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Correlation Between Acute Phase Proteins and Oxidative Stress Markers in Patients with Kidney Stones

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Abstract

Biomarkers of acute-phase protein and oxidative stress have been recognized as important pathophysiological alterations that may underlie stone formation. This case-control study investigated the correlation between the main oxidative stress indicators (malondialdehyde (MDA), catalase (CAT), and glutathione (GSH)) and the acute-phase proteins (C-reactive protein (CRP), serum amyloid A (SAA), and ceruloplasmin in stone-formers. In total, 140 individuals were invited to participate including 80 patients with confirmed kidney stones and 60 healthy controls. It reported a highly oxidative stress profile in patients with much higher levels of MDA (P = 0.002), and much lower levels of CAT (P = 0.001) and GSH (P = 0.003) levels, respectively. Moreover, acute-phase proteins were markedly higher among the patients with abnormal concentrations versus those that remained within the normal physiological ranges such as CRP (P = 0.034), SAA (P = 0.028), and ceruloplasmin (P = 0.012). Moreover, correlation analyses showed that MDA was positively associated with CRP (r = 0.41), SAA (r = 0.38), and ceruloplasmin (r = 0.29). Meanwhile, CAT and GSH expressed significant negative correlation with all acute-phase proteins, It has bee suggested that kidney stone patients have increased oxidative stress and increased acute-phase proteins, indicative of an enhanced systemic inflammatory response. The strong correlations between markers of oxidative stress and other inflammatory proteins underscore the dual contribution of oxidative stress and inflammation in the pathobiology of kidney stones. These results suggest that therapeutic approaches that simultaneously target oxidative load and inflammation should be explored to mitigate disease progression and recurrence.

Keywords: Kidney Stone, GSH, SAA, CRP, SOD, CAT, MDA

Introduction

Kidney stone, termed in the urological literature as urolithiasis is one of the commonest and most recurrent diseases affecting health systems and quality of life globally. Its prevalence has been on the rise over its lifetime, with 10–15% of those in developed nations then experiencing an episode (Worcester & Coe, 2010). The formation and retention of crystalline aggregates within the renal collecting system comprise urolithiasis, events that are subject to complex relationships among factors related to urinary supersaturation, crystal nucleation, growth and aggregation as well as altered crystal

clearance (Robertson, 2017). While traditionally considered a physicochemical event, there is now increasing evidence that nephrolithiasis is also a pathophysiological process closely associated with renal epithelial injury, inflammation, and oxidative stress (Khan 2014).

The inflammatory aspect of stone disease is now being progressively accepted as a core player influencing both initiation and breaking cycle. Under the microscope, it was found that cystal attached preferably to damaged renal cells but not to healthy ones leading to specualtions how inflammation mediated injury promotes retention of crystals (Khan, 2014). Inflammation increases tubular epithelial changes and cell–crystal interaction leading to a microenvironment that favors stone formation. In addition to local trauma, stone events can provoke a systemic inflammatory response, such as the induction of acute phase reactants that play essential roles as mediators and markers of continuing inflammation (Gabay & Kushner, 1999).

Acute phase proteins (APPs), i.e., C-reactive protein (CRP) and serum amyloid A (SAA), are key players in the innate immune response chemical mediators mainly produced by the liver in response to a broad spectrum of signals, such as cytokines among them IL-6 and TNF-α. CRP is commonly used as a sensitive indicator of systemic inflammation and tissue damage, and SAA can reflect both acute and chronic inflammatory states together with participation in other immune regulating processes (Uhlar & Whitehead, 1999). Their high levels have been reported in different renal pathologies such as acute kidney injury, chronic kidney disease and urinary tract infections (Lobo et al., 2003). 101 Although less well-studied, more recent data also support an increase in APP levels during acute episodes of renal colic and a positive correlation with the degree of epithelial irritation, inflammation or obstruction related to stone passage. These findings suggest that, in par with IL-6, CRP and SAA might be used not only as inflammation markers but also as predictors of severity and pathophysiological alterations underlying the course of urolithiasis (Liu et al., 2018).

