Investigating Myo-Inositol Oxygenase and Renal Biomarkers in Acute Kidney Injury

Abdullah Abdulsattar Raeef[1], Abdulla A. Al-dulaimi[2] and Bilal A. Dylan[3]
[1]*Department of Medical Laboratories Techniques, College of Health and Medical Technology, University of Al Maarif, 31023 Al Anbar, Iraq*
[2]*College of Nursing, University of Al Maarif, 31023 Al Anbar, Iraq*
[3]*College of Pharmacy, University of Anbar, 31001 Ramadi, Anbar, Iraq*
abdullah.abdulsatta@uoa.edu.iq, abdullah.ahmed@uoa.edu.iq, ph.bilalaldyla@uoanbar.edu.iq, abdullah.abdulsatta@uoa.edu.iq

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Abstract: Acute kidney injury (AKI) refers to an abrupt renal damage episode or failure, which can occur within a few hours or days. Myo-inositol oxygenase (MIOX) is an enzyme involved in the breakdown of myo-inositol. MIOX catalyzes the oxidation of myo-inositol to form D-glucuronate, an important step in the metabolism of myo-inositol. Research has suggested potential links between MIOX and kidney function. The objective of this study to show the role of MIOX on kidney diseases. Methods: Case-control study was conducted in Anbar Dialysis Center. 50 participants suffering from AKI and the other group of 50 participants of healthy participants. Demographic information for both groups was obtained (age, Body Mass Index "BMI", duration of disease), in addition to laboratory tests (urea, creatinine, uric acid, calcium, and MIOX). Groups were compared using the t-test and descriptive analysis. Pearson's correlation coefficient was used to find the relationship between different variables. Results: In this case-control study Urea, creatinine, and uric acid have higher concentrations and are statistically significant in acute kidney injury cases than in healthy controls. In addition to a decrease in the concentration of calcium and MIOX with high significant differences between the two groups. Conclusion: Acute kidney injury is associated with an elevation in urea, creatinine, and uric acid and a decrease in calcium and MIOX. Studies have shown that MIOX expression levels are up-regulated in response to renal injury, suggesting a role for this enzyme in the pathogenesis of AKI.

1 INTRODUCTION

Acute kidney injury (AKI) is when kidneys suddenly stop working properly. It can range from minor loss of kidney function to complete kidney failure. AKI normally happens as a complication of another serious illness [1]. MIOX is a renal-specific, proximal tubule protein that is increased in the plasma of animals and critically ill patients with AKI. MIOX preceded the elevation in Serum creatinine by approximately two days in human patients [2]. Myo-inositol oxygenase (MIOX) is an enzyme that plays a critical role in inositol metabolism by catalyzing the oxidative cleavage of myo-inositol to glucuronic acid. While the understanding of inositol and its metabolic pathways has advanced in recent years, the specific involvement of inositol oxygenase in Acute Kidney Injury (AKI) is an emerging area of research [3]. Recent studies have indicated that alterations in inositol metabolism, particularly changes in the activity of inositol oxygenase, may contribute to the pathogenesis of AKI. Dysregulation of inositol metabolism has been implicated in oxidative stress and inflammatory responses, both of which are key contributors to the development and progression of AKI [4].

In this study, we investigated the role of MIOX enzyme in the diagnosis of AKI as an early biomarker as compared with diagnostic parameters such as urea, creatinine, uric acid, and calcium.

2 METHODS

2.1 Study Design

This study was prepared during the period from November 2023 to February 2024. 100 people participated in it. They are split into two groups. The first group consisted of 50 patients with Acute Kidney Injury, (male and female) to evaluate levels of Urea, Creatinine, Calcium, Uric acid, and Myo-Inositol Oxygenase. Inclusion criteria included patients with abdominal pain or typical symptoms suggestive of Acute Kidney Injury who presented to the Dialysis Center, Anbar Health Department Depending on the diagnosis, the diagnosis was based on clinical presentation and history of AKI, which was confirmed by Ultrasound, CT-Scan, and Lab tests. The exclusion criteria were patients with liver diseases, renal transplant, and pregnant women. The second group included 50 controls (male, female), Healthy people without any disease, and was parameters were measured like the previous group (cases). The age period for the case study was 30-70 years and for the control group was 26-65 years. This study received ethical approval from the University of Anbar, Ethical Approval Committee, (Project No. 06) on 06/07/2024.

