

CrossMark  
click for updates

## An update on allopurinol and kidney failure; new trend for an old drug

Amirhesam Alirezaei<sup>1</sup>, Hassan Argani<sup>1\*</sup>, Masoumeh Asgharpour<sup>2</sup>, Ayad Bahadorimonfared<sup>3</sup>, Mahmood Bakhtiyari<sup>4,5</sup>

<sup>1</sup>Clinical Research and Development Center at Shahid Modarres Hospital, Department of Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Nephrology, Rouhani Hospital of Medical Sciences, Babol, Iran

<sup>3</sup>Department of Health & Community Medicine, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>4</sup>Department of Community Medicine, School of Medicine, Alborz University of Medical Sciences, Karaj, Iran

<sup>5</sup>Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

### ARTICLE INFO

#### Article Type:

Review

#### Article History:

Received: 28 April 2017

Accepted: 10 September 2017

Published online: 29 September 2017

#### Keywords:

Allopurinol, Free radicals, Hyperuricemia, Renal ischemia, Nephrotoxicity, Contrast-induced nephropathy/injury

### ABSTRACT

Allopurinol is an inhibitor of xanthine oxidase (XO) enzyme. This drug is a reducer of uric acid in the body and one of the golden drugs with worldwide administration. XO is an important biological source of free radical generation. Allopurinol as an antioxidant, has direct and indirect antioxidant activity on these free radicals such as hydroxyl radical and superoxide anion. The purpose of this paper is to determine the impact of allopurinol on some aspects of renal disturbances such as renal ischemia/reperfusion injury (IRI), nephrotoxicity and contrast-induced nephropathy (CIN).

#### Implication for health policy/practice/research/medical education:

Findings of this review show that treatment with allopurinol as a purine inhibitor of xanthine oxidase enzyme can decrease oxidative stress and uric acid levels and may help to restore the endothelial function and slow down the progression of renal disorder to end stage renal disease.

*Please cite this paper as:* Alirezaei A, Argani H, Asgharpour M, Bahadorimonfared A, Bakhtiyari M. An update on allopurinol and kidney failure; new trend for an old drug. J Renal Inj Prev. 2017;6(4):297-302. DOI: 10.15171/jrip.2017.57.

### Introduction

Uric acid is the end-product of the purine catabolic pathway. The enzyme xanthine oxidoreductase (XOR) is involved in formation of uric acid from hypoxanthine and xanthine. The XOR exists in two distinct functional forms including xanthine dehydrogenase and xanthine oxidase (XO) (1). Allopurinol or 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one, is a purine inhibitor of the enzyme XO. This substance as an important drug for hyperuricemia can inhibit the synthesis of uric acid. Since 50 years ago, it has been administered in the treatment of gout (2). In 1946, allopurinol was developed by Elion

and colleagues, at the Burroughs-Wellcome Company (3). Allopurinol is quickly oxidized by XO to hypoxanthine and xanthine, respectively. Moreover, allopurinol at low concentrations is competitive inhibitor of the XO and at higher concentrations is a noncompetitive inhibitor of this enzyme. Allopurinol after oral administration is rapidly absorbed and has a short half-life in plasma (about 2-3 hours) (4). XO is a significant biological source of free radical generation and allopurinol, as an antioxidant, has direct and indirect antioxidant activity on these free radicals. Furthermore, it can scavenge free radicals such as hydroxyl radical and superoxide anion and numerous



\*Corresponding author: Hassan Argani, Email: hassanargani@hotmail.com

studies have shown these effects of allopurinol (5). Oxidative tissue damage after the ischemic diseases such as renal IRI (ischemia/reperfusion injury) is related to the XO and using allopurinol can reduce the renal ischemia-induced oxidative tissue damage (6). Besides the role of XO in hyperuricemia in the past two decades, renal ischemic and various types of tissue injuries, inflammatory diseases and chronic and acute renal failure has been studied extensively. Allopurinol revealed beneficial effects in the treatment of some renal disorders both in experimental and clinical trials (4). The goal of this paper is to give comprehensive information about positive and negative therapeutic effects of allopurinol as an antioxidant agent in some diseases including hyperuricemia, renal IRI, nephrotoxicity and contrast-induced nephropathy (CIN).