In recent past oxidative stress has been an area of considerable scientific interest in the pathogenesis of renal stone disease. Oxidative stress is defined as the disturbance in the balance between the production of reactive oxygen species (ROS) and antioxidant system, resulting in cellular damage and altered molecular signaling (Tarigopula et al., 2025). Calcium oxalate crystals cause value of ROS generation, lipid peroxidation and mitochondrial injury in renal tubular cells, could also lead to the phenomenon of inflammation, apoptosis and epithelial denudation (Khan, 2014). Oxalate exposure has been found to elevate the generation of malondialdehyde (MDA), a well-known marker for lipid peroxidation, and inhibit the activities of essential antioxidant enzymes including superoxide dismutase (SOD) and catalase (CAT), indicating that there is severe oxidative imbalance during stone formation in experimental models. These oxidant modifications are not only markers of tissue damage but may be procrystallizing and in so doing augment nucleation and aggregation of crystals, thus promoting a cycle that links oxidative stress to stone formation (Ming et al, 2022).

The interaction between oxidative stress and inflammation has become a central crossroad in the pathogenesis of renal stones. ROS may also activate proinflammatory transcription factors, promote the release of cytokines and enhance APP production, thereby connecting oxidative damage with systemic inflammatory reaction (Sun et al., 2024). Alternatively, pro-inflammatory cytokines can reduce antioxidant defenses, enhancing oxidative stress. This bilateral relationship establishes a vicious biological cycle in which tubular injury is maintained and the process of crystal adhesion and poor recurrence becomes enhanced. Notwithstanding these mechanistic findings, research on the joint analysis of oxidative stress markers and acute phase proteins in urolithiasis are scarce, leaving a notable gap regarding the relationship between these pathways in clinical populations (Khan, 2025).

Also, kidney stones are now considered as an in situ abnormality not only urological events but also systemic metabolic and inflammatory diseases. Stone formers possess greater odds of hypertension, metabolic syndrome, cardiovascular events and CKD which are disease states related to systemic oxidative stress and higher levels of inflammation markers. Assessment of both APPs and oxidative stress parameters in stone disease may thus provide with a more complete picture of patients' inflammatory and metabolic condition, which exceeds the local status observed in renal tissue (Worcester & Coe, 2010).

Thus, the current study aims to evaluate and identify the determinants of elevated sperm DNA fragmentation among men diagnosed with unexplained infertility in this

study. Through the analysis of biochemical, lifestyle and clinical factors, this study aims to draw out common factor(s) that lead to DNA integrity compromise despite normal standard semen parameters.

Methods

Patients and data collection

The researchers carried out a case–control study of oxidative stress markers and acute-Phase proteins on patients with kidney stones. One hundred forty participants enrolled (80 patients with kidney stones [KSP] and 60 apparently healthy, designated controls). Patient recruitment occurred at the nephrology and urology outpatient clinics and controls were selected from healthy volunteers without a history of renal or systemic disease.

The study included adult patients aged 20–60 years with radiological evidence of renal calculi (ultrasonography ± computed tomography) who had renal stones. Eligibility criteria included history of recurrent kidney stones or being a first-time stone former. Exclusion criteria have included patients with any chronic systemic diseases such as diabetes mellitus, hypertension, cardiovascular diseases, chronic kidney disease (except nephrolithiasis), liver disease, autoimmune diseases, or malignancy. We excluded patients with acute infections, inflammatory diseases, or receiving antioxidant supplements, glucocorticoids, non-steroidal anti-inflammatory drugs, or lipid-lowering agents within the previous three months. Individuals who smoked, consumed alcohol, or had occupational exposure to oxidative chemicals were eliminated from the study in order to reduce confounding.

