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THE EFFECT OF ALLOPURINOL ON SERUM URIC ACID, BLOOD UREA AND SERUM CREATININE IN CHRONIC KIDNEY DISEASE PATIENTS WITH HIGH URIC ACID

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Abstract:

Background; -Chronic kidney disease is a long-term condition in where the kidneys loss their function lead to several biochemical changes, including the high levels of blood urea, s.creatinine and serum uric acid (hyperuricemia).High uric acid activates the inflammatory response in renal parenchyma leading to renal damage. Allopurinol which is xanthine oxidase enzyme inhibitor is used to lower uric acid concentration. Aim of the study is to study the effect of use of allopurinol on serum level of uric acid, blood urea, serum creatinine in chronic kidney disease patients. Patients and **Methods;** - A one hundred participant involved , 35 of them were a control group and 65 patients have chronic kidney disease stages 2 to 4 with high uric acid ,from whom 35 patient were on allopurinol. The patients were attending to the outpatient clinic of the Iraqi Center for Kidney Diseases and Renal Transplantation at the Medical City Teaching Hospital Complex, Baghdad, Iraq. The period of study from June to October 2022. Clinical data were collected and the following investigation were done to all; serum uric, blood urea, serum creatinine and estimated glomerular filtration rate.

Results The average of s.uric acid in control group was within normal 6.2 mg/dl , while it was high in CKD patients with allopurinol(6.793mg/dl) and higher in chronic kidney disease patients without allopurinol (8.240 mg/dl),with significant P value (0.0013). All level of serum uric, blood urea , serum creatinine found to be lower in chronic kidney disease patients who are using allopurinol treatment than in those who are not, with a significant p values.

Conclusion The use of allopurinol in chronic kidney disease patients associated with lower levels of uric acid, b.urea and s,creatinine

Keywords: allopurinol, uric acid, urea , creatinine, chronic kidney disease

INTRODUCTION Chronic kidney disease is classified in five stages depending on the reduction in the glomerular filtration rate (GFR), Stage 1: >90 mL/min; Stage 2: 60–89 mL/min; Stage 3: 30–59 mL/min; Stage 4: 15–29 mL/min; and Stage 5:< 15 ml / min[1]. Creatinine is the cyclic anhydride of creatine which is an end product of the dissociation of phosphocreatine [2]. Creatine is manufactured primarily in the liver from the methylation of glycocyamine (guanidino acetate, in the kidney are manufactured from the amino acids arginine and glycine) by S - adenosyl methionine. Then transported through blood to the other organs, muscle, and brain, where, during phosphorylation, it becomes the high-energy compound phosphocreatine [3] The biochemical pathway of creatine synthesis and its uses for energy supply, together with the final serum/plasma creatinine buildup is already well documented

Urea is a small water-soluble molecule that is freely filtered by the glomeruli and absorbed by the proximal and distal tubules of the kidney. Several urea transporters are involved in urea handling along the nephron[4]. Urea has quantitatively the highest serum concentration among the different organic solutes retained in patients with CKD [5] [Blood urea nitrogen (BUN) is traditionally one of the indicators for evaluating kidney function, and BUN levels are inversely correlated

