Original Article

Impact of Activity of Xanthine Oxidase on Some Biomarkers in Patients with Kidney Stones in Iraqi Patients

Ali Abdul Rasool[1], Mawj Abdel Razzak Ahmed[2]

[1]Department of Chemistry and Biochemistry, College of Medicine, Mustansyriah University, Baghdad, [2]Department of Baghdad Health, Karkh, Ministry of Health, Baghdad, Iraq

Abstract

Objective: Kidney stones are crystalline concrete that often develops inside the kidneys. Urinary tract problems are getting worse and worse for human health. The risk of end-stage kidney failure has been associated with increase the level of a new biomarker (like xanthine oxidase) to assess severity of kidney injury. **Methods:** The eighty patients, who attended the government clinics in Yarmouk Teaching Hospital, and the forty healthy people were used as a control group. Colorimetric assays were used to assess serum xanthine oxidase (XO) and other biochemical parameters. Using an enzyme-linked immunosorbent assay was determined. **Results:** The mean serum XO activity (8.8525 IU/L) was significantly greater than the corresponding values for the controls (6.5825 IU/L). Patients with kidney stones showed abnormal activity of uric acid levels in 78.33% of cases, while XO activity showed highly sensitive (70%) and high specificity (79%). XO has been found to be an excellent biomarker for detecting damage of the kidney in people suffering from kidney stones.

Keywords: Kidney stones, kidney injury, xanthine oxidase

Introduction

A kidney stone is a microscopic piece of debris that has originated inside the kidney where urine accumulates. Its other names include kidney stones and, more generally, urinary tract stones. Kidney stones are crystalline aggregates of minerals that have undissolved in urine and solidified into a mass.[1,2] The range size of stone in the kidney is from a few millimeters to a few centimeters. Many stones form and pass through the body unnoticed, usually through the urethra.[3]

These particles are often calcium crystals. The blockage prevents urine from leaving the kidney, often causing severe discomfort. Before the stones pass through the ureter, the tube that empties the kidneys into the bladder, they often cause other problems. Stones usually consist of mineral salts and acids. In general, stones are formed by increased urine concentrates, allowing minerals to solidify and stick together.[4]

The large stone (>3 mm in diameter) may lead to urinary tract obstruction. This obstruction is associated with muscle spasms and causes the upper ureter and renal pelvis to grow or dilate. The pain in flank and lower abdomen are increasing when the stone passage, which can lead to severe seizures.[3] Kidney stones come in diverse forms worldwide based on geography and genetic predisposition.[3] The prevalence and frequency of kidney stones are increasing worldwide. Many factors, such as age, gender, level of obesity, and general health, were considered.[3]

The pathophysiology of kidney stones and the contributory factors to the pathogenesis are still poorly understood. Besides variables including hygiene, water quality, and the patient's primary metabolic disease, food consumption may also contribute to gallstone production.[3] A disease caused by stones is accompanied by severe stomach discomfort because the movement of stones causes mechanical irritation of urinary tissues. The degree of patient experience is often closely related to the size and roughness of the stone, and

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_27_23

Address for correspondence: Asst. Lect. Ali Abdul Rasool, Department of Chemistry and Biochemistry, College of Medicine, Mustansyriah University, Baghdad, Iraq.
E-mail: ali_abd54144@yahoo.com

Submitted: 23-Apr-2023 **Revised:** 19-May-2023 **Accepted:** 22-May-2023 **Published:** 07-Aug-2023

How to cite this article: Rasool AA, Ahmed MA. Impact of activity of xanthine oxidase on some biomarkers in patients with kidney stones in Iraqi Patients. Mustansiriya Med J 2023;22:138-43.

specifications vary from patient to patient. Urinary tract stones are unique to each patient and have variable chemical compositions. Stone creations include both biological and inorganic materials. According to their composition, kidney stones can be divided into five groups: calcium oxalate (70%), calcium phosphate (5%–10%), uric acid (10%), struvite (15%–20%), and cysteine (1%).[5-7] Singh and Ray provided a good description of the classification of stones into limestone and nonlimestone as well as their qualities. One form of crystal acts as a nucleus for heterogeneous crystallization in many stones due to its mixed composition.