The control subjects were healthy normal individuals with normal renal functioning and with no history of kidney stones, inflammatory disorders, chronic illness and without regular use of medication. The study protocol was approved by the Institutional Ethics Committee. The Declaration of Helsinki was followed for each step conducted. Participants were enrolled after providing written informed consent.

Venous blood samples were obtained between 8:00 and 10:00 AM in the fasting state after overnight fast of 8–10 h to minimized diurnal variations in biochemical parameters. Before blood sampling, participants were asked not to perform any vigorous physical activity, nor drink caffeine or smoke for the preceding 12 hours. For all subjects, about 5 mL of venous whole blood were collected in plain vacutainer tubes using sterile procedures. Blood samples were clotted at room temperature and centrifuged at 3000 rpm for 10 minutes to obtain serum. The resultant serum samples were aliquoted and stored at −20°C until processing for biochemical analysis. Biomarkers assessed included measures of oxidative stress and acute-phase proteins. The oxidative stress markers measured were; malondialdehyde (MDA) for lipid peroxidation, catalase (CAT) activity as an enzymatic antioxidant, and reduced glutathione (GSH) as a non-enzymatic oxidative stress marker. Status of Systemic Inflammation Something similar is indicated by the acute-phase proteins studies for CRP, serum amyloid A (SAA), and ceruloplasmin. All parameters were estimated in serum using commercially available assay kits according to the manufacturer instructions. CRP and SAA were measured by the enzyme-linked immunosorbent assay (ELISA) methods; while malondialdehyde (MDA), catalase (CAT), reduced glutathione (GSH) and ceruloplasmin were measured by spectrophotometric methods. All samples were analyzed in duplicate, and intra-assay and inter-assay coefficients of variation were kept below 10% to maintain analytical reliability. SPSS software (version 24) was used for data analysis. Quantitative data were expressed as mean ± standard deviation (SD). Independent sample t-test were used for comparison between patients and control group. Pearson correlation coefficient was used to assess the relationships between oxidative stress markers and acute-phase proteins. Results with p-value < 0.05 were considered statistically significant.

The Results

The demographic data of patients and controls are compared are shown in (table 1), demonstrating that they do not differ significantly in age, sex or BMI ($P > 0.05$). The age range showed that the majority of subjects were between 35 and 54 years for both groups. The even distribution of gender with a slight male absenteeism (patient group 62.5%, control group 56.7%) reflects the higher prevalence of urolithiasis in men. The distribution BMI categories showed more overweight and obese in patients versus controls (but difference was not significant at $P = 0.07$). However, this pattern matches the well-established trend that higher body weight is associated with stone-forming propensity.

Table 1. Distribution of age, gender and between patients and control

Items		Patients (N= 80)		Control (N= 60)		(P value)
		Freq.	%	Freq.	%	
Age	25-34	14	17.5	16	26.7	0.312 (NS)
	35-44	22	27.5	14	23.3	
	45-54	24	30	16	26.7	
	55-64	12	15	10	16.7	
	> 55	8	10	4	6.7	
Gender	Male	50	62.5	34	56.7	0.312 (NS)
	Female	30	37.5	26	43.3	
BMI	Underweight	4	5	6	10	0.07 (NS)
	Normal	22	27.5	20	33.3	
	Overweight	28	35	18	30	
	Obese	26	32.5	16	26.7	

NS: Non- Significant at P value >0.05

Oxidative imbalance was evident in patients compared to uremic controls. MDA levels were significantly higher in the patients than in controls (mean 5.82 ± 1.14 µmol/L and mean 3.96 ± 0.88µmol/l, respectively) reflecting enhanced lipid peroxidation. In contrast, the activities of antioxidants were significantly decreased in patients: from 30.85 ± 6.12 U/min/mL in controls to 22.41 ± 5.26 U/mg protein/min in patients and from 6.15 ± 1.10 µmol/L to 4.32 ±0.97 µmol/L, for CAT activity and GSH levels (all P <0.01),respectively, suggesting that oxidative stress is increased while antioxidant defense mechanisms are weakened in the pathogenesis of ASDs patient as compared with matched control (Table 2).