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with kidney function[6] Besides glomerular filtration, BUN levels are also influenced by tubular resorption and production of urea. Uric acid is the last enzymatic product from the degradation of purine nucleosides [7,8] the structure is shown in the figure1. Uric acid generates by enzymatic conversion of hypoxanthine to xanthine which converts to uric acid at presence of xanthine oxidase, as shown in figure 2. Uric acid is the end product of purine degradation in humans, but it is further metabolized to allantoin by uricase in other mammals. The level of uric acid in humans (~6.0 mg/dL) is much higher than that in other mammals (<2.0 mg/dL) because of the absence of uricase . Loss [9] of the uricase gene in humans could be a result of evolution since uric acid is a powerful antioxidant that accounts for up to 60% of the antioxidant capacity of human plasma . [10] and when blood uric acid levels 7mg/dl body fluid become saturated, the uric acid then precipitates to urate crystals and then develop gouty arthritis in joint or ureic acid stones in the kidneys [11] Uric acid exerts antioxidant effects by scavenging a free radical and chelating a metal ion [12,13]. Indeed, uric acid is known to exert a protective effect against neurodegenerative diseases such as Parkinson's and Alzheimer's disease [14]. The high metabolic rate of the human brain makes it vulnerable to oxidative stress, potentially suggesting that the human body is willing to pay a premium for a potent endogenous antioxidant. This advantageous feature of uric acid is limited by the fact that it acts as an antioxidant only in the hydrophilic environment of biological fluids, particularly in the presence of ascorbic acid[15] . In modern society, an elevated uric acid level seems to be a disadvantageous inheritance. Since Garrod discovered that hyperuricemia is the cause of gout in the 19th century, the deleterious effects of uric acid on cardiovascular and kidney disease have been continuously documented.[16,17,18] The normal range for uric acid in blood (2.7-7.3 mg/dl) women , and (3.7-7.3 mg/dl) in men . Hyperuricemia is defined when the serum uric acid level is 6.8 mg/dL, at which point uric acid reaches saturation at physiological temperature and pH[19,20] . Although an elevated uric acid level is a key factor for monosodium urate (MSU) crystal formation, urate solubility is also influenced by temperature, pH, and various ion concentrations as well as serum, synovial fluid, and cartilage contents[20,21,22] . This variety of factors involved in MSU crystallization explains why only a minority (~0.5– 4.9% annually) of individuals with hyperuricemia develop gout [23]. Because hyperuricemia in people without gout does not cause any symptoms and appears to be inert, asymptomatic hyperuricemia had not drawn much attention by the medical community for a few decades. Such asymptomatic hyperuricemia is frequently observed in patients with kidney impairment and thought to be merely a result of decreased renal clearance.

Uric acid and inflammation in kidney disease Inflammation is a main pathophysiological mechanism in acute kidney injury (AKI) and CKD, including metabolic diseases such as diabetic kidney disease (DKD). Although the inflammatory response to injury is initially aimed at tissue repair and recovery, prolonged and uncoordinated inflammation promotes glomerulosclerosis and tubulointerstitial fibrosis. How does Uric acid activate the inflammatory response in the kidneys The kidneys harbor several classes of resident immune cells, such as dendritic cells, macrophages, and lymphocytes, although these cells account for a small population in normal kidneys [24] . Upon kidney injury, the inflammatory response is boosted by the concerted interaction of these immune cells with endothelial, mesangial, and tubular epithelial cells , leading to the recruitment of circulating immune cells. This is the potential mechanisms by which uric acid is implicated in an inflammatory process according to the kidney compartments (vasculature, glomerulus, and tubulointerstitial area) with a focus on renal parenchymal cells.

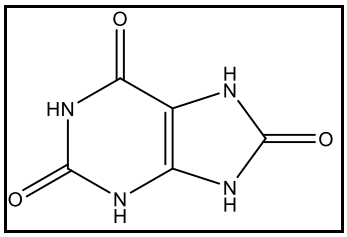

Figure 1. Uric acid structure [25]

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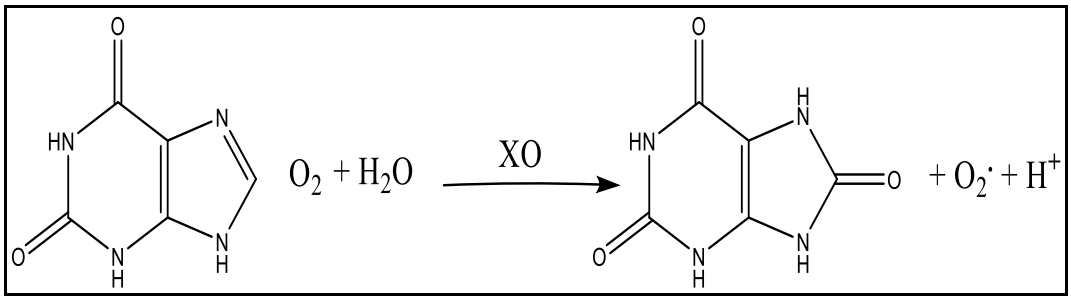

Figure 2. Conversion xanthine to uric acid by Xanthine Oxidase [25]

Allopurinol is a xanthine oxidase inhibitor in Figure 2, which in result cause the inhibition of formation of uric acid (insoluble) and increase the concentration of hypoxanthine and xanthine (soluble) in the body which can be easily excreted out. Allopurinol itself as well as its active metabolite Oxypurinol also known as Alloxanthine plays an important role in inhibiting xanthine oxidase enzyme. Oxypurinol cause prolong inhibition as compared to parent drug Allopurinol. In patient having extremely high rate level when given allopurinol can form xanthine stones but they can be dissolved by alkalization of urine or excessive intake of water. Allopurinol used in hyperuricemia, Gout, Tumor lysis syndrome which is caused by chemotherapy, it also helps in delaying progression of renal diseases. Hypersensitivity reactions such as skin rashes are common side effect of Allopurinol. [26] , it is 80% absorbed orally. Allopurinol has 1-2 hours of half-life while Oxypurinol has 15-18 hours of half-life. Allopurinol is considered as 1st line therapy for chronic gout. Allopurinol comes as 100mg and 300mg tablets and is only available on prescription. It should be taken with NSAID or colchicine or glucocorticoids in the start of therapy later on they can be discontinued.

