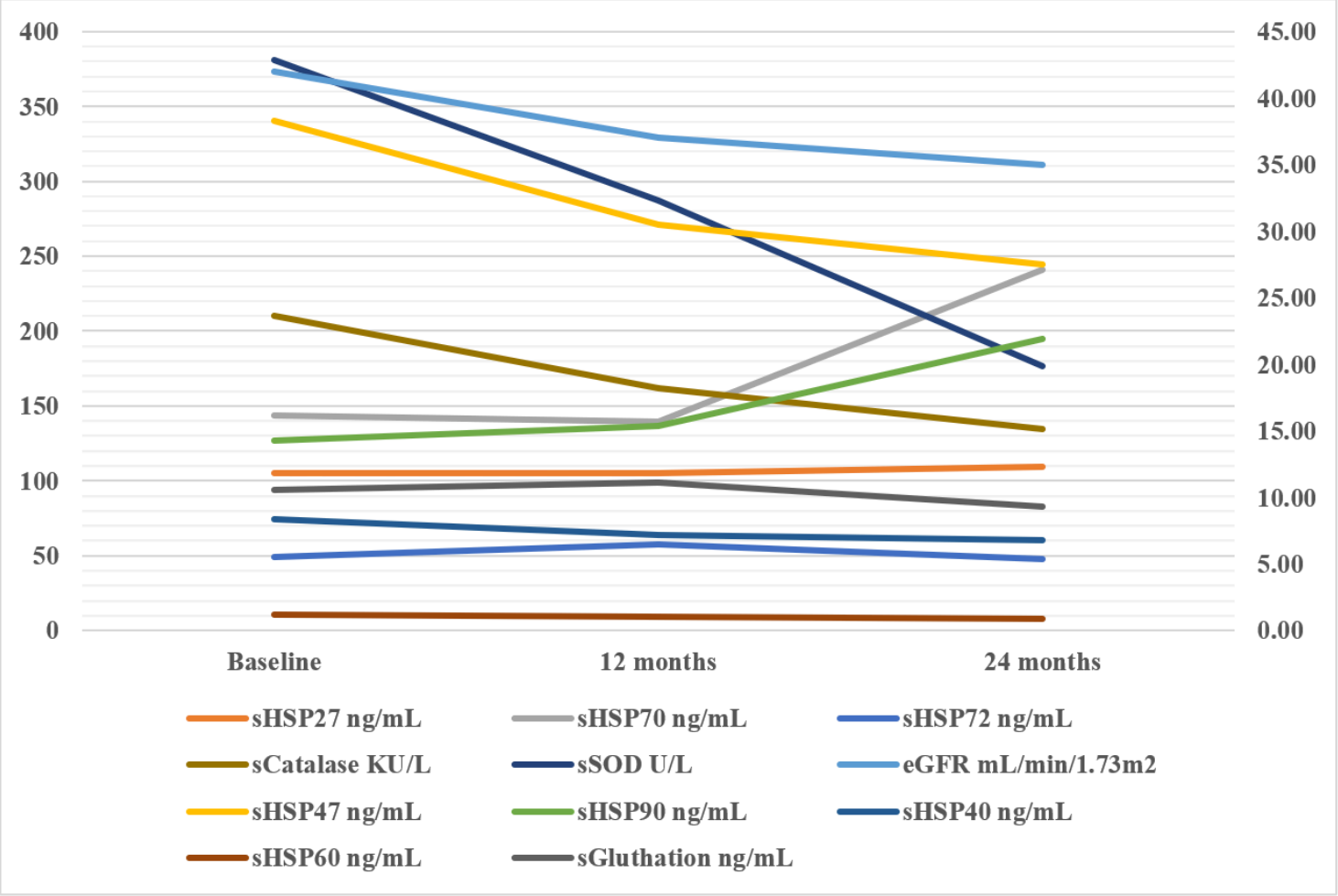


Figure 1

The course of eGFR, serum antioxidant biomarkers and serum HSPs over time. eGFR: estimated glomerular filtration rate. s: urine, SOD: superoxide dismutase, HSP: heat shock protein. Serum catalase, superoxide dismutase, HSP27, 70 and 72 were given on the primary axis (left side); eGFR, serum glutathione, HSP40, 47, 60, 90 data were given on the secondary axis (right side)