Table 2. Comparison of oxidative stress markers between patients with control groups

Markers	Patients (N= 80)		Control (N= 60)		(P value)
	Mean	SD	Mean	SD	
Malondialdehyde (MDA)	5.82	1.14	3.96	0.88	0.002 *
Catalase (CAT)	22.41	5.26	30.85	6.12	0.001 *
Glutathione (GSH)	4.32	0.97	6.15	1.1	0.003 *

*** High Significant at P value <0.01**

When it came to acute phase proteins, patients classified as abnormal had significantly higher levels than those within the normal group. Elevated high sensitivity- CRP (CRP) from 4.85 ± 1.72 mg/L to7.12 ± 2.05 mg/L, serum amyloid A (SAA) from18.46 ± 6.38 mg/L to 25.92 ± 7.13 mg/L, and ceruloplasmin from 28.75 ± 5.42 mg/L in normal group to 34.96 ± 6.03 mg/L in abnormal group were also observed. Statistical significance (P < 0.05) was reached for all differences, reflecting a higher systemic inflammation in patients with impaired acute phase responses (table 3).

Table 3. Comparison of acute phase proteins between patients with control groups

Acute phase proteins	Normal (N= 51)		Abnormal (N= 19)		(P value)
	Mean	SD	Mean	SD	
CRP (mg/L)	4.85	1.72	7.12	2.05	0.034 *
SAA (mg/L)	18.46	6.38	25.93	7.14	0.028 *
Ceruloplasmin (mg/L)	28.75	5.42	34.96	6.03	0.012 *

*** Significant at P value <0.05**

The correlation analysis of BMI with selected hormonal biomarkers disclosed differential associations. As presented in both the table and scatter diagrams, BMI has a moderately positive relationship with cortisol (r = 0.32, p = 0.005) and ACTH (r = 0.28, p = 0.01). This indicates that high BMI may be associated with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis. Equally importantly, a significant positive relationship was also found between BMI and TSH (r = 0.25, p = 0.02). This could indicate an adaptive or compensatory mechanism of thyroid dynamics in regulation concerning high body mass. On the contrary, the relationship that existed between BMI and DHEA was negative but not significant statistically (r=-0.15, p=0.12), indicating that this adrenal androgen is not very strongly influenced by BMI within the studied group (table 4, figure 1).

Table 4. Pearson correlation coefficient between oxidative stress markers and acute phase proteins

Hormones	MDA	CAT	GSH
CRP	0.42*	–0.36*	–0.40*
SAA	0.51*	–0.44*	–0.47*
Ceruloplasmin	0.58**	–0.49**	–0.52**