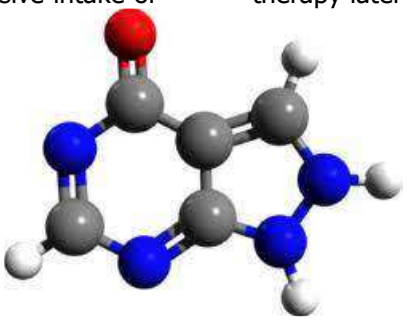

Figure 3. Structural formula of Allopurinol.

Aims To study the effect of xanthine oxidase inhibiter (allopurinol) on concentration of Serum uric acid , Blood urea , Serum creatinine , e GFR in chronic kidney disease patients with high uric acid.

Patients and methods ;- This is a cross sectional study involved a total of one hundred participants, 63 were males and 73 were females, with an average age of the 42.54 years (25-72). A sixty five of them were patient with CKD (stages 2 to 4) who were attending for regular follow up at the outpatient clinic at The Iraqi Center for Kidney Disease and Transplantation , Medical City Teaching Hospital, Baghdad, Iraq. The period of study was from June 2022 to October 2022. The 35 controls were selected from the relatives of the patients who were having no past history of any chronic complicating medical illnesses and on no any treatment. A written informed consents were signed by all the participants. They were divided in to three groups. The first is a control group of 35 healthy individuals. The second group consists of 30 CKD patients who have high uric acid they were not using allopurinol. The third group consisted of 35 CKD patients with high uric acid on treatment with allopurinol tablet (100 -300 mg) once daily at least for the last 3 months . Patients and controls were interviewd for name, age sex , history of CKD and treatment with allopurinol . The following investigation were done;- serum uric acid, Blood urea and serum creatinine.The Estimated Glomerular Filtration Rate(eGFR) as ml/min/1.7 m.sq. were calculated according to CKD-EPI formula, (Chronic Kidney Disease Epidemiology Collaboration).

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CKD-EPI

$$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times (1.018 \text{ if female}) \times (1.159 \text{ if African American})$$

*S_{cr} is serum creatinine in mg/dL
κ is 0.7 for females and 0.9 for males
α is -0.329 for females and -0.411 for males
min indicates the minimum of S_{cr}/κ or 1
max indicates the maximum of S_{cr}/κ or 1

A verbal consents were taken from all the control and the patient groups to participate in this study. This study was approved by the ethical committee for research at the College of Medicine University of Baghdad.
Statistical Analysis Statistical package for social sciences (SPSS) version 20 was used for data entry and analysis. Student T-tests for two independent samples and paired t-tests for two dependent samples (before and after Ckd data) are used to analyze the difference between normally distributed continuous variables. Pearson's correlation was used to estimate the correlation between two continuous variables. The significance level was set at a P-value equal to or less than 0.0001.

RESULTS; - This study involved 100 participants, 65% of them were having chronic kidney disease stage 2 to 4 and 35% were the control group. The age and sex distribution shown in table 1.

Table .1 Age and sex distribution of the control and Chronic Kidney Disease groups.

Variables		Control group	CKD Patients (stages 2- 4)	Total No. (%)
Age (year)		43.5 (26 to 61)	42.54 (25-72)	
sex	male	19	34	53 (53%)
	female	16	31	47 (47%)
Total No. (%)		35 (35%)	65 (65 %)	100 (100%)