### Materials and Methods

For this review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; allopurinol, free radicals, hyperuricemia, renal ischemia, nephrotoxicity, contrast-induced nephropathy, hydroxyl radical, ischemia/reperfusion injury, antioxidant, uric acid and xanthine oxidase. Manuscripts published in English as full-text articles and or as abstracts were included in the study.

### Allopurinol and hyperuricemia

About two-thirds of uric acid is eliminated by the kidneys and one-third is excreted via the gastrointestinal tract (7). Hyperuricemia is a term describing abnormal high level of uric acid in the blood ( $>6.0$  mg/dL in female and  $>7.0$  mg/dL in male individuals). Increase in level of serum uric acid is associated with various biological effects such as increased oxidative stress, platelet aggregation, high level of inflammatory markers and endothelial dysfunction (8). Hyperuricemia caused oxidative stress in patients with gout and treatment with 100 mg every 8 hours of allopurinol reduced oxidative stress and serum uric acid after 1 and 3 months. In these patients after treatment, the level of serum malondialdehyde, as a marker of lipid peroxidation, was significantly decreased and erythrocyte superoxide dismutase and erythrocyte catalase levels were significantly increased (5). Additionally, hyperuricemia is related to declining glomerular filtration rate (GFR) and progression of chronic kidney disease (CKD) and acute kidney injury (AKI) in different disease states (9). Hyperuricemia and GFR decline was shown in 40% to 60% of patients with CKD stages I to III and 70% of patients with CKD stages IV or V (7). Hyperuricemia could disturb endothelial function by increasing C-reactive protein, leukocytes, TNF- $\alpha$  and interleukins as inflammatory markers. Treatment with allopurinol (100 mg/d) decreased uric acid level in CKD patients and this effect caused a significant decrease in serum C-reactive protein level, and an increase in GFR. It also caused

progression of renal disorder in a prospective, randomized trial (10). A study on 30 patients with stage 2-4 CKD and serum uric acid level over 5.5 mg/dL reported that oral treatment of those patients with allopurinol (300 mg/d) for 3 months, significantly decreased the level of serum uric acid from  $7.9 \pm 1.6$  mg/dL to  $6.4 \pm 1.7$  mg/dL ( $P=0.001$ ) (9). In a prospective randomized controlled trial, 54 hyperuricemic patients with mild to moderate CKD received allopurinol (100 to 300 mg/d) for 12 months and at the end of follow-up the levels of serum uric acid were significantly decreased (11).

Hyperuricemia accelerates diabetic kidney injury induced by streptozotocin. Treatment with allopurinol (10 mg/kg) regulated kidney urate transport-related proteins, reducing hyperuricemia and lipid metabolism-related genes to alleviate kidney lipid accumulation in streptozotocin-treated rats (12).

In a randomized parallel-controlled trial, the effect of long-term treatment (3 years) with allopurinol on 176 patients with type 2 diabetes and asymptomatic hyperuricemia was investigated. This article compared the changes in the levels of serum creatinine, GFR and urinary albumin excretion rate and incidence of hypertension and new-onset diabetic nephropathy in patients before and after 3 years of treatment with allopurinol between two groups. Allopurinol was effective in reducing the urinary albumin excretion rate, serum creatinine and serum uric acid. Additionally, it increased levels of GFR and declined the incidence of new-onset diabetic nephropathy and hypertension (13). Furthermore, administration of allopurinol for 3 months lowered uric acid and improved systemic inflammation and insulin resistance in asymptomatic hyperuricemia patients (14).