Aim of study to determine relation shipe between serum xanthine oxidase (XO) activity and kidney stones , also to assess the feasibility of a novel biomarker (xanthine oxidase (XO) activity) for evaluation the kidney damage stage.

Methods

Eighty patients were diagnosed with kidney stones (untreated males and females), aged 30 years and over. The blood samples were collected at Yarmouk Teaching Hospital in Baghdad, Iraq. The work was performed from August 2, 2021, to October 28, 2022. All patients were diagnosed by specialized doctors (nephrologists) and the other group consisted of 40 healthy people of women and men, all subjects aged 30 years and over.

Exclusion criteria

The current study excluded participants with serious illnesses such as heart disease, diabetic nephropathy, alcohol abuse history, type 2 diabetes, use of potent antioxidants, and pregnant women.

Inclusion criteria

Only kidney stone patients who volunteered to participate in the study and were admitted to the Urology Department of Al-Yarmouk Teaching Hospital and the Outpatient Department were included. Evaluation of kidney stone patients, usual physical examination, and biochemicals test like (blood urea, creatinine, uric acid, cortisol, ferritin, zinc, and cholesterol).

Methods and principles

Determination of xanthine oxidase activity

XO activity is determined by an enzyme assay. One unit of XO is defined as the amount of enzyme that catalyzes xanthine oxidation, resulting in 1.0 mmol of uric acid and hydrogen peroxide per minute at 25°C. Using an ultra-violet-visible spectrophotometer device for determination of xanthine oxidase activity (MODEL CECIL 7200) from UK (Heinz, 1979).[8]

Determination of uric acid (urate) level

The Biomaghreb kit was used to determine serum uric acid by enzymatic assay. The principal outlined the process of uric acid oxidation leading to the creation of hydrogen peroxide and allantoin. With peroxidase present, hydrogen peroxide reacts with chromogen to form quinonimine, a complex that is red. At 520 nm, the absorbance was measured (Tietz, 1999).[9]

Determination of urea level

The Randox kit was used to conduct a colorimetric assay. In this principle, urea is converted into ammonia and water, and then, in the presence of hypochlorite and salicylate, a green complex is created (Tiffany, 1972).[10]

Determination of creatinine level

This approach is based on an adjusted version of the primary picrate reaction.[1] It is known that creatinine forms a reddish complex when it reacts with picrate ions under alkaline conditions. By measuring the increase in absorbance in a predetermined period, the complex formation rate is proportional to creatinine concentration (Bartels, 1971).[11]

Determination of cholesterol concentration

Cholesterol oxidase acts on free cholesterol in the cholesterol assay protocol. Cholesterol esterase is used to break down the cholesterol ester into free cholesterol. Subtract free cholesterol from total cholesterol will give the amount of cholesterol ester (Yu *et al*., 2018).[12]

Determination of zinc level

Zinc present in the sample is chelated by nitro-PAPS in the reagent. The formation of this complex is measured at a wavelength of 570 nm (Saito, 1982).[13]

Determination of calcium level

In an alkaline medium, a purple complex is formed when calcium is combined with o-cresolphthalein complexone. The color-formed intensity is straightly proportional to the quantity of calcium content in the sample (Ray Sarkar, 1967).[14]

Determination of cortisol level

Enzyme immunoassay use for the quantitative measurement of active free cortisol in human serum. Based on the principle of competitive binding, the cortisol enzyme-linked immunosorbent assay (ELISA) kit is a solid-phase ELISA. The concentration of cortisol in the sample has an inverse relationship with the intensity of the color produced. The absorbance is measured at 450 nm with a microtiter plate reader (Fleiner, 2015, and De Steenwinkel, 2014).[15,16]

Determination of ferritin level

The principle of the ferritin ELISA assay kit enzyme immunoassay test follows a typical one-step capture or "sandwich" type assay. The assay makes the use of two highly specific monoclonal antibodies (Bailey, 2021).[17]