Figure 4 showed the number and percent of groups in the study

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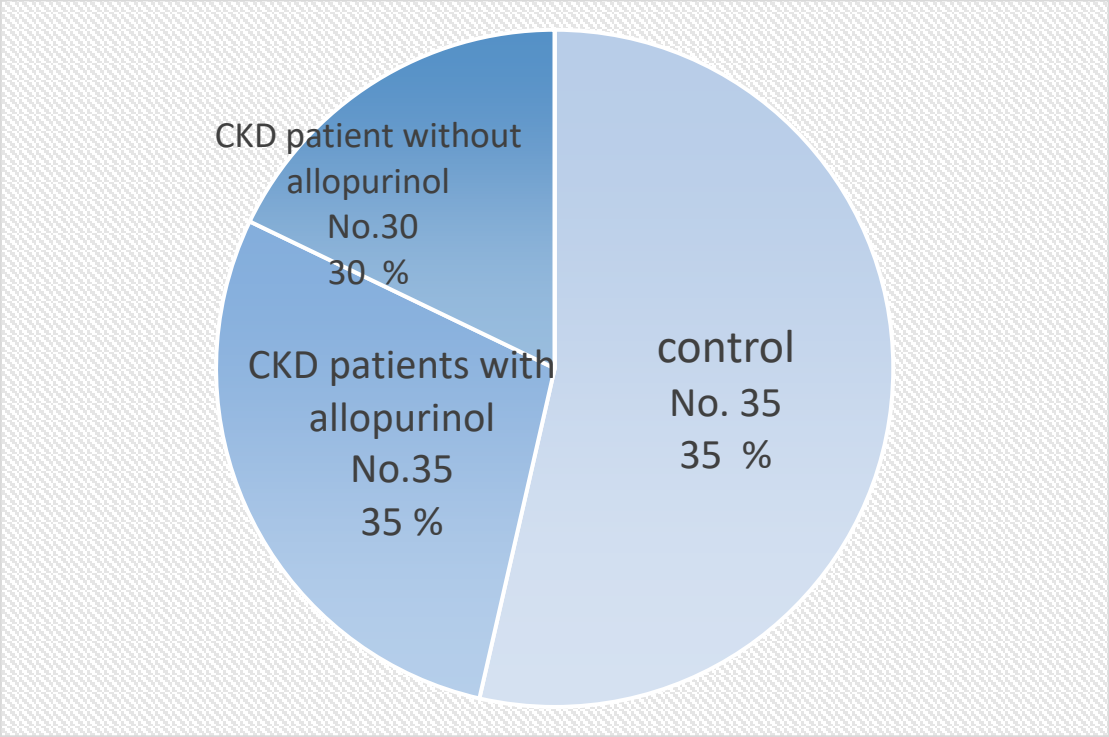

Figure 4. Distribution of data according to the present study group.

This study showed that the average of s.uric acid was within normal in the control group while it was high in CKD group , 6.26 versus 7.53 mg/dl respectively with a P value of 0.0013 as shown in figure 5.

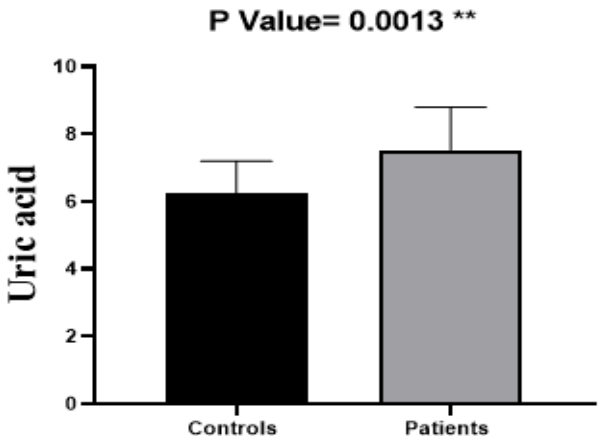

Figure 5. Serum uric acid levels for control and CKD groups.

The average of s.uric acid in control group was within normal 6.2 mg/dl , while it was high in CKD patients with allopurinol(6.793mg/dl) and higher in CKD patients without allopurinol (8.240 mg/dl),with significant P value. Table. 2

Table. 2 S.uric acid control and Chronic Kidney Disease groups

Group No.	S uric acid (mg/dl) Mean SD	P-Value
Control	6.260 (0.936)	0.0013

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CKD with allopurinol	6.793 (1.317)	0.0006
CKD without allopurinol	8.240 (0.57)	0.0006

The average of blood urea and s.creatinine were higher in CKD patients without allopurinol with a statistical significant. Tables 3 & 4.

Table. 3 Blood urea in the control and Chronic Kidney Disease groups

Group	Blood urea mg/dl Mean SD	P-Value
Control	26.73 (7.923)	0.0001
CKD with allopurinol	68.67 (15.36)	0.0001
CKD without allopurinol	45.33 (10.77)	0.0001

Table. 4 . Serum creatinine in the control and Chronic Kidney Disease groups

Group	S. creatinine mg/dl Mean SD	P-Value
Control	0.790 (0.129)	0.0001
CKD with allopurinol	1.222 (0.1850)	0.0001
CKD without allopurinol	1.824 (0.4081)	0.0001

The (eGFR) was higher in CKD patients with allopurinol compared to CKD patient with allopurinol with a statistical significant. Tables 5.