2.2 Procedure

A venous blood sample was collected in position from the anticubital vein of each case and control subject. Four milliliters of blood samples from patients (cases) and control. The blood samples were collected in a gel tube and left for 20 minutes at room temperature. After coagulation, sera were separated by centrifugation at 2000 xg for 10 min and divided into small aliquots. Immediate measurements of Creatinine, Uric acid, Calcium, and urea, were done using appropriate enzymatic and colorimetric methods. The rest of the sera was stored at -20 ˚C until assayed for serum Myo-Inositol Oxygenase it was measured using enzyme-linked immunosorbent assay (ELISA) kits by ELK Biotechnology kit (Lot No. 46661314).

2.3 Statistical Analysis

The statistical analysis was done by Statistical Package for the Social Sciences (SPSS) and used a descriptive model to show the results of demographic information. In addition, a paired t-test was conducted to find significant differences between the variables of the study groups. Also, person correlation to find the relation between study parameters. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were used to assess the specificity and sensitivity of the study parameters.

3 RESULTS

A total sample size of 100 was collected, out of which 50 were cases and 50 were controls, and the data obtained was subjected to statistical analysis. The results are presented under the headings of various parameters considered for this study.

Table 1 and Figures 1 and 2 show demographic information for the sample study for case and control groups. To find the comparison between Age and BMI, a paired t-test and found Mean± SD with a range of values. The significant differences between groups were determined with confidence interval (CI) (99.9) and probability (less than 0.01). The results showed the mean ± SD of age for cases was 51.9 ± 11.8 years with a range (30-70) years while the mean ± SD for the control group was 44.1±11.8 years and the range was (26-65) years with high significant differences between the groups of the study and a p-value (0.002). Also, the results of BMI showed that the control group had a high mean± SD value of 25.5± 3.96 with a range (17.7-35.1) while the case group had a BMI mean± SD 24.1± 3.64 and the range was (18.6-34.5) with p= (0.049).

The distribution of sex and duration of disease for the study samples (cases and controls) groups was analyzed by using frequency analysis. The result of sex showed the male participant was 24 samples with a percentage (48%) for patients and 29 samples with percent (52%) for the control group. In addition, the female participants for patients was 26 samples with percent (52%), and for the control 21 samples with percent (42%).

Duration of disease is very important to be noted and studied because it determines whether the disease is in the acute stage or chronic stage. The study was designed to take the duration of the disease by weeks. Table 1 showed that 17 samples of the study samples had a duration of disease with a range from 1 to 4 weeks, also 8 participants had a duration of disease from 5 to 8 weeks. 18 samples had a duration of disease from 9 to 12 weeks and at last 7 participants had more than 12 weeks of disease duration.

Table 1: The sociodemographic information (age, sex, BMI and duration of disease for the sample study.

Characteristics		Cases	Controls	P-value
Age (Years)	Mean ± SD	44.1 ± 11.8	51.9 ± 11.8	0.002
	Range	30 - 70	26 - 65	
Sex [n(%)]	Male	24 (48%)	29 (58%)	0.390 NS
	Female	26 (52%)	21 (42%)	0.390 NS
	Total sample size	50 (100%)	50 (100%)	
BMI (Kg/m2)	Mean ± SD	24.1 ± 3.64	25.5 ± 3.96	0.049
	Range	18.6 – 34.5	17.7 – 35.1	
Duration of disease (weeks) [n(%)]	1-4	17 (34%)	0	
	5-8	8 (8%)	0	
	9-12	18 (36%)	0	
	More than 12	7 (14%)	0	
Statistically significant if P<0.01; *P values from unpaired t-test (Age, BMI). *P value from Z test for two proportions (sex) Duration of disease (AKI) for cases without a control group.				

