Uric Acid & CRF: Assessment of Serum Uric Acid level in Patients with Chronic Renal Failure in PMCH Nawabshah, a tertiary care hospital.

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ABSTRACT

Background: Increased uric acid levels affect the prognosis and the disease outcome in CRF (chronic renal failure) patients.

Objective: The present research was aimed to observe connection among CKD & increased uric acid levels.

Material & Methods:

Design: Current research was cross sectional study.

Place: Carried at PMCH Nawabshah.

Duration: From 1st January 2017 to 30th June 2018.

Subjects: Our study included patients with CKD visiting the haemodialysis department and the serum uric acid levels were checked in all subjects.

Results: In current study 168 subjects were included. Subjects were known CKD patients and presented with high serum creatinine levels. Out of these, 125 were male while 43 were female subjects.

Mean age of subjects was 45.82 SD±12.91 years. The mean serum uric acid was 7.75 SD±1.49 mg/dl. Mean levels of serum creatinine were 5.15 SD±3.55 mg/dl. Normal uric acid levels were detected in 41(32.8%) males and 12 (27.9%) females. Abnormal uric acid levels were present in 84 (67.2%) males and 31(72.1%) females. Normal creatinine level was present in 5 males and 01 female. Abnormal creatinine levels were present in 120 males and 42 females.

Conclusion: Increased levels of serum uric acid commonly seen in subjects with chronic renal failure, additional researches are required to assess the link between CKD prognosisand outcome with hyperuricemia as an essential part for the management of CKD.

Key words: chronic renal failure, uric acid, hyperuricemia, PMCH Nawabshah.

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Introduction:

Increased levels of uric acid are mostly seen in subjects with CKD (chronic kidney disease), though the statistics concerning the association among levels of serum UA and continuing consequences in patients of CKD have been restricted [1].It is observed that Chronic kidney disease (CKD) is a universal well-being issue[2]. Hypertension and Diabetes Mellitus are well known modifiable risk factors for developing CKD. Early identification and control of these factors are imperative for prevention of CKD. In subjects with CKD higher value of serum UA are observed, though the raised value of UA are just marker of the altered renal function or had a factual part in altred renal function still remains questionable[3,4]. Afferent arteriolopathy, glomerulosclerosis, and tubulointerstitial fibrosis were associated with hyperuricemia associated renal injury in experimental rat models[5,6,7]and this possibly will be inverted by urate lowering drugs[8,9]. The kidneys are the main route of uric acid excretion; in studies it is stiff to assess the

underlying effect of UA on the development of chronic kidney disease[4]. Occurrence of CKD was seen to be associated with increased levels of uric acid as reported in a meta-analysis[10]still the role of UA is unclear in the progress of chronic kidney disease. In subjects with CKD stage 3 to 5 there was no decrease or speedy development to ESRD (end stage renal disease) related to hyperuricemia as reported in Swedish Renal Registry cohort [11] In United States, Taiwan and Europe experts had observed that the great variation in renal function and its progression to ESRD (end stage renal disease) and there are recommendations for making conclusions [12,13,14,15]

Our study was aimed to provide evidence for the continuing discussion regarding the part of serum UA values on the CKD progression in a Pakistani populace sample from Nawab shah.

Material and methods:

Objective: The current study is aimed to observe the relationship among increased levels of serum UA and CKD (chronic kidney disease).

Design: This was descriptive and analytical study.

Place: Conducted at PMCH Nawabshah.

Duration: From 1st January 2017 to 30th July 2018.

Subjects: Our study included every patient with CKD visiting at hemodialysis department and serum uric acid levels checked in all subjects.

Operational definitions: Hyperuricemia is defined as Serum UA (uric acid) values >7.0 mg/dl is well defined as hyperuricemia [22].

Chronic kidney disease staging was based on estimated GFR. Stage 1 CKD = GFR > 90 mL/minute, Stage 2 CKD = GFR 60 to 89 mL/minute, Stage 3 CKD = GFR 30 to 59 mL/minute, Stage 4 CKD = GFR 15 to 29 mL/minute and Stage 5 CKD = GFR < 15 mL/minute.

Dyslipidemias were defined as serum cholesterol levels more than 200 mg/%, and/or serum HDL more than 135 mg/% and/or serum triglyceride levels more than 150 mg/% [16].