Table. 5 The Estimated GlomerularFiltration Rate (eGFR) in control and Chronic Kidney Disease groups

Group	eGFR ml/min Mean SD	P-Value
Control	134.3 21.59	0.0001
CKD with allopurinol	65.87 12.75	
CKD without allopurinol	38.65 10.92	

DISCUSSION

The data in figure 4 showed that the serum uric acid concentration in CKD group was significantly higher than in the control group (7.531 versus 6.260 mg/dl) with (p value <0.0013). This increasing of serum uric acid in CKD patients is due reduce renal excretion of uric acid in CKD patients even they are on normal or low protein diet leading to hyperuricemia . These result come in an agreement with studies done by (Yu et al. 2010), (Kusano & Ferrari, 2008 , and (Yusof et al. 2015).

As shown in table 2 s.uric acid was higher in CKD patients with allopurinol treatment than those without (6.793versus 8.240 mg/dl),with significant P value.

The treatment with allopurinol which is a xanthine oxidase inhibitor, causes inhibition of formation of uric acid (insoluble) and increase the concentration of hypoxanthine and xanthine (soluble) in the body which can be easily excreted out. [27,28].

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Blood urea and s.creatinine concentrations are the main important parameters to be considered when dealing with chronic kidney disease pateints., Creatinine is a breakdown product of creatine phosphate in muscle and is usually produced at a constant rate by the body depending on the muscle mass. While Urea is major nitrogenous end product of the amino acid and protein catabolism, produced by liver and distributed throughout intracellular and extracellular fluid ,, The data of this study showed that the levels of both blood urea (table 3) and serum creatin ine (table 4) were higher in CKD patients than in control group , and they were highest in CKD patients who were not treated with allopurinol, (p value<0.0001). This mean that the use of allopurinol was associated with decrease b.urea and s.creatinine which means an improvement in renal function. This may be explained by the fact that lowering uric acid leads to decrease of the activation of inflammatory responses in the kidney which was triggered by high uric acid level . this inflammatory response is boosted by the concerted interaction of the immune cells with endothelial, mesangial, and tubular epithelial cells , leading to the recruitment of circulating immune cells. This is the potential mechanisms by which uric acid is implicated in an inflammatory process according to the kidney compartments (vasculature, glomerulus, and tubulointerstitial area) with a focus on renal parenchymal cells.The results of the present study are in consistent with researchers done by Gowda et al 2010[29]..; & Pagana, 2017[30].. and Rule et al. 2011[31]..) Table 5 showed that eGFR values in the CKD patient was significantly lower (p< 0.001) than that of the control group , and it was better ; higher, in CKD patients on allopurinol treatment than those without. These findings were in agreement with studies done by Sedaghat [10]and Amis [12.].

CONCLUSION; - In this study, we can conclude that chronic kidney disease patients have higher uric. The use of allopurinol in chronic kidney disease patients was associated with lower levels of uric acid , b.urea and s,creatinine with higher level of estimated glomerular filtration rate.
We do recommend the use of allopurinol for patient with chronic kidney disease and high uric acid.