Statistical analysis

The statistical program (SPSS version 24) (USA) was applied for the analysis of the data. Entire groups exhibited a normal distribution, and the mean ± standard deviation (SD) was used in the selections. Statistical t-test significance relathon ship betwen patients and controls was defined as $P < 0.05$, also measurement the correlation between the parameters in patients' samples, also we use the measuer sensitvity and

Table 1: The relationship between biochemical analysis between patients and controls

	n	Mean±SD	*P*
Zinc			
Patients	80	38.78±8.807	0.001
Controls	40	97.20±13.803	
Calcium			
Patients	80	9.0983±0.56279	0.001
Controls	40	2.2648±1.11720	
Cholesterol			
Patients	80	282.40±66.975	0.001
Controls	40	170.88±74.367	
Ferritin			
Patients	80	633.16±187.373	0.001
Controls	40	180.60±143.474	
Creatinine			
Patients	80	6.7245±3.69399	0.001
Controls	40	3.8940±2.40532	
Uric acid			
Patients	80	6.1650±2.42199	0.001
Controls	40	5.7758±1.96738	
Urea			
Patients	80	42.88±11.380	0.001
Controls	40	32.30±13.654	
Cortisol			
Patients	80	14.0520±6.71222	0.001
Controls	40	2.0089±1.37546	
XO			
Patients	80	8.8525±4.58730	0.001
Controls	40	6.5825±2.66938	

XO: Xanthine oxidase, SD: Standard deviation

specificity of XO to diagnose the kidney stone patients by the receiver operating characteristic (ROC) curve.

Results

Table 1 shows that the level of zinc in the serum of healthy controls was higher than in the serum of patients with kidney stones, while the levels of serum calcium, uric acid, cortisol, cholesterol, ferritin, creatinine, and XO were higher in the patients with kidney stone than in the serum of healthy controls.

The level of blood urea was significantly positively correlated with the level of serum creatinine. In addition, the level of cortisol was positive significantly with both the level of blood urea and the level of serum calcium. Moreover, the activity of XO also appeared strongly positive significantly with the level of creatinine [Table 2].

In Table 3, shown the significance positive correlation between calcium and cortisol also between cortisol and ferritin as well as a positive significance between creatinine with urea and also strong positive significance with XO while the uric acid was a strong positive significant between and XO, urea and uric acid.

The activity of XO was more sensitivity and specificity than ferritin when distinguished between two groups (patients with kidney stones and healthy controls), as shown in Figure 1 and Table 4.

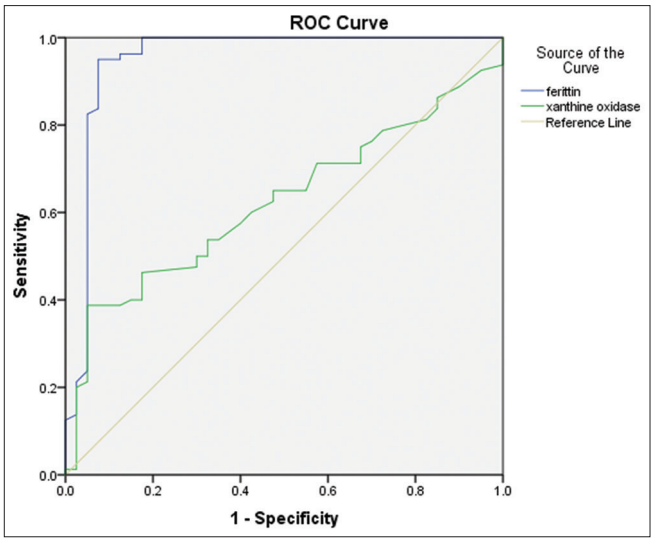

Figure 1: The ROC curve betweenpatients and controls for the activity of XO and ferritin, ROC: Receiver operating characteristic, XO: Xanthine oxidase, AUC: Area under the curve