Arterial hypertension: Blood pressure of more than 140/90 mmHg is labelled as Arterial Hypertension.

Smoking: Tobacco use throughout the previous one month before consultation.

Inclusion criteria: Allsubjects with diagnosis of CKD and Hyperuricemia reported at hemodialysis department at tertiary care hospital.

Exclusion criteria: Subjects not willing to participate, with blood disorders, having comorbidities causing hyperuricemia, and drugs with effect on serum uric acid levels.

Data collection: TheMean values with SD (standard deviation) were included in the continuous variables, frequencies and percentages were included as categorical variables. Chi-square test was used for statistical alterations amongst uric acid strata, and for categorical and continuous variables one-way ANOVA was used respectively. After altering for possible confounders like age at consultation, gender, BMI (body mass index), existence of CVD (cardiovascular disease), Blood Pressure (systolic), D M (Yes versus No), proteinuria (Yes versus No), and s. creatinine at baseline multivariable modeling was achieved. A prior exploratory subcategory scrutiny stratified by proteinuria status was too achieved by consuming the analogous modeling method. For sequential eGFR alteration and hazard of ESRD, the interaction among uric acid and proteinuria were established by multivariable models. SPSS Version 20 was used to conduct the all analyses. α = 0.05 was set as the 2-sided statistical significance level.

Data analysis: Data were analyzed using windows-based SPSS version 20. $P < 0.05$ were considered significant statistically.

Results:

This research comprised 168 patients; from them 125 males and 43 females.

Descriptive Statistics.

The age ranged between18.00 years to 69.00 years, and mean age was of 45.82 SD±12.91 years (p=<0.00). The hemoglobin range was 7.0 to 14 g% with mean 8.61 SD±1.90 (p=<0.00). Uric acid level ranged from 3.80 - 12.20 mg/d with mean value of 7.75 SD±1.49 (p=<0.00). Serum creatinine ranged from 1.0-26.20 with mean of 5.15 SD±3.55(p=<0.00). eGFR range was 05-59 with mean of 22.79 SD±12.10 (p=<0.00).**Table 1.**

Demographic Statistics

Out of 168 subjects with renal failure 60 belonged lower, 78 & 30 belonged to middle & upper class respectively, 125 were male and 43 were female, 155 married and 13 unmarried, 90 from rural areas and 78 from urban areas, 35 house wives, 67 manual workers, 45 office workers and 20 with no occupation, education wise 87 subjects were primary to matric, 56 intermediate to above and 25 were uneducated, 110 from lower class while 46 and 12 from middle and upper class respectively.**Fig: 1.**

Comorbidities

118 without DM and 50 with DM, HTN was present in 152 and absent in 16 patients, 146 were HBsAg negative while 22 were positive, 139HCV negative while 29 positive, 165 HIV negative while 03 positive, 142 were anemic while 26 were not anemic.**Fig:2.**

Serum Uric Acid * Serum Creatinine Level * Gender Crosstabulation

Normal uric acid level was present in 41(32.8%) males and abnormal uric acid levels were present in 84(67.2%) males. Normal uric acid level was present in 12 (27.9%) femalesand abnormal uric acid levels were present in 31(72.1%) females.P=0.003.

Normal creatinine level was present in 5(4%) males and 01 (2.3%) female. Abnormal creatinine levels were present in 120 (96.0%) males and 42(97.7%)females. p=0.279.**Table 2.**

Correlations

The correlation between age HB% p= **.000**, UA level p=**.039**, S.Creatinine p=**.014** and eGFR was p=**.002** statistically significant.The correlation between HB% and age p= **.000**, UA level p= **.000**, S.Creatinine p= **.000**and eGFR was p= **.000**statistically significant.The correlation between UA level and age p= **.039**, HB% p= **.000**, S.Creatinine p= **.000**and eGFR was p= **.000**statistically significant.The correlation between S.Creatinine and age p= **.014**, HB% p= **.000**, UA level p= **.000**and eGFR was p= **.000**statistically significant.The correlation between eGFR and age p= **.002**, HB% p= **.000**, S.Creatinine p= **.000**and UA level was p= **.000**statistically significant.**Table 3.**

Paired Sample Test

Paired sample test with 95% C I of the difference shown statistically significant relationship between Uric Acid level – age p < 0.00, U A level – Hemoglobin p<0.00, U A level - serum creatinine p<0.00 and UA level - eGFR value p < 0.00.**Table 4.**