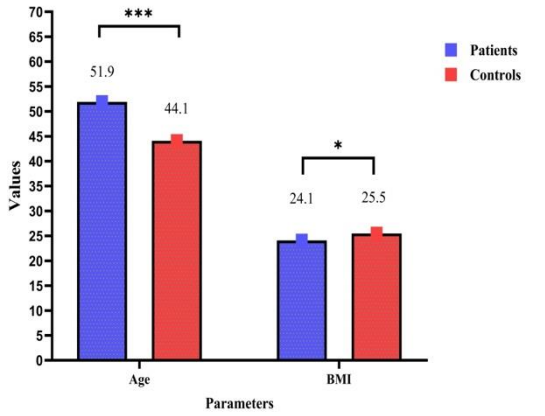

Figure 1: The mean and p-value of age and BMI for study samples.

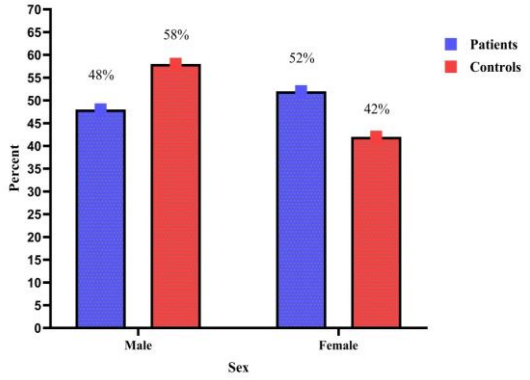

Figure 2: The distribution of Sex for study samples.

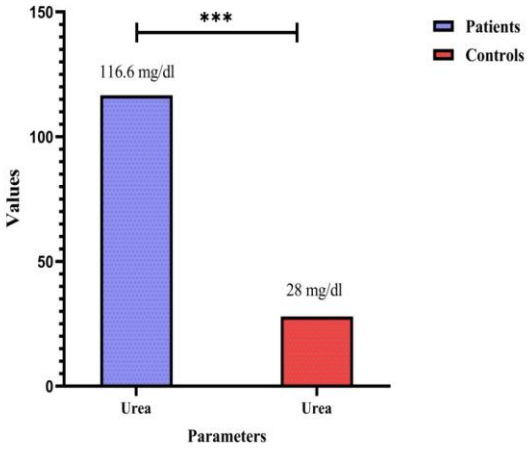

Figure 3: The mean and p-value of Blood Urea for study samples.

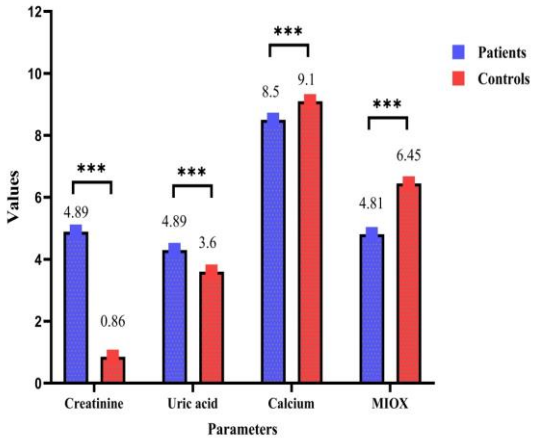

Figure 4: The mean and p-value of serum Creatinine, Uric acid, Calcium, and MIOX for study samples.

Table 2: The Mean ± SD, range, and differences of study parameters among study groups.

Characteristics		Case	Control	P-value
Urea (mg/dl)	Mean ± SD	116.6 ± 45.9	28.0 ± 5.3	0.0001
	Range	62.00 - 241.00	19.00 - 37.00	
Creatinine (mg/dl)	Mean ± SD	4.89 ± 2.2	0.85 ± 0.21	0.0001
	Range	2.0 – 10.6	0.50 – 1.20	
Uric acid (mg/dl)	Mean ± SD	4.3 ± 1.2	3.6 ± 0.43	0.001
	Range	2.9 – 7.8	3.0 – 4.7	
Calcium (mg/dl)	Mean ± SD	8.5 ± 0.53	9.1 ± 0.71	0.0001
	Range	7.9 – 10.0	8.0 – 11.0	
MIOX (ng/ml)	Mean ± SD	4.81 ± 1.7	6.45 ± 1.3	0.0001
	Range	2.0 – 7.5	4.1 - 9.2	
Statistically significant if P<0.05; *P values from unpaired t-test (Urea, creatinine, uric acid, calcium, MIOX).				