Discussion

More than half of the urology patients in the clinic have stones. It is still unclear how kidney stones can grow to a clinically significant size and how they originate in the system. It may be a very long period of clinical silence for stones. However, if stones become larger than the urinary system so during normally eliminate may lead to infection, obstruction, irreversible kidney damage, and eventual kidney loss.[18] When comparing patients to controls, the amount of uric acid in the blood was significantly increased [Table 1]. Several studies have shown how uric acid affects kidney cells and hyperuricemia. First, endothelial dysfunction and inflammation are caused by hyperuricemia.[19]

In addition, mesangial cells can create reactive oxygen species and contract[20,21] when exposed to uric acid. We know no other case of kidney stone patients displaying increased ecto-5'-nucleotidase and XO activity. An alternative reported that mesangial cells and glomeruli both express ecto-5'-nucleotidase, which helps in adenosine production. It is minimally stained by ecto-5'-nucleotidase in the cortical pars recta of the proximal tubule, but it is strongly stained in the medullary pars recta. It is prominent to see ecto-5'-nucleotidase staining in the first loops of the proximal contorted tubules of the luminal brush boundary membrane.[21]

Based on Table 1, calcium levels are higher in patients with kidney stones than in healthy controls, for the reason that the kidney has to filter out calcium all the time due to hyperparathyroidism. A kidney stone is caused by the presence of too much calcium in the urine and kidney; a protein called

Table 2: Correlation between biochemical analysis in patient group

	Zinc	Calcium	Cholesterol	Ferritin	Creatinine
Zinc					
r	1	0.058	−0.058	0.012	−0.010
P		0.610	0.611	0.914	0.933
n	80	80	80	80	80
Calcium					
r	0.058	1	0.093	−0.150	−0.158
P	0.610		0.411	0.185	0.160
n	80	80	80	80	80
Cholesterol					
r	−0.058	0.093	1	−0.107	0.069
P	0.611	0.411		0.343	0.545
n	80	80	80	80	80
Ferritin					
r	0.012	−0.150	−0.107	1	0.066
P	0.914	0.185	0.343		0.561
n	80	80	80	80	80
Creatinine					
r	−0.010	−0.158	0.069	0.066	1
P	0.933	0.160	0.545	0.561	
n	80	80	80	80	80
Uric acid					
r	0.080	0.060	−0.104	0.079	0.107
P	0.478	0.596	0.361	0.486	0.344
n	80	80	80	80	80
Urea					
r	0.059	−0.040	0.213	0.090	0.237*
P	0.603	0.725	0.058	0.429	0.034
n	80	80	80	80	80
Cortisol					
r	0.170	0.244*	−0.048	0.230*	0.059
P	0.133	0.029	0.670	0.040	0.603
n	80	80	80	80	80
XO					
r	−0.022	−0.170	−0.100	0.181	0.307**
P	0.847	0.133	0.376	0.109	0.006
n	80	80	80	80	80

**P* less than 0.05; ***P* less than 0.05. XO: Xanthine oxidase

Table 3: Correlation between biochemical markers with other chemical analyses

	Uric acid	Urea	Cortisol	XO
Zinc				
r	0.080	0.059	0.170	−0.022
P	0.478	0.603	0.133	0.847
n	80	80	80	80
Calcium				
r	0.060	−0.040	0.244*	−0.170
P	0.596	0.725	0.029	0.133
n	80	80	80	80
Cholesterol				
r	−0.104	0.213	−0.048	−0.100
P	0.361	0.058	0.670	0.376
n	80	80	80	80
Ferritin				
r	0.079	0.090	0.230*	0.181
P	0.486	0.429	0.040	0.109
n	80	80	80	80
Creatinine				
r	0.107	0.237*	0.059	0.307**
P	0.344	0.034	0.603	0.006
n	80	80	80	80
Uric acid				
r	1	0.414**	0.124	0.398**
P		0.000	0.274	0.000
n	80	80	80	80
Urea				
r	0.414**	1	0.051	0.410**
P	0.000		0.653	0.000
n	80	80	80	80
Cortisol				
r	0.124	0.051	1	−0.166
P	0.274	0.653		0.141
n	80	80	80	80
XO				
r	0.398**	0.410**	−0.166	1
P	0.000	0.000	0.141	
n	80	80	80	80