### Allopurinol and renal IRI

Renal IRI is an important causative factor for AKI and oxygen-free radicals are thought to play a key role in the pathogenesis of renal IRI. Excessive production of reactive oxygen species (ROS) elevates renal IRI through affecting the function of cellular DNA, lipids and proteins (3,15). XO, mitochondrial respiration chain and NADPH oxidase are involved in generation of ROS during IRI. Numerous studies showed the effect of various doses of allopurinol in kidney IRI and most of them reported that allopurinol was effective in attenuating renal damage induced by ischemia/reperfusion. Positive effects have been reported in ranging 3, 40, 50, 100 and 150 mg/kg of allopurinol and the most commonly used dose was 50 mg/kg (3). Summaries of allopurinol's effects against renal IRI are shown in Table 1.

In a recently published study, 30 rats were divided into five groups including 1) sham group, 2) renal IR control group, 3) allopurinol group, 4) apocynin group and 5) allopurinol and apocynin group. Rats were pretreated with allopurinol (50 mg/kg, i.p.) and apocynin (20 mg/kg, i.p.) alone as well as together. Treatment with allopurinol alone or in co-administration prevented IR-induced

**Table 1.** Allopurinol's effects against renal IRI

Year	Model	Duration of Treatment	Dosages	Effects	Ref.
1969	Dog	20 min after reperfusion	50 mg/kg	Positive impacts reported just for the combination of allopurinol and hypoxanthine drugs.	15
1972	Dog	30 min before ischemia and 48 h before ischemia and immediately after operation	100 and 120 mg/kg	Positive effects reported for pretreatment with 100 mg/kg and negative effect reported for 120 mg/kg.	16
1974	Dog	2 days before ischemia/reperfusion and the day of the experiment	50 mg/kg	Allopurinol reduced the renal injury-induced by IR.	17
1974	Rat	20 min before reperfusion	100 mg/kg	Significantly higher concentrations of adenosine triphosphate, adenosine diphosphate and adenosine monophosphate were showed in the kidneys of allopurinol-treated rats during ischemia and post-ischemic recovery.	18
1985	Rat	2 min before reperfusion	100 mg/kg	Inhibition of XO throughout reperfusion enhanced survival rates and reduced renal dysfunction after 45 minutes of ischemia.	19
1986	Rabbit	Immediately before renal ischemia/reperfusion	50 mg/kg	Pretreatment with allopurinol reduced serum creatinine and sodium excretion and returned the urine osmolality to normal level.	20
1989	Rat	35 min after ischemia and before reperfusion	40 mg/kg	Allopurinol reduced the post-ischemic kidney failure with a less significant increase of creatinine.	21
1994	Rabbit	10 min before ischemia	50 mg/kg	Allopurinol increased the activity of Na <sup>+</sup> /K <sup>+</sup> ATPase and was effective in predicting the results of the renal ischemic injury in hypoxic conditions and oxidant stress.	22
1995	Rat	5 min before ischemia	50 mg/kg	Treatment with allopurinol increased the rate of reperfusion of oxygenated blood that seen in control rats and improved the rate of tissue oxygenation during early reperfusion.	23
1995	Rat	Before and after ischemia	3 mg/kg	The necrotic area was significantly smaller and the activity of gamma-GTP in the kidney was higher in allopurinol group than in the enflurane group.	24
1996	Rat	5 min before reperfusion	50 mg/kg	Administration of allopurinol may be effective on antioxidant defenses against IRI of rat kidneys.	25
2002	Rat	5 h and 1 h before renal ischemia	50 mg/kg	Allopurinol attenuated tubular atrophy and interstitial fibrosis	26
2006	Rat	After reperfusion	40 mg/kg	Allopurinol was not protective against renal IR damage in spontaneously hypertensive rats.	27
2007	Rat	8 min before ischemia and 8 min before reperfusion	40 mg/kg	Allopurinol significantly attenuated production of nitric oxide by renal tissue.	28
2007	Dog	30 min before ischemia	100 mg/kg	Pre-ischemia administration of allopurinol abolished the hemorrhological changes including blood and plasma viscosity, relative cell transit time and fibrinogen level.	29
2012	Rat	5 min before reperfusion	100 mg/kg	Allopurinol protected the kidney from ischemic changes caused by clamping the renal hilum.	30
2012	Human	8 weeks before renal ischemia	150 mg/d	Improvement in endothelial dysfunction by treatment with allopurinol.	31
2013	Rat	Immediately before renal clamping	100 mg/kg	Allopurinol decreased isoprostane levels, to baseline levels and reduced reperfusion injury in rat kidneys	32
2015	Rat	1 h before the ischemia	50 mg/kg	Treatment with allopurinol alone or in co-administration with apocynin prevented IR-induced renal damage through lowering serum blood urea nitrogen, creatinine and malondialdehyde levels and increasing superoxide dismutase levels.	33