Table 1. Descriptive Statistics. n=168

	Minimum	Maximum	Mean	Std. Deviation	Asymp. Sig.
Age	18.00	69.00	45.8214	12.91489	.000
Hemoglobin	7.0	14.00	8.6179	1.90393	.000
Uric Acid Level	3.80	12.20	7.7583	1.49303	.000
Serum Creatinine	1.00	26.20	5.1530	3.55280	.000
eGFR value	5.00	59.00	22.7976	12.10511	.000

Fig: 1. Demographic Statistics

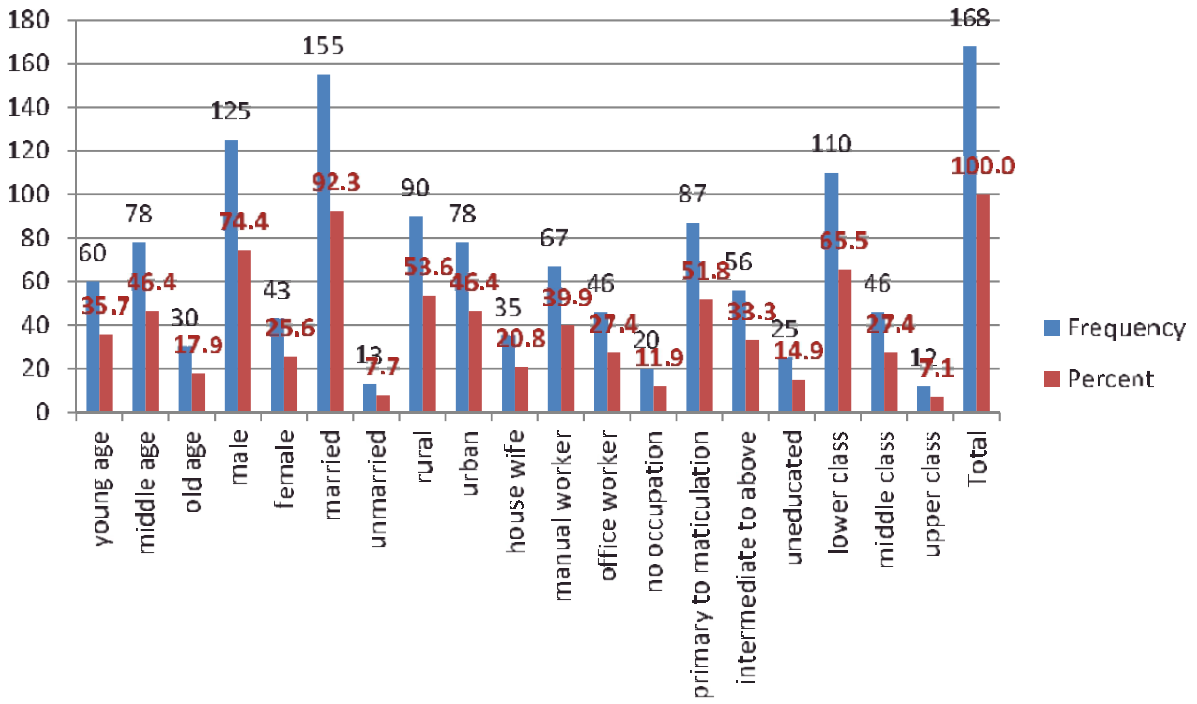

Fig:2. Comorbidities

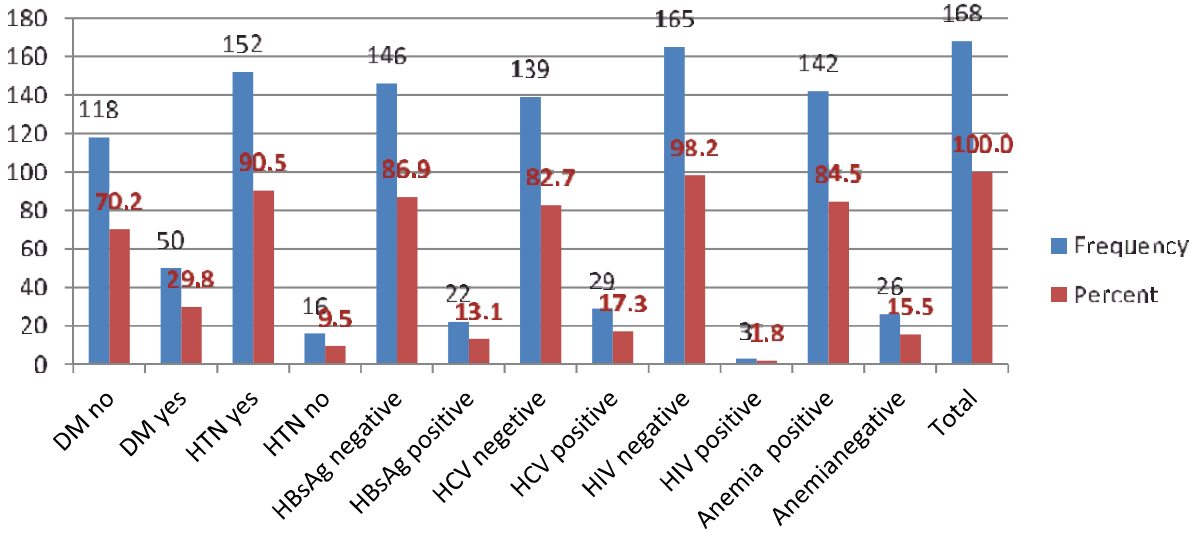

Table 2. Serum Uric Acid * Serum Creatinine Level * Gender Crosstabulation

Gender				Serum Creatinine Level		Total	P-Value
				Normal	Abnormal		
Male	Serum Uric Acid	Normal	Count	5	36	41	.003
			% Of Total	4.0%	28.8%	32.8%	
		Abnormal	Count	0	84	84	
			% Of Total	.0%	67.2%	67.2%	
	Total		Count	5	120	125	
			% Of Total	4.0%	96.0%	100.0%	
Female	Serum Uric Acid	Normal	Count	1	11	12	.279
			% Of Total	2.3%	25.6%	27.9%	
		Abnormal	Count	0	31	31	
			% Of Total	.0%	72.1%	72.1%	
	Total		Count	1	42	43	
			% Of Total	2.3%	97.7%	100.0%	

Table 3. Correlations. n=168

		age	Hemoglobin	Uric Acid level	serum creatinine	eGFR value
age	Pearson Correlation	1	-.332**	.159*	.189*	-.243**
	Sig. (2-tailed)		.000	.039	.014	.002
Hemoglobin	Pearson Correlation	-.332**	1	-.433**	-.549**	.576**
	Sig. (2-tailed)	.000		.000	.000	.000
Uric Acid level	Pearson Correlation	.159*	-.433**	1	.393**	-.345**
	Sig. (2-tailed)	.039	.000		.000	.000
serum creatinine	Pearson Correlation	.189*	-.549**	.393**	1	-.391**
	Sig. (2-tailed)	.014	.000	.000		.000