Table 2 in addition to Figures 3 and 4 shows the mean, standard deviation (SD), and range with Asymptotic significant differences for Urea, Creatinine, Uric acid, Calcium, and Myo-Inositol oxygenase (MIOX) for cases and control group.

The result appears that urea concentration was higher in cases than controls with mean±SD (116.6±45.9) and the range of value was (62-241 mg/dl) while the control group had mean±SD (28±5.3) and range (19.0-37.0 mg/dl) with high significant differences and p = (0.0001). Serum creatinine is considered an indicator of kidney diseases and is used as a diagnosis parameter for acute and chronic kidney injury [5]. The result in Table 2 showed the mean±SD for cases was (4.89±2.2) and range (2.0-10.6 mg/dl) while the mean±SD for the control group was (0.85±0.21) and the range was (0.5-1.2 mg/dl) with significant differences and p = (0.0001)

The metabolism and excretion of uric acid were done inside the kidney. Uric acid is a waste product that's from purine breakdown, so when the kidney has an injury it leads to decreased excretion of uric acid and concentration elevated in blood circulation [6]. The result of a recent study showed that the mean±SD concentration of uric acid for patients was (4.3±1.2) with range (2.9-7.8 mg/dl), while the mean±SD concentration for the control group was (3.6±0.43) and the range was (3.0-4.7 mg/dl) with significant differences and p = (0.001).

Most percent of total calcium in the human body is reabsorbed by kidney tubules. Kidney injury or any disease that affects on kidney leads to decreased reabsorption of calcium to blood and decreased concentration in the body [7]. The study result showed that the mean±SD concentration of calcium decreased in cases (8.5±0.53) and the range was (7.9-10.0 mg/dl) while the mean±SD concentration in the control group was (9.1±0.71) and the range was (8.0-11.0 mg/dl) with high significant differences and p = (0.0001).

Myo-inositol oxygenase (MIOX) is mainly expressed in the kidneys. There is little information available on the function of the MIOX enzyme in the diagnosis of AKI, even though it is one of the rare organ-specific enzymes, specifically a renal-specific enzyme [2]. The study results showed that the mean±SD of MIOX for patients was less than the cases group (4.81±1.7) with range (2.0-7.5 ng/ml) while the mean±SD concentration for control groups was (6.45±1.3) and the range was (4.1-9.2 ng/ml) with high significant differences between the study groups and the p = (0.0001).

The study results showed a high correlation between blood urea and serum creatinine with r = 0.466 and p = (0.0001). In addition, the uric acid concentration relation has an inverse correlation with age which means the concentration decreases with age increase with r= -0.421 and p = (0.001). The explanation for this result is that kidney function decreases when age increases same thing with all body organs. The study found also a high correlation between uric acid and urea for AKI patients with r = 0.492 and a p = (0.0001). On the other side, the result showed a high correlation between uric acid and creatinine with r=0.618 and p = (0.0001). Myo-inositol oxygenase (MIOX) concentration showed a correlation with creatinine and uric acid with r = 0.256, 0.302, and p = (0.037 and 0.017) respectively. The results of the correlation are clarified in Table 3.

Table 3: Spearman's ρ correlation coefficient between AKI clinical parameters, biochemical parameters, and MIOX.

Parameters Patients	Pearson r	P-Value
Urea - Creatinine	0.466**	0.0001
Uric acid - Age	- 0.421**	0.001
Uric acid - Urea	0.492**	0.0001
Uric acid - Creatinine	0.618**	0.0001
MIOX - Creatinine	0.256*	0.037
MIOX – Uric acid	0.302*	0.017
**Correlation is significant at the 0.01 level (1-tailed). * Correlation is significant at the 0.05 level (1-tailed). NS: Non-significant		

Table 4: Receive Operator Curve analysis for study parameters to diagnose AKI.