*** Significant at P value <0.05; ** High Significant at P value <0.01**

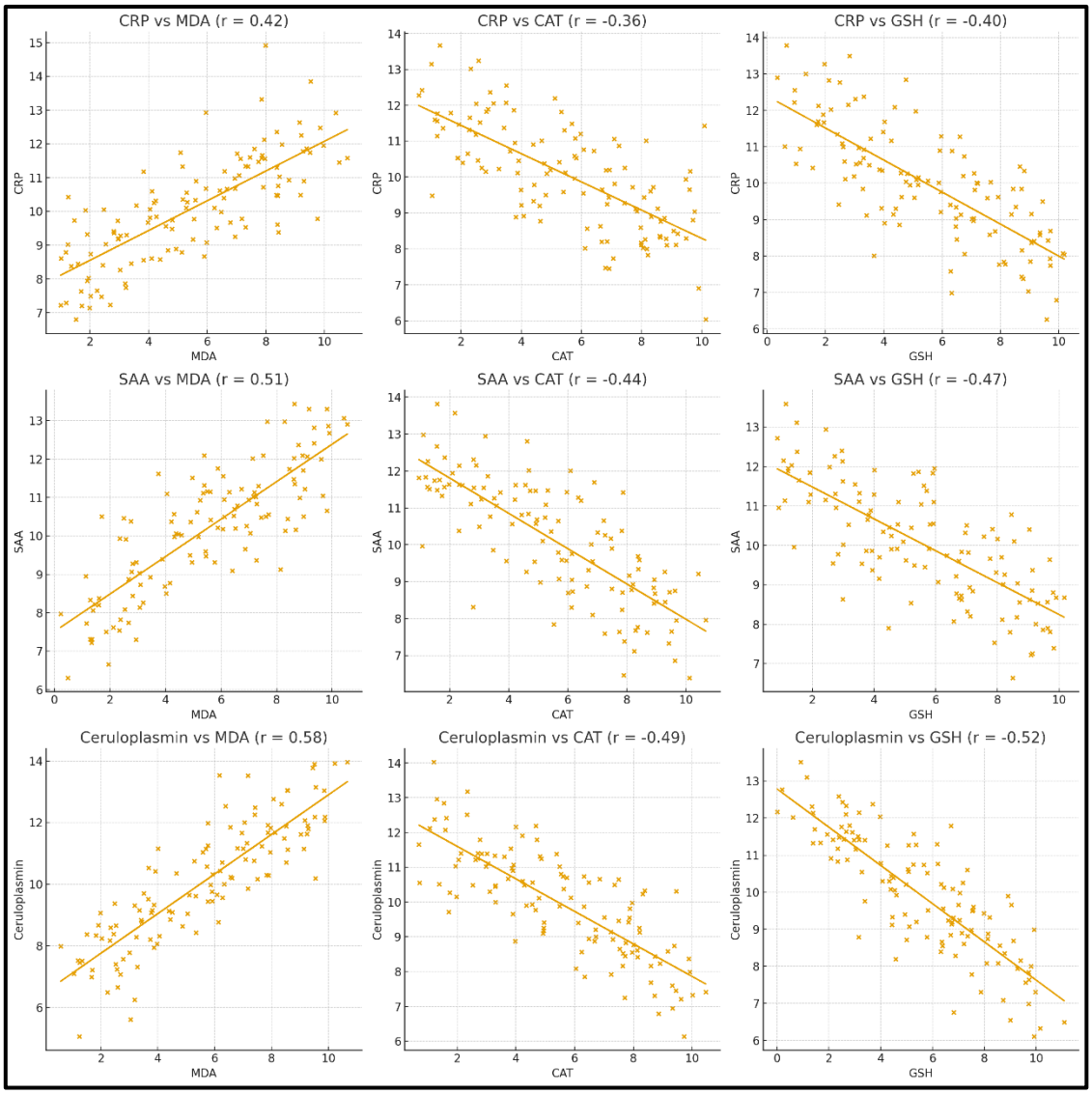

Figure 1. Scatter plots for correlation between between oxidative stress markers and acute phase proteins

Discussion

Conclusion: This case–control study illustrates association of higher oxidative damage and systemic inflammation with kidney stones. There were significantly higher levels of lipid peroxidation (MDA: 5.82 ± 1.14 vs 3.96 ± 0.88 µmol/L, P = 0.002) and significantly lower enzymatic and non-enzymatic antioxidant capacities (CAT: 22.41 ± 5.26 vs 30.85 ± 6.12 U/mL, P = 0.001; GSH: 4.32 ± 0.97 vs 6.15 ± 1.10 µmol/L, P = 0.003) in stone patients compared with controls. Other acute phase reactants were also elevated among the abnormal group (CRP, SAA =ceruloplasmin; all P < 0.05). In line with this, correlation analysis showed moderate positive associations of MDA with APPs (e.g., MDA versus ceruloplasmin r = 0.58, Table 4) and inverse associations of antioxidant markers with APPs (e.g., GSH versus ceruloplasmin r = −0.52), consistent with an interdependent relationship between oxidative injury and systemic inflammation in urolithiasis.