eGFR value	Pearson Correlation	-.243**	.576**	-.345**	-.391**	1
	Sig. (2-tailed)	.002	.000	.000	.000	

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4. Paired Samples Test

Paired Differences					Sig. (2-tailed)
			95% Confidence Interval of the Difference		
pairs	Mean	Std. Deviation	Lower	Upper	
Uric Acid level - age	-38.06310	12.76218	-40.00701	-36.11918	.000
Uric Acid level - Hemoglobin	-.85952	2.88364	-1.29875	-.42029	.000
Uric Acid level - serum creatinine	2.60536	3.26779	2.10761	3.10310	.000
Uric Acid level - eGFR value	-15.03929	12.69802	-16.97343	-13.10515	.000

Discussion:

The occurrence of raised levels of serum uric acid (Hyperuricemia) and CKD (chronic kidney disease) has been rising steadily. It is still uncertain about the role of raised uric acid levels and hypouricemicagents in the progression of CKD. The current research was aimed to estimate the role of hyperuricemia and effectiveness of hypouricemic agents in chronic kidney disease progression. This research supported that increased levels of serum uric acid are related with a substantial instability in kidney function and an increased risk of renal failure progression. It is seen that raised levels of uric acid are associated with decrease in renal functions & increases the threat of CKD in patients with proteinuria in comparison to subjects without proteinuria. In the humans uric acid is the end metabolic purine product, uric acid is mainly excreted by kidneys and also has the antioxidant properties [23]