Parameter	Area-under curve	Specificity	Sensitivity	Cut-off value	Sig.
MIOX	0.738	78%	58%	6.41	0.0001
Urea	1.0	100%	100%	49.5	0.0001
Creatinine	1.0	100%	100%	1.6	0.0001
Uric acid	0.666	98%	38%	4.25	0.0001
Calcium	0.188	100%	0 %	12.0	0.004

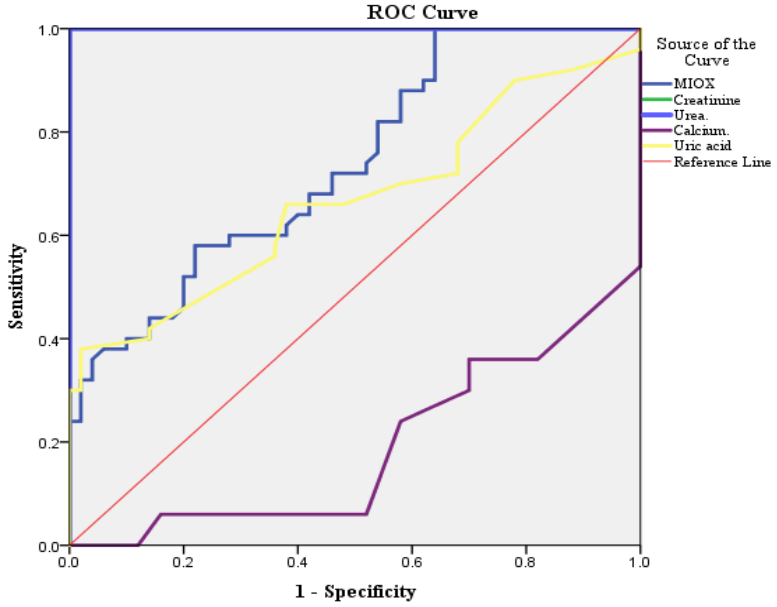

Figure 5: The ROC curve, specificity and sensitivity for Urea, Creatinine, uric acid, MIOX, and calcium among study groups.

The receiver operating characteristic (ROC) curves were generated for MIOX and other parameters to give an initial assessment of critical values for a diagnosis of AKI. As shown in Table 4 and Figure 5, the area under the curve (AUC) was calculated as 0.738 for MIOX with a cut-off value (6.41) and significant differences with p = (0.0001). Other parameters showed highly significant differences for AUC with different Specificity and sensitivity. The cut-off value indicates that the value is considered as critical value for acute kidney injury disease.

4 DISCUSSION

Our study showed that progress in age leads to an increased probability of acute kidney injury. Acute

kidney injury (AKI) is becoming more common in people of all ages, but older patients (those over 65) are more vulnerable to developing AKI because of the age-related kidney damage that affects their structure and function, their decreased renal reserve, the presence of comorbidities, and their diminished capacity to recover [8]. This study corresponds with our study.

There are multiple possible processes explaining the correlation between a high body mass index and the development of AKI. Initially, obesity leads to certain hemodynamic alterations in the glomerulus, including glomerular hyper perfusion and hyper filtration because of compromised natriuretic-related renin and angiotensin system activation [9]. Second, obesity can lead to a decrease in the number of functional nephrons in obese patients by increasing the hemodynamic and metabolic load on each glomerulus [10]. Third, in obese patients, adipocytes may serve as a location of production for oxidative stress and activated inflammatory cytokines [11].

Paller et al showed that the duration of ischemia for 60 minutes was sufficient for ischemia-reperfusion injury to occur. Serum BUN and creatinine levels indicated adequate renal damage because they were higher in all ischemia-reperfusion groups as compared to the control group [12]. This study agrees with our study results.