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed). XO: Xanthine oxidase

calcium-sensing receptor (CASR) is created by the CASR gene; CASR is responsible for making CASR in the body. Cells in the kidney contain CASR. Filtering fluids and waste products from the body and reabsorbing nutrients are the functions of the kidneys. Calcium is reabsorbed from the urine by the kidney when the parathyroid glands produce more parathyroid hormone (PTH). Meanwhile, PTH activates Vitamin D to 1,25(OH) Vitamin D (also known as calcitriol). Therefore, the blood and kidney contain more calcium, PTH, and calcitriol when patients have hyperparathyroidism. With an increase in PTH levels, the absorption of calcium from urine rises; however, higher calcium and calcitriol levels work on the CASR located in the kidney to lower calcium reabsorption from urine. The activation of the CASR by elevated calcium and calcitriol overpowers the effect of PTH, resulting in a greater accumulation of calcium in the urine, which ultimately results in calcium kidney stones.[22]

The level of zinc was low in kidney stone patients compared with the healthy control that lead the growth of the calcium oxalate crystals that make up the stones. It alters the surfaces of crystals which encourages further growth causes the deterioration of renal function accompanied by an elevation in systemic blood pressure primarily through superoxide radical-induced oxidative stress these lead to zinc was interaction with these crystals leading to kidney stone.[23] The cortisol level increase in patients with kidney stone than in healthy controls, hormonal imbalance-rarely, an increase in the hormones produced by the parathyroid glands can lead to hypercalcemia (too much calcium), which can cause stones

Table 4: The test result of the area under receiver operating characteristic curve between the xanthine oxidase activity and ferritin in patients with kidney stone and healthy groups

Test result variable(s)	AUC	Sensitivity	1 - specificity	Cut off value
Ferritin	0.950	92	99	346.00
XO	0.624	70	79	19

XO: Xanthine oxidase, AUC: Area under the curve

to form.The effects of cortisol on tubular and glomerular function may directly affect renal function. Data revealed that in both animals and humans, exogenous cortisol increased a glomerular filtration rate (GFR) acutely, whereas excessive endogenous cortisol decreased GFR over the long term.[24] The level of uric acid was increased in kidney stone patients compared to normal healthy control because the patients have more ability to preduce too much uric acid, and/or the kidneys cannot abiliy to remove uric acid in urine, lead to builds up small uric acid stones also the purine digestion by xanthine oxidase which is converted to uric acid.[25] Chronic kidney disease (CKD) patients with glomerular disease and proteinuria (50) have been reported to have high ferritin levels. Patients with CKD may have increased C-reactive protein levels on a chronic basis, and 40% to 70% of these patients will have chronic inflammation.[26] When CKD is involved, cholesterol levels increase in patients with kidney stones; inflammation can be a chronic condition triggered by a variety of factors. The wall of the arteries is suggested to be damaged by inflammation and high blood pressure. Bad cholesterol (low-density lipoprotein) can stick around in the body because of inflammation. Accumulation of bad cholesterol can lead to the development of fatty streaks that eventually turn into plaque, which can cause the artery to narrow as it thickens. A blood clot or blockage may occur when this plaque breaks off. Regrettably, this may result in a heart attack or stroke.[27] The level of urea and creatinine increase in kidney stone patients more than healthy control, and kidney stones can cause enough damage to lower it. Usually, the reduction is very modest, but sometimes, stones can cause kidney failure (indirect measurement of glomerular filtration is serum creatinine level since creatinine is filtered by the glomerulus. Creatine and urea concentrations rise in the plasma due to a decrease in GFR).[28] Increase XO level in kidney stone patients compared to healthy control. The inability of xanthine dehydrogenase to convert xanthine into uric acid leads to an increase in blood levels, and urinary excretion of xanthine and hypoxanthine. Since these substances have a lower solubility in urine, they accumulate in the urinary system leading to the formation of stones.[29]