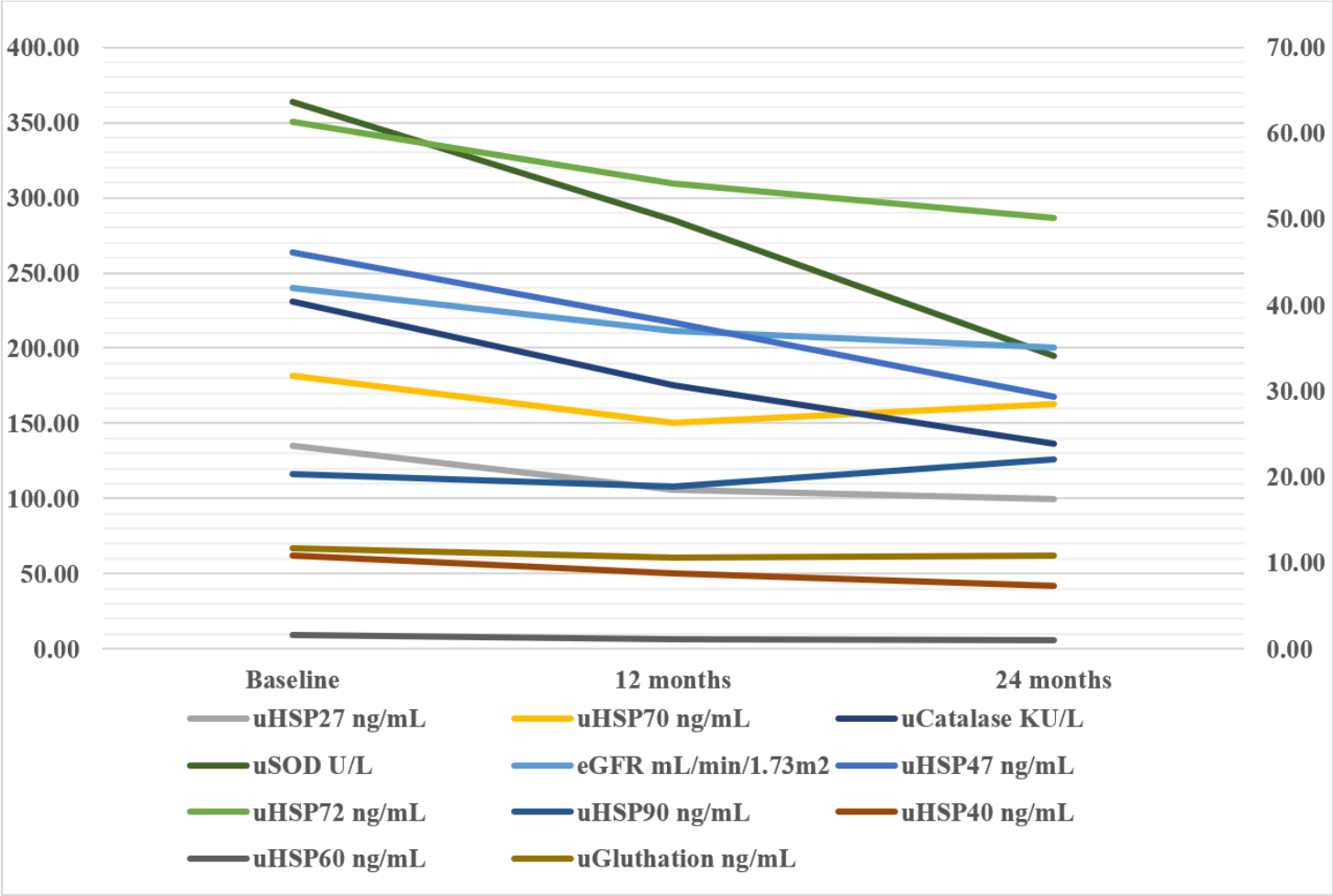


Figure 2

The course of eGFR, urine antioxidant biomarkers and urine HSPs over time. eGFR: estimated glomerular filtration rate. u: urine, SOD: superoxide dismutase, HSP: heat shock protein. Urine catalase, superoxide dismutase, uHSP27 and 70 were given on the primary axis (left side); eGFR, urine glutathione, HSP40, 47, 72, 60, 90 data were given on the secondary axis (right side)

Supplementary Files

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