renal damage via lowering serum blood urea nitrogen, creatinine and malondialdehyde levels and increasing superoxide dismutase level (33).

Degradation products of lipid peroxidation can prevent enzymes such as Na<sup>+</sup>/K<sup>+</sup> ATPase, which is essential for maintaining cell viability and it is exceedingly sensitive to lipid peroxidation. The function of allopurinol is connected to protection of Na<sup>+</sup>/K<sup>+</sup> ATPase activity and so

it has protective ability against oxidative injury in kidneys (3). According to this ability, the collection of adenosine and its degradation by-products adenine nucleotides, xanthine and hypoxanthine inhibited by allopurinol and therefore, ATPase pump could operate adequately. Moreover, allopurinol by blocking the activation of NOD-like receptor 3 (NLRP3) inflammasome, which mediate inflammation in the development of renal injury in this

process, could decrease lipid accumulation in kidneys and reducing kidney damage. The activation of Na<sup>+</sup>/K<sup>+</sup> ATPase was low in ischemic and re-perfused kidney and treatment with allopurinol (50 mg/kg) increased the activity of this enzyme (3,22). Clamping of the renal hilum in rat significantly increased 8-isoprostane level as the real-time biomarker for renal ischemia. Keel et al demonstrated that the largest increase in 8-isoprostane level was occurred after 60 minutes of clamp time in rats and pretreatment with allopurinol (100 mg/kg) significantly decreased isoprostane level to baseline level (32).

### Allopurinol and nephrotoxicity

Nephrotoxicity by drugs is one of the most significant kidney problems and especially occurs when the body is exposed to more than one nephrotoxic drug (34,35). Cisplatin, as an antineoplastic drug with dose-dependent renal toxicity, is administered for the treatment of solid tumors. Kidneys accumulate cisplatin more than other organs of body and contribute to cisplatin-induced nephrotoxicity. It is well recognized that reactive oxygen species like singlet oxygen, hydroxyl radical and superoxide anion radical play a key role in the nephrotoxicity of some drugs such as cisplatin. The combination of allopurinol and ebselen reduced cisplatin-induced nephrotoxicity by reducing ROS generation and inhibiting XO (34). However, Erdinç et al investigated the effect of allopurinol (50 mg/kg/d) for 5 days on nephrotoxicity induced by a single dose of 5 mg/kg cisplatin in male albino rats. However, allopurinol was not able to inhibit cisplatin-induced lipid peroxidation in the kidney and severely augmented this nephrotoxicity (35). Similarly, Namikawa et al reported the same results about negative effects of allopurinol in this nephrotoxicity (36).

Gentamicin is an aminoglycoside antibiotic that can act against gram-negative infections, however, it has limited therapeutic utility due to nephrotoxicity (37). Gentamicin accumulates in renal proximal convoluted tubules, causing loss of its brush border integrity. It seems that allopurinol as OH<sup>-</sup> scavenger, can ameliorate the the formation of free radicals including hydroxyl and superoxide radicals that are involved in gentamicin induced acute renal tubular necrosis. Two studies reported that allopurinol was unable to protect gentamicin-induced renal toxicity in rats (37,38). Smyth et al revealed that, after oral treatment of rats with allopurinol (40 mg/kg) twice daily for 4 days, the alterations in serum gentamicin, serum creatinine, body weight, blood pressure, urinary N-acetyl-beta-D-glucosaminidase excretion and urinary output were equivalent in gentamicin with allopurinol and gentamicin only treatment groups (38).