REFERENCES

1. Schwartz, G.J.; Muñoz, A.; Schneider, M.F.; Mak, R.H.; Kaskel, F.; Warady, B.A.; Furth, S.L. New Equations to Estimate GFR in Children with CKD. J. Am. Soc. Nephrol. 2009, 20, 629–637.
2. G. M. Preminger, "Renal calculi: pathogenesis, diagnosis, and medical therapy," in Seminars in nephrology, 1992, pp. 200-216.
3. Department of Health. Estimating glomerular filtration rate (eGFR): Information for laboratories, April 2006.
4. Grubb A, Nordin G. Notable steps in obtaining improved estimates for glomerular filtration rate. Clin Chem 2006. Feb;52(2):169-170
5. Lamb EJ, Wood J, Stowe HJ, O'Riordan SE, Webb MC, Dalton RN. Susceptibility of glomerular filtration rate estimations to variations in creatinine methodology: a study in older patients. Ann Clin Biochem 2005. Jan;42(Pt 1):11-18
6. Swedko PJ, Clark HD, Paramsothy K, Akbari A. Serum creatinine is an inadequate screening test for renal failure in elderly patients. Arch Intern Med 2003. Feb;163(3):356-360
7. Stöckler, S. et al. Creatine defciency in the brain: a new, treatable inborn error of metabolism. Pediatr. Res. 36, 409–413 (1994).
8. Y. Y. Sautin and R. J. Johnson, "Uric acid: the oxidant-antioxidant paradox," Nucleosides, Nucleotides, and Nucleic Acids, vol. 27, pp. 608-619, 2008.
9. Johnson RJ, Titte S, Cade JR, Rideout BA, Oliver WJ. Uric acid, evolution and primitive cultures. Semin Nephrol 25: 3–8, 2005.
10. Sedaghat S, Hoorn EJ, van Rooij FJ, Hofman A, Franco OH, et al. (2013) Serum uric acid and chronic kidney disease: the role of hypertension. PLoS One 8: e76827.
11. R. Dunnick, C. Sandler, and J. Newhouse, Textbook of uroradiology: Lippincott Williams & Wilkins, 201239. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 78: 6858 – 6862, 1981.
12. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 78: 6858 –6862, 1981.
13. Frei B, Stocker R, Ames BN. Antioxidant defenses and lipid peroxidation in human blood plasma. Proc Natl Acad Sci USA 85: 9748 – 9752, 1988.
14. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. J Pharmacol Exp Ther 324: 1–7, 2008.
15. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 27: 608 –619, 2008.
16. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-15, October 2022
ISSN: 2749-3644

renal hypertension. N Engl J Med 275: 457–464, 1966
17. Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 24: 691–697, 2001
18. Tuttle KR, Short RA, Johnson RJ. Sex differences in uric acid and risk factors for coronary artery disease. Am J Cardiol 87: 1411–1414, 2001.
19. Van de Kamp, J. M., Mancini, G. M. & Salomons, G. S. X-linked creatine transporter defciency: clinical aspects and pathophysiology. J. Inherit. Metab. Dis. 37, 715–733. https://doi.org/10.1007/s10545-014-9713-8 (2014).
20. Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum 15: 189 –192, 1972. D
21. Chhana A, Lee G, Dalbeth N. Factors influencing the crystallization of monosodium urate: a systematic literature review. BMC Musculoskelet Disord 16: 296, 2015.
22. Martillo MA, Nazzal L, Crittenden DB. The crystallization of monosodium urate. Curr Rheumatol Rep 16: 400, 2014.
23. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. Am J Med 82: 421–426, 1987
24. Turner JE, Becker M, Mittrücker HW, Panzer U. Tissue-resident lymphocytes in the kidney. J Am Soc Nephrol 29: 389 –399, 2018.
25. M. K. Eberhardt, Reactive oxygen metabolites: chemistry and medical consequences: CRC press, 2000.
26. D. A. Schulsinger, Kidney Stone Disease: Say NO to Stones!: Springer International Publishing, 2014
27. Dossetor JB. Creatininemia versus uremia. The relative significance of blood urea nitrogen and serum creatinine concentrations in azotemia. Ann Intern Med. 1966;65(6):1287–1299. pmid:5928490.
28. Matsue Y, van der Meer P, Damman K, Metra M, O'Connor CM, Ponikowski P, et al. Blood urea nitrogen-to-creatinine ratio in the general population and in patients with acute heart failure. Heart. 2017;103(6):407–413. pmid:27658757.
29. Gowda, S., Desai, P. B., Kulkarni, S. S., Hull, V. V., Math, A. A., & Vernekar, S. N. (2010). Markers of renal function tests. North American journal of medical sciences, 2(4), 170.
30. Walser M. Keto-analogues of essential amino acids in the treatment of chronic renal failure. Kidney Int Suppl. 1978;(8):S180–184. pmid:278888.
31. Di Iorio BR, Minutolo R, De Nicola L, Bellizzi V, Catapano F, Iodice C, et al. Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. Kidney Int. 2003;64(5):1822–1828. pmid:14531817.
32. Movilli E, Cancarini GC, Zani R, Camerini C, Sandrini M, and Maiorca R. Adequacy of dialysis reduces the doses of recombinant erythropoietin independently from the use of biocompatible membranes in haemodialysis patients. Nephrol Dial Transplant. 2001;16(1):111–114. pmid:11209002.
33. Mostofsky E, Schwartz J, Coull BA, Koutrakis P, Wellenius GA, Suh HH, et al. Modeling the association between particle constituents of air pollution and health outcomes. Am J Epidemiol. 2012;176(4):317–326. pmid:22850792.