Hyperuricemia has been suggested to associate with various diseases Since the 19th century it is suggested that uric acid is associated with various ailments [24] The uric acid is not documented as an independent risk agent in the previously available literature. As the excretion of UA is by kidneys, in renal failure excretion of uric acid is decreased and thus causing hyperuricemia. The disease is thought to be deteriorated by the deposition of sodium urate in the interstitial. The causal association among uric acid and kidney disease has been contentious, though conflicting evidence has been proposed [25,26]

It is suggested by the writers that as uric acid exhibit a negative relationship, so it may be a predictive factor for evaluating nephron integrity. The current study and many other studies had been carried out to observe the UA; a risk element for chronic kidney ailment, but still the part of raised serum UA in progression of the chronic kidney disease remains contentious [12,27,31]. It had been assessed in subjects with diabetes mellitus, nephropathy (IgA), and renal transplantation that there is relationship amongst the raised levels of UA and the steady deterioration in kidney functions [21,32,35]

Numerous biotic actions have been related with uric acid [36]It plays an antioxidant role in the extracellular environment [37], that plays a key part in the neurologic diseases [38,39]. The immunity and proinflammatory pathways are also affected by uric acid. In immune system, the appreciation of apoptotic cells by dendritic cells and in the stimulation of CD8 cells may be facilitated by uric acid[40]The protein kinase and transcription of proinflammatory cytokines and chemokines are facilitated by increased concentrations of intracellular uric

acid and also incites proximal tubular dysfunction by releasing the inflammatory chemokines[9,41,42]Similarly, functions of uric acid are connected to several systems associated to the kidneys.

UA levels more or equal 70 mg/L (420 µmol/L) in male and 60 mg/L (360 µmol/L) in females is defined as hyperuricemia. It is observed in many studies that hyperuricemia is a risk agent of CKD progression. Current available data draw a parallel relationship of raised levels of serum uric acid with CKD, hypertension (arterial), and cardio-vascular ailments, therefore favoring role of preventive treatment in the avoidance of kidney ailments.

In this article there was a large difference in the reference point characters, and a few of variables acted as confounders, such as gender, age and value of serum UA at base line. Furthermore a number of agents were correlated with increased values of UA including many foods & medicines. This analysis dose not fully reflects the all aspects due to limitation of statistics. Also the number of subjects taking the medicine was smaller in comparison to the subjects with hyperuricemia. So the statistical significance could not be established in current research. To determine the effect of hypouricemic agents on chronic kidney disease progression further more studies are required.

Conclusions:

Current study analyzed that increased levels of serum uric acid were significantly related with a noteworthy damage in kidney functions and a high risk agent for progress of the CKD in Pakistani populace. Effect of the increased levels of serum UA on impairing the renal function and progress to renal failure was high in in study subjects. It is concluded that hyperuricemia is a prospective changeable risk agent for progress of chronic kidney disease.

Refferences:

1. Miyaoka T[1], Mochizuki T, Takei T, Tsuchiya K, Nitta K. Serum uric acid levels and long-term outcomes in chronic kidney disease. Heart Vessels. 2014 Jul;29(4):504-12. doi: 10.1007/s00380-013-0396-0. Epub 2013 Aug 9.
2. Carney EF. Epidemiology: Global Burden of Disease Study 2013 reports that disability caused by CKD is increasing worldwide. Nature reviews Nephrology. 2015;11(8):446. Epub 2015/06/24. [PubMed] [Google Scholar]
3. Odden MC, Amadu AR, Smit E, Lo L, Peralta CA. Uric acid levels, kidney function, and cardiovascular mortality in US adults: National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 1999–2002. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2014;64(4):550–7. Epub 2014/06/08. PubMed Central PMCID: PMC4177300. [PMC free article] [PubMed] [Google Scholar]
4. Nashar K, Fried LF. Hyperuricemia and the progression of chronic kidney disease: is uric acid a marker or an independent risk factor?Advances in chronic kidney disease. 2012;19(6):386–91. Epub 2012/10/24. 10.1053/j.ackd.2012.05.004 [PubMed] [CrossRef] [Google Scholar]
5. Sanchez-Lozada LG, Tapia E, Avila-Casado C, Soto V, Franco M, Santamaria J, et al. Mild hyperuricemia induces glomerular hypertension in normal rats. American journal of physiology Renal physiology. 2002;283(5):F1105–10. Epub 2002/10/10. 10.1152/ajprenal.00170.2002 [PubMed] [CrossRef] [Google Scholar]
6. Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney international. 2005;67(1):237–47. Epub 2004/12/22.