According to the results in Table 2, the urea was a positive correlation with creatinine due to the urea act as the nitrogenous end products of metabolism of amino acid. Urea is the primary metabolite derived from dietary protein and tissue protein turnover. Creatinine is the product of muscle creatine catabolism, so elevated urea and creatinine indicate that the kidneys are not working (called renal failure). Although urea is filtered into the urine by the kidney, some of the filtered urea will get reabsorbed and reused by the body; indirect measurement of glomerular filtration is serum creatinine level since creatinine is filtered by glomerulus. Creatine and urea concentrations rise in the plasma due to a decrease in GFR.[30]

As well as the cortisol was positively significant with calcium in kidney stones patients that lead to blocks calcium from entering your bones result the body is not as efficient at absorbing calcium that cause the kidney stone. Consequently, cortisol could reduce the density of bone by changing bone turnover, renal reabsorption of calcium and impairing intestinal absorption, and inhibiting reproductive hormones in premenopausal women.[31]

Depending on the ROC curve, the result showed the high sensitivity for XO and ferritin to discrimination between the patient and control groups of the study.

Furthermore, the level of cortisol was positively significant with the level of ferritin. A significant relationship exists between erythrocytosis and sex hormones, particularly testosterone, as that hormone stimulates iron into the erythrocyte and hepcidin controls the process. The difference in hemoglobin at puberty might be a result of testosterone increasing the upper limit of hemoglobin in humans and was associated with lower limits of hemoglobin, serum ferritin, and red blood cell count in humans. In contrast, testosterone was inhibited by hepcidin and that resulted in further serum-free iron, while estradiol inhibited hepcidin and increased iron absorption. However, hepcidin was positively correlated with levels of serum ferritin and transferrin receptor, suggesting that these proteins were both involved in iron metabolism and subject to hepcidin's regulation.[32,33]

Conclusions

According to the current study, elevated serum concentrations of XO may be utilized as biomarkers to diagnose kidney failure in kidney stone patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Collins EC. A short course in medical terminology. Lippincott Williams & Wilkins; 2005.
2. Weaver SH, Jenkins P. Renal and urological care. In: Illustrated Manual of Nursing Practice. 3rd ed. Lippincott Williams & Wilkins; 2002.
3. Rao NP, Preminger GM, Kavanagh JP. Urinary Tract Stone Disease. London: Springer; 2011.
4. Scales CD Jr., Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. Eur Urol 2012;62:160-5.