Mechanistically, our results, therefore, support the emerging concept that ROS and mitochondrial dysfunction lead to direct renal tubular damage and crystal retention which represent early events in stone disease. Renal tubular epithelial cells exposed to oxalate and calcium oxalate crystals stimulate reactive oxygen species (ROS) production, lipid peroxidation and apoptotic signaling cascade; these processes promote crystal adhesion, secretion of proinflammatory mediators, and formation of nidus like Randall s plaques. In summary, the elevation of MDA that we observed in our patients is therefore biologically plausible, and consistent with experimental and clinical literature demonstrating overexpression of lipid peroxidation products in stone disease (Wigner et al., 2021; Liu et al., 2025).

Here, the reciprocal pattern—that is, higher APPs are correlating with lower antioxidant activity—also reflects well-described pleiotropy between inflammation and oxidative stress. Cytokines (e.g., IL-6, TNF-α) released following epithelial injury, upregulate the acute phase reactants (APPs) CRP and SAA, which in addition to being markers of systemic inflammation secondary to renal injury, further propagate oxidative signaling (Lasota et al., 2023). The relative positive correlations we found between MDA and CRP/SAA/ceruloplasmin ($r \approx 0.42–0.58$) and concurrent negative correlations of CAT and GSH with the same APPs ($r \approx -0.36$ to -0.52) suggest a feed-forward cycle: oxidative damage enhances inflammation, and inflammatory signaling diminishes antioxidant defenses, together driving both tissue injury and the environment permissive for stone formation.

These findings are consistent with previous studies in patients that have shown increased evidence of lipid peroxidation and decrease of catalase or glutathione in stone formers (Rostampour et al., 2017), and complemented those findings by including direct measures of oxyand oxidative state and linking responses directly to systemic APPs and across multiple ACTs. In agreement with the above mechanistic reports, these concordant clinical observations suggest that mitochondrial perturbations disrupt redox homeostasis and increase ROS production in models of hyperoxaluria and CaOx exposure and therefore provide a potential cellular source for the systemic oxidative signals we measured (Chaiyarit & Thongboonkerd, 2020).

The clinical implications are twofold. Identification of potential extended targets for SGLT2 therapy and endocrine modulation could shift future trials of SGLT2 inhibition for prevention of progression from diabetes to CKD to early stages of insulin resistance and metabolic syndrome (Stielow et al.,2025). Second, our data lend support for therapeutic strategies designed to reestablish redox homeostasis; many of the preclinical treatments that promote the level of antioxidant defenses (eg, metformin and other compounds that decrease oxidative stress in animal models of nephrolithiasis) have been shown to yield increases in stone burden and may be a unifying proposal for clinical translation to diminish recurrence (Yang et al., 2016).

However, there are a few limitations that should be noted. The cross-sectional design does not allow us to infer causality: increased MDA and APPs may result from stone passage, obstruction or secondary infection rather than mediating stone formation. While we adjusted for the usual confounders and demonstrated demographic matching (age and sex NS), residual confounding such as diet, fluid intake, stone composition or recent analgesic/anti-antibiotic exposure cannot be excluded. Additionally, urinary markers of tubular injury or other cytokines (e.g., IL-6) were not measured in our biochemical panel and would further strengthen the mechanistic chain linking local renal injury to systemic APP elevations. Finally, whilst a number of recent reviews and studies lend support to the role of oxidative–inflammatory interactions in nephrolithiasis, larger prospective cohorts are required to determine whether such biomarkers can predict recurrence or are responsive to antioxidant/inflammatory-targeted therapies (Wigner et al., 2021; Lasota et al., 2023).

Conclusion

The current study illustrates a reproducible pattern of elevated lipid peroxidation, lowered antioxidant ability, and elevated acute phase proteins in kidney stone patients, and strong correlations between these domains. These data bolster the notion of interconnectedness of oxidative stress and systemic inflammation in nephrolithiasis and further justify continued investigation of biomarkers and treatments directed against the oxidative-inflammatory axis as integral components of holistic stone prevention efforts.

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