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Uric acid – a renal and non-renal risk factor

Kwas moczowy – nerkowy i nienerkowy czynnik ryzyka

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Summary

As human beings are deprived of uricase, the final metabolite of purines is uric acid and not allantoin. This metabolite was the subject of scientific interest predominantly in patients with hereditary or acquired forms of gout respectively. In the last years uric acid became an important pathogenetic factor involved not only in accelerating progression of different acute and chronic nephropathies but also as a cardiovascular toxin involved in the pathogenesis of arterial hypertension, vascular injury, heart failure and abnormalities of carbohydrate metabolism. These facts were the reason why inhibition of uric acid synthesis became an important therapeutic target. This interest rose even more when the presence of a metabolic link between uric acid and fructose (which is assumed to be a cardiovascular toxin) was proven.

This review is summarizing our contemporary knowledge about uric acid as a culprit of cardiovascular and renal events and as a target of therapeutic intervention.

Key words: uric acid, renal and extrarenal complication, therapeutic events

Streszczenie

Niedobór urykazy u człowieka sprawia, że produktem końcowym przemiany zasad purynowych jest nie alantoina, lecz kwas moczowy. Ten metabolit był przedmiotem intensywnych badań głównie u chorych z wrodzoną lub nabytą skazą dna. W ostatnich latach wykazano, że kwas moczowy jest ważnym winowajcą poważnych powikłań sercowo-naczyniowych (nadciśnienie tętnicze, miażdżyca naczyń), ale i nerkowych (przyspieszenie progresji różnych nefropatii) i metabolicznych (aberracje gospodarki węglowodanowej). Powyższe fakty sprawiły, że zahamowanie syntezy kwasu moczowego stało się ważną tarczą terapeutyczną. Zainteresowanie kwasem moczowym wzrosło jeszcze bardziej, kiedy wykazano występowanie metabolicznego jego związku z fruktozą uważaną za związek kardio- i waskulotoksyczny.

Przedstawiona praca jest podsumowaniem współczesnej wiedzy dotyczącej patogenetycznych i leczniczych aspektów urykemii.

Słowa kluczowe: kwas moczowy, efekty nerkowe i pozanerkowe, aspekty lecznicze

WHAT IS THE EVIDENCE FOR URIC ACID AS A RENAL RISK FACTOR?

Hyperuricemia may be the result of uric acid overproduction or diminished renal uric acid excretion (and as recently suggested apart from renal perhaps also non-renal urate excretion) (1).

Overproduction may be the result of genetic disease, e.g. HGPRT mutation (hypoxanthine-guanine phosphoribosyltransferase) or PRPPS mutations (phosphoribosyl-pyrophosphate synthase). Acquired conditions are myeloproliferative or lymphoproliferative disease and most frequently dietary causes interacting with genetic background.

Diminished renal excretion of urate may be caused by primary nephropathies causing renal failure or be

caused by genetic variants of urate transporters; recent genome-wide association analyses (Köttgen, Nature Genetics, in press) had identified a number of loci coding for tubular reabsorption which are associated with elevated serum urate concentrations.

In the past lead intoxication was an important cause of elevated urate concentration, but this has virtually disappeared in Mid Europe.

Cases of familial hereditary disease causing hyperuricemia, e.g. familial juvenile hyperuricemic nephropathy type 1 (FJHN2), medullary cystic renal disease type 2 (MCKD2) or glomerulocystic renal disease are associated with progressive renal failure. There is currently uncertainty whether in these genetic diseases caused by urate transporter mutations Allopurinol

causes less progression of renal function by reducing serum uric acid concentration (2, 3).

Urate and chronic kidney disease (CKD)

In the past, there had been discussions whether elevated serum uric acid concentration in chronic kidney disease (CKD) is pathogenetically irrelevant or whether it contributes to progressive reduction of renal function. The causal function of uric acid in mediating progression of CKD had been clearly documented in the remnant kidney model by Kang (4). One recently identified mechanism is uric acid induced epithelial to mesenchymal transition (Ryu, *Am. J. Physiol. Renal*, 2013 (e-pub).

Today, there is also increasing clinical evidence that uric acid concentrations (even within the range of normal concentrations) actively promote loss of renal function. Therefore current studies evaluate whether uric acid is a novel target for therapeutic intervention. On the one hand there is strong observational evidence that urate is a factor contributing to onset and progression of CKD: for instance in a recent 10.2 year follow-up study uric acid was a significant risk factor for CKD, at least in males, for individuals in the fourth quartile of serum uric acid concentration the risk of CKD was significantly ($p < 0.0001$) increased by a factor of 2.1 (5). Similarly a study in Taiwan (6) – confirmed in Thailand (Satirapoj, *Nephrology*, Carlton; in press) – showed that the risk of onset of chronic kidney disease is significantly increased by a factor of 1.03 (95% CI 1.1-1.6) per > 1 mg/dl higher serum uric acid concentration. In a health check-up study by Yamada (7) the onset of CKD was progressively higher from the first to the fourth quartile of serum urate concentration (1.00; 1.85; 2.57; 3.54) in males and in females as well. In cross-sectional studies, uric acid concentration is also correlated to the presence of CKD (8) and furthermore an increase of plasma uric acid concentration is correlated to the decrease of renal function, i.e. progression of CKD as shown in a prospective cohort study; in the 4th quartile, the adjusted odds ratio was higher by a factor of 2.86 and uric acid increase > 1 mg/dl was associated with a risk of CKD higher by 1.63 (CI 1.25-2.12) (9).