### Allopurinol and contrast-induced renal toxicity

CIN is one of the most significant popular causes of hospital-acquired AKI and is defined as the impairment

of renal function and increase in serum creatinine of 0.5 mg/dL or 25% from baseline within 48-72 hours of intravenous contrast administration. CIN is detected in up to 50% of patients with pre-existing renal impairment and diabetic nephropathy and less than 2% of patients with normal renal function (39,40).

A randomized controlled clinical trial by Erol et al, in 2013, described the effectiveness of allopurinol pretreatment for prevention of CIN. In this study, 159 patients undergoing cardiac catheterization/interventions with stable serum creatinine levels  $\geq$ 1.1 mg/dL, received allopurinol (300 mg, p.o.) 24 hours before administration of contrast agent. In the allopurinol group, they showed that median serum creatinine concentration decreased significantly 4 days after radio contrast administration. On the other hand, allopurinol along with hydration reduced the prevalence of CIN in individuals with impaired kidney function (39). In another report in 2014, the patients received either of 3 drugs including saline hydration (1 mL/kg/h), allopurinol (300 mg/d) and N-acetylcysteine (600 mg bid) 12 hours before and after administration of contrast agent. Results of this article demonstrated that prophylactic oral administration of allopurinol along with hydration had protective effect against CIN in patients undergoing coronary procedures, even better than N-acetylcysteine and saline hydration alone (40).

### Conclusion

The role of XO in hyperuricemia, renal ischemic and various types of tissue injuries, chronic and acute renal failure has been studied extensively. Findings of this review showed that treatment with allopurinol as a purine inhibitor of XO enzyme could decrease oxidative stress and uric acid levels and might help to restore the endothelial function and slow down the progression of renal disorder to end stage renal disease. The results of many studies indicated that allopurinol was effective to attenuate hyperuricemia, renal damage induced by ischemia/reperfusion and CIN, although, some studies also reported the negative effects of allopurinol on nephrotoxicity induced by drugs including cisplatin and gentamicin. Further experimental and clinical investigations are necessary to estimate the positive effects of allopurinol on renal disorders especially nephrotoxicity.

### Authors' contribution

AHA, HA, MA, AB and MB searched the data. AHA and HA prepared the manuscript. All authors read and signed the final paper.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

### Conflicts of interest

The authors declared no competing interests.

**Funding/Support**

None.