The concept that uric acid, an ancient biological component, may be causing inflammatory pathways that exacerbate acute kidney damage has led to the resuscitation of uric acid as a possible mediator of acute kidney injury (AKI) [13]. Mild hyperuricemia has since been shown to have pro-inflammatory and anti-angiogenic properties [14]. Renin-angiotensin system activation, increased reactive oxygen radicals, inflammatory mediators (MCP-1, ICAM), vascular responsiveness, and vascular smooth muscle proliferation and migration are all brought on by uric acid [15]. There is a study that proves mounting evidence that uric acid is a potential causative agent in AKI. Uric acid may increase the risk for AKI via both systemic effects of hyperuricemia and local effects due to crystalline and non-crystalline effects of urinary uric acid on tubules [16]. A linear correlation has been observed recently between the development of dialysis-dependent AKI during hospitalization and blood uric acid levels [17]. All previous studies correspond with our study that was conducted on AKI patients and appears that uric acid as a waste product increases in AKI patients.

The findings of a study conducted by Thongprayoon, C. et al. showed a significant correlation between the risk of AKI in the hospital and the blood calcium level of cases admitted into the hospital. Additionally, it has been suggested that abnormality in calcium levels has an impact on vascular tone, especially renal arteries [18]. This study agrees with the results obtained in our study. Prior research has indicated the risk of AKI in patients with different serum calcium levels [19], [20]. Low serum ionized calcium might be related to the severity of the illness or sepsis [21], [22]. The illness-related release of inflammatory cytokines reduces the parathyroid gland's ability to secrete parathyroid hormone (PTH) and increases end-organ resistance to PTH [23]. Furthermore, calcitriol production is also suppressed during this severe illness [24].

Myo-inositol oxygenase is a novel biomarker that may be used as an indicator for AKI. Our study found that MIOX is decreased in patients and this study agrees with the previous study [25], [26]. The study done by Cuma Mertoglu, et al. found MIOX values were significantly higher in the AKI group compared to the control group with a P = (0.0016) [25]. This study was conducted with our result. Gaut et al. demonstrated that MIOX is a renal-specific proximal tubule protein using the Western blot approach. In the present investigation, we also found that the MIOX levels in the AKI group were considerably higher. Furthermore, for AKI, MIOX's diagnostic sensitivity and specificity were 53.8% and 81.5%, respectively. Naturally, this outcome is crucial for using MIOX in AKI diagnosis. Nonetheless, as MIOX is an enzyme found in the proximal kidney tubules, MIOX elevations may result from any type of tubular injury [2]. Previous studies agree with this study's results. Another recent study by Tominaga, T. et al. has shown that overexpression of MIOX is responsible for the overproduction of reactive oxygen species (ROS), which contributes to tubulointerstitial injury in obesity [27]. Moreover, in a new study, MIOX overexpression increased renal injury in diabetic nephropathy due to oxidative stress, increased ROS, and led to the disruption of antioxidant systems [28]. Moreover, MIOX expression has been reported to be low in extra-renal organs with diabetic complications such as neuropathy, retinopathy, and cataracts [29]. The study of (Tom Jose Kakkanattu, et.al,) found that serum MIOX levels and Urine Protein Creatinine Ratio (UPCR) upon hospital discharge may be utilized alone or in combination with other variables, such as serum creatinine, as a predictive biomarker for renal recovery from community-acquired AKI [26].

4 CONCLUSIONS

This study highlights the clinical significance of Myo-Inositol Oxygenase (MIOX) as a potential biomarker for acute kidney injury (AKI), alongside traditional renal function indicators such as urea, creatinine, uric acid, and calcium. The findings clearly demonstrate that patients with AKI exhibit significantly elevated levels of urea, creatinine, and uric acid, and significantly decreased levels of calcium and MIOX compared to healthy individuals. These patterns affirm the role of oxidative stress and impaired renal filtration in AKI pathogenesis. The decline in MIOX concentration among AKI patients is particularly noteworthy, considering MIOX is a kidney-specific enzyme expressed in proximal tubules. Although earlier studies indicated MIOX overexpression in renal stress models, our findings align with clinical observations where severe or sustained AKI may lead to tubular injury and enzyme depletion or impaired release. The ROC analysis confirms the diagnostic utility of MIOX, showing moderate sensitivity and good specificity, indicating its value in supporting early detection strategies for AKI when combined with traditional markers.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study received ethical approval from the University of Anbar, Ethical Approval Committee, (Project No. 06) on 06/07/2024.

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