10.1111/j.1523-1755.2005.00074.x [PubMed] [CrossRef] [Google Scholar]

7. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. American journal of physiology Renal physiology. 2002;282(6):F991–7. Epub2002/05/09. 10.1152/ajprenal.00283.2001 [PubMed] [CrossRef] [Google Scholar]
8. Sanchez-Lozada LG, Tapia E, Soto V, Avila-Casado C, Franco M, Zhao L, et al. Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricaemia. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2008;23(4):1179–85. Epub 2007/12/01. [PubMed] [Google Scholar]
9. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. Journal of the American Society of Nephrology: JASN. 2002;13(12):2888–97. Epub 2002/11/22. [PubMed] [Google Scholar]
10. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: A systematic review and meta-analysis based on observational cohort studies. BMC nephrology. 2014;15:122Epub 2014/07/30. PubMed Central PMCID: PMC4132278. 10.1186/1471-2369-15-122 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Nacak H, van Diepen M, Qureshi AR, Carrero JJ, Stijnen T, Dekker FW, et al. Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2015. Epub 2015/07/18. [PMC free article] [PubMed] [Google Scholar]
12. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, et al. Uric acid and long-term outcomes in CKD. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2009;53(5):796–803. Epub 2009/03/24. PubMed Central PMCID: PMC2691553. [PMC free article] [PubMed] [Google Scholar]
13. Liu WC, Hung CC, Chen SC, Yeh SM, Lin MY, Chiu YW, et al. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. Clinical journal of the American Society of Nephrology: CJASN. 2012;7(4):541–8. Epub 2012/02/04. 10.2215/CJN.09420911 [PubMed] [CrossRef] [Google Scholar]
14. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F, Group MS. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. Experimental gerontology. 2008;43(4):347–52. Epub 2008/02/26. 10.1016/j.exger.2008.01.006 [PubMed] [CrossRef] [Google Scholar]
15. Nacak H, van Diepen M, de Goeij MC, Rotmans JI, Dekker FW, group P-s. Uric acid: association with rate of renal function decline and time until start of dialysis in incident pre-dialysis patients. BMC nephrology. 2014;15:91Epub 2014/06/19. PubMed Central PMCID: PMC4075499. 10.1186/1471-2369-15-91 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

16. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2006;47(1):51–9. Epub 2005/12/27. [PubMed] [Google Scholar]
17. Goicoechea M, Garcia de Vinuesa S, Verdalles U, Verde E, Macias N, Santos A, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2015;65(4):543–9. Epub 2015/01/18. [PubMed] [Google Scholar]
18. Bose B, Badve SV, Hiremath SS, Boudville N, Brown FG, Cass A, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2014;29(2):406–13. Epub 2013/09/18. [PubMed] [Google Scholar]
19. Gibson T, Rodgers V, Potter C, Simmonds HA. Allopurinol treatment and its effect on renal function in gout: a controlled study. Annals of the rheumatic diseases. 1982;41(1):59–65. Epub 1982/02/01. PubMed Central PMCID: PMC1000865. [PMC free article] [PubMed] [Google Scholar]
20. Momeni A, Shahidi S, Seirafian S, Taheri S, Kheiri S. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. Iranian journal of kidney diseases. 2010;4(2):128–32. Epub 2010/04/21. [PubMed] [Google Scholar]
21. Shi Y, Chen W, Jalal D, Li Z, Chen W, Mao H, et al. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. Kidney & blood pressure research. 2012;35(3):153–60. Epub 2011/11/26. PubMed Central PMCID: PMC3242707. [PMC free article] [PubMed] [Google Scholar]
22. Yamanaka, H. & Metabolism, T. G. Essence of the revised guideline for the management of hyperuricemia and gout. *Japan Medical Association journal: JMAJ***55**, 324–329 (2012)
23. Becker, B. F. Towards the physiological function of uric acid. *Free radical biology & medicine***14**, 615–631 (1993).
24. Kohn, P. M. &Prozan, G. B. Hyperuricemia; relationship to hypercholesteremia and acute myocardial infarction. *Journal of the American Medical Association***170**, 1909–1912 (1959)
25. Berger, L. & Yu, T. F. Renal function in gout. IV. An analysis of 524 gouty subjects including long-term follow-up studies. *The American journal of medicine***59**, 605–613 (1975).
26. Kumagai T, Ota T, Tamura Y, Chang WX, Shibata S, Uchida S. Review Time to target uric acid to retard CKD progression. ClinExpNephrol. 2017 Apr; 21(2):182-192.[PubMed] [Ref list]
27. Srivastava, A., Kaze, A. D., McMullan, C. J., Isakova, T. &Waikar, S. S. Uric Acid and the Risks of Kidney Failure and Death in Individuals With CKD. *American journal of kidney diseases: the official journal of the National Kidney Foundation***71**, 362–370, https://doi.org/10.1053/j.ajkd.2017.08.017 (2018).
28. 28 Weiner, D. E. *et al*. Uric acid and incident kidney disease in the community. *Journal of the American Society of Nephrology: JASN***19**, 1204–1211, https://doi.org/10.1681/asn.2007101075 (2008).