**References**

1. Carro MD, Falkenstein E, Radke WJ, Klandorf H. Effects of allopurinol on uric acid concentrations, xanthine oxidoreductase activity and oxidative stress in broiler chickens. *Comp Biochem Physiol C Toxicol Pharmacol*. 2010;151:12-7.
2. Sun Y, George J, Rocha S. Dose-dependent effects of allopurinol on human foreskin fibroblast cells and human umbilical vein endothelial cells under hypoxia. *PLoS One*. 2015;10:e0123649. doi: 10.1371/journal.pone.0123649.
3. Prieto-Moure B, Carabén-Redaño A, Aliena-Valero A, Cejalvo D, Toledo AH, Flores-Bellver M, et al. Allopurinol in renal ischemia. *J Invest Surg*. 2014;27:304-16. doi: 10.3109/08941939.2014.911395.
4. Pacher P, Nivorozhkin A, Szabó C. Pharmacol Rev. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. *Pharmacol Rev*. 2006;58:87-114.
5. Acharya CR, Sharma AK, Kantharia ND. Involvement of oxidative stress in patients of gout and antioxidant effect of allopurinol. *Int J Med Sci Public Health*. 2015;4:168-172.
6. Augustin AJ, Böker T, Blumenröder SH, Lutz J, Spitznas M. Free radical scavenging and antioxidant activity of allopurinol and oxypurinol in experimental lens-induced uveitis. *Invest Ophthalmol Vis Sci*. 1994;35:3897-904.
7. Prasad Sah OS, Qing YX. Associations between hyperuricemia and chronic kidney disease: a review. *Nephrourol Mon*. 2015;7:e27233. doi: 10.5812/numonthly.7(3)2015.27233.
8. Joung KW, Jo JY, Kim WJ, Choi DK, Chin JH, Lee EH, Choi IC. Association of preoperative uric acid and acute kidney injury following cardiovascular surgery. *J Cardiothorac Vasc Anesth*. 2014;28:1440-7. doi: 10.1053/j.jvca.2014.04.020.
9. Bayram D, Tuğrul Sezer M, İnal S, Altuntaş A, Kızır V, Orhan H. The effects of allopurinol on metabolic acidosis and endothelial functions in chronic kidney disease patients. *Clin Exp Nephrol*. 2015;19:443-9.
10. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincón A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol*. 2010;5:1388-93.
11. 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. *Am J Kidney Dis*. 2006;47:51-9.
12. Wang C, Pan Y, Zhang QY, Wang FM, Kong LD. Quercetin and allopurinol ameliorate kidney injury in STZ-treated rats with regulation of renal NLRP3 inflammasome activation and lipid accumulation. *PLoS One*. 2012;7:e38285.
13. Liu P, Chen Y, Wang B, Zhang F, Wang D, Wang Y. Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin Endocrinol (Oxf)*. 2015;83:475-82.
14. Takir M, Kostek O, Ozkok A, Elcioglu OC, Bakan A, Ereğ A, et al. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. *J Investig Med*. 2015;63:924-9. doi: 10.1097/JIM.0000000000000242.
15. Crowell JW, Jones CE, Smith EE. Effect of allopurinol on hemorrhagic shock. *Am J Physiol*. 1969;216:744-8.
16. Vasko KA, DeWall RA, Riley AM. Effect of allopurinol in renal ischemia. *Surgery*. 1972;71:787-90.
17. Owens ML, Lazarus HM, Wolcott MW, Maxwell JG, Taylor JB. Allopurinol and hypoxanthine pretreatment of canine kidney donors. *Transplantation*. 1974;17:424-7.
18. Cunningham SK, Keaveny TV, Fitzgerald P. Effect of allopurinol on tissue ATP, ADP and AMP concentrations in renal ischaemia. *Br J Surg*. 1974;61:562-5.
19. Baker GL, Autor AP, Corry RJ. Effect of allopurinol on kidneys after ischemia and reperfusion. *Curr Surg*. 1985;42:466-9.
20. Hansson R, Johansson S, Jonsson O, Pettersson S, Scherstén T, Waldenström J. Kidney protection by pretreatment with free radical scavengers and allopurinol: renal function at recirculation after warm ischaemia in rabbits. *Clin Sci (Lond)*. 1986;71:245-51.
21. Marx A, Heberer M, Gale J, Landmann J. Reduction of renal reperfusion damage following warm ischemia by allopurinol and superoxide dismutase. *Helv Chir Acta*. 1989;56:539-42.
22. Aricioğlu A, Aydın S, Turkozkan N, Durmus O. The effect of allopurinol on Na+K+ATPase related lipid peroxidation in ischemic and reperfused rabbit kidney. *Gen Pharmacol*. 1994;25:341-4.
23. Vaughan DL, Wickramasinghe YA, Russell GI, Thorniley MS, Houston RF, Ruban E, Rolfe P. Is allopurinol beneficial in the prevention of renal ischaemia-reperfusion injury in the rat? Evaluation by near-infrared spectroscopy. *Clin Sci (Lond)*. 1995;88:359-64.
24. Sameshima T, Miyao J, Oda T, Minoda Y, Yoshida H, Yoshimura N. Effects of allopurinol on renal damage following renal ischemia. *Masui*. 1995;44:349-56.
25. Alataş O, Sahin A, Colak O, İnal M, Köken T, Yaşar B, Karahüseyinoglu E. Beneficial effects of allopurinol on glutathione levels and glutathione peroxidase activity in rat ischaemic acute renal failure. *J Int Med Res*. 1996;24:33-9.
26. Rhoden Teloken C, Lucas M, Rhoden C, Mauri M, Zettler C, et al. Protective effect of allopurinol in the renal ischemia-reperfusion in uninephrectomized rats. *Gen Pharmacol*. 2000;35:189-93.
27. Radovic M, Miloradovic Z, Popovic T, Mihailovic-Stanojevic N, Jovovic D, Tomovic M, et al. Allopurinol and enalapril failed to conserve urinary NOx and sodium in ischemic acute renal failure in spontaneously hypertensive rats. *Am J Nephrol*. 2006;26:388-99.
28. Tripatara P, Patel NS, Webb A, Rathod K, Lecomte FM, Mazzon E, et al. Nitrite-derived nitric oxide protects the rat kidney against ischemia/reperfusion injury in vivo: role for xanthine oxidoreductase. *J Am Soc Nephrol*. 2007;18:570-80.
29. Peto K, Nemeth N, Brath E, Takacs IE, Baskurt OK, Meiselman HJ, et al. The effects of renal ischemia-reperfusion on hemorheological factors: preventive role of allopurinol. *Clin Hemorheol Microcirc*. 2007;37:347-58.
30. Wang Z, Colli JL, Keel C, Bailey K, Grossman L, Majid D, et al. Isoprostane: quantitation of renal ischemia and