5. Menon M, Resnick MI. Urinary lithiasis: Etiology, diagnosis, and medical management. In: Campbell MF, Walsh PC, Retik AB, editors. Campbell's Urology. 8th ed. Philadelphia: Saunders Miller; 2002.
6. Singh JP, Thakur SN. Laser Induced Breakdown Spectroscopy. Amsterdam: Elsevier; 2007.
7. Sarkar BC, Chauhan UP. A new method for determining micro quantities of calcium in biological materials. Anal Biochem 1967;20:155-66.
8. Heinz F, Reckel S, Kalden JR. A New Spectrophotometric Assay for Enzymes of Purine Metabolism. Determination of Xanthine Oxidase Activity. Enzyme, 1979;24:239-246.
9. Tietz NW. Text Book of Clinical Chemistry. 3rd Edition, C.A. Burtis, E.R. Ashwood, W.B. Saunders, 1999. p. 1245-50.
10. Tiffany TO, Jansen JM, Burtis CA, Overtin JB, Scott CD. Enzymatic Kinetic Rate and End-Point Analysis of Substrate Using a Gemasec Fast Analyzer. Clinical Chemistry, 1972;18:829-40.
11. Bartels H, Böhner M. Clin. Chim. Acta 1971;32:81.
12. Yusof F, Mehde AA, Mehdi WA, Ghazali H, Abd Rahman A. The effect of renal stones on serum adenosine aminohydrolase and AMP-aminohydrolase in Malaysia. Asian Pac J Trop Biomed 2015; doi: 10.1016/j.apjtb.2015.04.003.
13. Saito M, Makino T. Clinica Chimica Acta 1982;120:127-35.
14. Ray Sarkar BC, Chauhan UPS, Biochem A. 1967;20:155.
15. Fleiner T, Zijlstra W, Dauth H, Haussermann P. Evaluation of a hospital-based day-structuring exercise programme on exacerbated behavioural and psychological symptoms in dementia – the exercise carrousel: study protocol for a randomised controlled trial. BioMedCentral 2015;16:228.
16. De Steenwinkel FDO, Hokken-Koelega ACS, Hazes JMW, Dolhain RJEM. The influence of foetal prednisone exposure on the cortisol level in the offspring Clinical Endocrinology 2014;80:804-10.
17. Bailey DK, Clark W, Kosman DJ.. The iron chelator, PBT434, modulates transcellular iron trafficking in brain microvascular endothelial cells. PLoS One 2021;16:e0254794. DOI: 10.1371/journal.pone.0254794.
18. Buchholz NP, Abbas F, Afzal M, Khan R, Rizvi I, Talati J. The prevalence of silent kidney stones – An ultrasonographic screening study. J Pak Med Assoc 2003;53:24-5.
19. Yu MA, Sánchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010;28:1234-42.
20. Albertoni G, Maquigussa E, Pessoa E, Barreto JA, Borges F, Schor N. Soluble uric acid increases intracellular calcium through an angiotensin II-dependent mechanism in immortalized human mesangial cells. Exp Biol Med (Maywood) 2010;235:825-32.
21. Convento MS, Pessoa E, Dalboni MA, Borges FT, Schor N. Pro-inflammatory and oxidative effects of noncrystalline uric acid in human mesangial cells: Contribution to hyperuricemic glomerular damage. Urol Res 2011;39:21-7.
22. Craven BL, Passman C, Assimos DG. Hypercalcemic states associated with nephrolithiasis. Rev Urol 2008;10:218-26.
23. Tasian GE, Ross ME, Song L, Grundmeier RW, Massey J, Denburg MR, *et al*. Dietary zinc and incident calcium kidney stones in adolescence. J Urol 2017;197:1342-8.
24. Rahman SH, Papadakis GZ, Keil MF, Faucz FR, Lodish MB, Stratakis CA. Kidney stones as an underrecognized clinical sign in pediatric Cushing disease. J Pediatr 2016;170:273-7.e1.
25. Dawson J, Walters M. Uric acid and xanthine oxidase: Future therapeutic targets in the prevention of cardiovascular disease? Br J Clin Pharmacol 2006;62:633-44.
26. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: To measure it or not to measure it in chronic kidney disease? Clin J Am Soc Nephrol 2006;1 Suppl 1:S9-18.
27. Torricelli FC, De SK, Gebreselassie S, Li I, Sarkissian C, Monga M. Dyslipidemia and kidney stone risk. J Urol 2014;191:667-72.
28. Pandya D, Nagrajappa AK, Ravi KS. Assessment and correlation of urea and creatinine levels in saliva and serum of patients with chronic kidney disease, diabetes and hypertension – A research study. J Clin Diagn Res 2016;10:C58-62.
29. Yusof F, Mehde AA, Mehdi WA, Ghazali H, Abd Rahman A. Study the effect of kidney stones on serum xanthine oxidase, ecto-5'-nucleotidase activity and E3 SUMO-protein ligase NSE2 (NSMCE2) in Malaysian individuals. Asian Pac J Trop Biomed 2015;5:684-8.
30. Brookes EM, Power DA. Elevated serum urea-to-creatinine ratio is associated with adverse inpatient clinical outcomes in non-end stage chronic kidney disease. Sci Rep 2022;12:20827.
31. Bedford JL, Barr SI. The relationship between 24-h urinary cortisol and bone in healthy young women. Int J Behav Med 2010;17:207-15.
32. Yang Q, Jian J, Katz S, Abramson SB, Huang X. 17β-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. Endocrinology 2012;153:3170-8.
33. Chen J, Enns CA. Hereditary hemochromatosis and transferrin receptor 2. Biochim Biophys Acta 2012;1820:256-63.