29. Krishnan, E. *et al.* Serum urate and incidence of kidney disease among veterans with gout. *The Journal of rheumatology***40**, 1166–1172, https://doi.org/10.3899/jrheum.121061 (2013).
30. Chini, L. S. N., Assis, L. I. S. &Lugon, J. R. Relationship between uric acid levels and risk of chronic kidney disease in a retrospective cohort of Brazilian workers. *Brazilian journal of medical and biological research = Revistabrasileira de pesquisasmedicas e biologicas***50**, e6048, https://doi.org/10.1590/1414-431x20176048 (2017).
31. Chonchol, M. *et al.* Relationship of uric acid with progression of kidney disease. *American journal of kidney diseases: the official journal of the National Kidney Foundation***50**, 239–247, https://doi.org/10.1053/j.ajkd.2007.05.013 (2007).
32. Ficociello LH, Rosolowsky ET, Niewczas MA, Maselli NJ, Weinberg JM, Aschengrau A, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. Diabetes care. 2010;33(6):1337–43. Epub 2010/03/25. PubMed Central PMCID: PMC2875450. 10.2337/dc10-0227 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. Altemtam N, Russell J, El Nahas M. A study of the natural history of diabetic kidney disease (DKD). Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2012;27(5):1847–54. Epub 2011/11/08. [PubMed] [Google Scholar]
34. Syrjanen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association—European Renal Association. 2000;15(1):34–42. Epub 1999/12/23. [PubMed] [Google Scholar]
35. Ohno I, Hosoya T, Gomi H, Ichida K, Okabe H, Hikita M. Serum uric acid and renal prognosis in patients with IgA nephropathy. Nephron. 2001;87(4):333–9. Epub 2001/04/05. [PubMed] [Google Scholar]
36. Viggiano, D. *et al.* Urate-Lowering Agents in Asymptomatic Hyperuricemia: Role of Urine Sediment Analysis and Musculoskeletal Ultrasound. *Kidney & blood pressure research***43**, 606–615, https://doi.org/10.1159/000489145 (2018).
37. Ames, B. N., Cathcart, R., Schwiers, E. & Hochstein, P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proceedings of the National Academy of Sciences of the United States of America***78**, 6858–6862 (1981).
38. Hooper, D. C. *et al.* Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. *Proceedings of the National Academy of Sciences of the United States of America***95**, 675–680 (1998).
39. Justicia, C. *et al.* Uric Acid Is Protective After Cerebral Ischemia/Reperfusion in Hyperglycemic Mice. *Translational stroke research***8**, 294–305, https://doi.org/10.1007/s12975-016-0515-1 (2017).
40. Shi, Y., Evans, J. E. & Rock, K. L. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature***425**, 516–521, https://doi.org/10.1038/nature01991 (2003).
41. Lanaspa, M. A. *et al.* Uric acid induces hepatic steatosis by generation of

mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *The Journal of biological chemistry***287**, 40732–40744, https://doi.org/10.1074/jbc.M112.399899 (2012).

42. Roncal, C. A. *et al.* Effect of elevated serum uric acid on cisplatin-induced acute renal failure. American journal of physiology. *Renal physiology***292**, F116–122, https://doi.org/10.1152/ajprenal.00160.2006 (2007).