- reperfusion injury after renal artery clamping in an animal model. *J Endourol.* 2012;26:21-5.
31. Yelken B, Caliskan Y, Gorgulu N, Altun I, Yilmaz A, Yazici H, et al. Reduction of uric acid levels with allopurinol treatment improves endothelial function in patients with chronic kidney disease. *Clin Nephrol.* 2012;77:275-82.
  32. Keel CE, Wang Z, Colli J, Grossman L, Majid D, Lee BR. Protective effects of reducing renal ischemia-reperfusion injury during renal hilar clamping: use of allopurinol as a nephroprotective agent. *Urology.* 2013;81:210.e5-10.
  33. Choi EK, Jung H, Kwak KH, Yeo J, Yi SJ, Park CY, et al. Effects of Allopurinol and Apocynin on Renal Ischemia-Reperfusion Injury in Rats. *Transplant Proc.* 2015;47:1633-8. doi: 10.1016/j.transproceed.
  34. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. *Am J Med Sci.* 2007;334:115-24.
  35. Erdiñç M, Erdiñç L, Nergiz Y, Işık B. Potentiation of cisplatin-induced nephrotoxicity in rats by allopurinol. *Exp Toxicol Pathol.* 2000;52:329-34.
  36. Namikawa K, Hirai K, Kitano T, Tanaka I, Miyauchi K, Minami T, et al. Effects of allopurinol for oxidative injury of cisplatin-induced nephrotoxicity in mice. *Yakugaku Zasshi.* 1999;119:936-44.
  37. Ulutas B, Kiral F, Birincioglu S. Unable to protect gentamicin-induced nephrotoxicity with allopurinol in rats. *Ankara Universitesi Veteriner Fakultesi Derg.* 2006; 53:65-68.
  38. Smyth BJ, Davis WG. Allopurinol fails to protect against gentamicin-induced renal damage in normotensive and spontaneously hypertensive rats. *Nephron.* 1994;68:468-72.
  39. Erol T, Tekin A, Katırcıbaşı MT, Sezgin N, Bilgi M, Tekin G, et al. Efficacy of allopurinol pretreatment for prevention of contrast-induced nephropathy: a randomized controlled trial. *Int J Cardiol.* 2013;167:1396-9. doi: 10.1016/j.ijcard.2012.04.068.
  40. Kumar A, Bhawani G, Kumari N, Murthy KS, Lalwani V, Raju ChN. Comparative study of renal protective effects of allopurinol and N-acetyl-cysteine on contrast induced nephropathy in patients undergoing cardiac catheterization. *J Clin Diagn Res.* 2014;8:HC03-7. doi: 10.7860/JCDR/2014/9638.5255.

**Copyright** © 2017 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.