Apart from all-cause CKD, hyperuricemia has also been identified as a risk factor for progression of primary kidney diseases, e.g. IgA glomerulonephritis (10). The role of uric acid concentration in the progression of IgA-GN was underlined by a biopsy study: no deterioration of renal function was seen in the patients with a serum uric acid concentration < 7.5 mg/dl (11). In line with this observation indirect evidence suggests renal vasoconstriction triggered by uric acid in patients with IgA glomerulonephritis (12).

Furthermore a recent kidney biopsy study in 167 patients with CKD documented a significant correlation between tertiles of serum uric acid concentration and hyalinosis as well as wall thickening (13).

Similarly, serum uric acid concentration has been shown to predict the onset of diabetic nephropathy in individuals with type 1 diabetes (14) and was even a

predictor of the onset type 2 diabetes in the off-spring cohort of the Framingham heart study (15). This has also been documented in a 15-year follow-up study (1986-2001) by Krishnan (16): individuals with a serum uric acid concentration > 7 mg/dl had a hazard ratio (HR) of 1.94 to develop diabetes, HR 1.46 to develop insulin resistance, and HR 2.15 to develop pre-diabetes. In a 5-year follow-up study on 449 type 2 – diabetic individuals with normal renal function and no proteinuria at baseline Zoppini (17) documented that hyperuricemia, defined as > 7 mg/dl in men and > 6.5 mg/dl in women, increased the odds ratio of developing kidney disease by a factor of 2.55 (CI 1.71-3.85; $p < 0.001$).

An adverse effect of serum uric acid on kidney damage has also been documented in recipients of kidney transplants (18) and in patients at risk of acute kidney injury: Lapsia (19) found that progressively higher serum uric acid concentrations were associated with a progressively higher incidence of AKI.

It deserves mentioning that recent evidence documents that elevated uric acid concentration increases the risk of acute kidney injury (19, 20).

Urate nephropathy

Classical urate nephropathy was quite common in the distant past, but in Europe it has currently virtually disappeared. It is characterized by amorphous or spindle-shaped uric acid deposits surrounded by inflammatory infiltrates. This has been reproduced in animal experiments (21): infusion of uric acid caused an inflammatory reaction in the kidney with activation of the tubular NF $_{\kappa}$ B pathway.

Specific causes of elevated uric acid increase

Gout is one specific cause of renal failure as shown back in the 19th century. This form of renal disease has been brilliantly been described in the classical review of Barlow and Beilin (22). Fortunately this form of kidney disease has nowadays become very rare in Middle Europe.

Historically another frequent cause of CKD was lead intoxication. While in Mid Europe, stringent safety rules have led to virtual disappearance of clinically relevant lead intoxication, Krishnan (23) showed that in patients with gout, in the US moderately elevated serum lead concentrations are seen even today, implicating that there is no such a thing as a safe level of exposure to lead. It is wise to be vigilant and think of lead intoxication in unclear cases as shown by the recent observation of lead intoxication from lead contaminated marijuana (24).

High fructose corn syrup has recently become a major cause of elevated serum uric acid concentration particularly in young individuals. High fructose corn syrup (HFCS) in the USA – in the European Union called “glucose-fructose syrup” – is produced from starch which is enzymatically broken down to glucose, is exposed to xylose isomerase yielding a mixture of glucose and fructose. High fructose intake is associated

with a number of adverse sequelae: amongst others it interferes with appetite control signal systems, causes cell ATP depletion, triggers oxidative stress and inflammation, etc. The relevance of HFCS for uric acid concentration has recently again been confirmed by Ling (International Journal Obesity, London 2012; in press) in a study on 2.272 adolescents, 25% of whom consumed more than 500 ml/day of high fructose beverage. A significant correlation was seen between consumption of fructose containing drinks and elevated serum uric acid concentration.

Finally, medication may impact on serum uric acid concentration, e.g. beta-blockers, diuretics, NSIAD.

Does lowering of uric acid concentration retard progression of chronic disease?

In a post hoc meta-analysis of the RENAAL study Miao (25) analysed the impact of lowering of serum uric acid concentrations by Losartan in type 2 diabetic patients. The rationale for this analysis was the fact that Losartan inhibits uric acid reabsorption in the kidney thus lowering uric acid concentration. The hazard ratio for the occurrence of a renal endpoint was less in individuals in whom serum uric acid concentrations decreased while renal events were more frequent in individuals with increasing decreasing serum uric acid concentration. A recent meta-analysis (26), based on Medline, Cochrane library and Chinese biomedical literature, identified 11 papers and concluded that effective uric acid lowering treatment was associated with reduction of serum creatinine concentration with an increase of eGFR. It is true that in a short 6-months study in 40 of patients with IgA glomerulonephritis, treatment with Allopurinol 100-300 mg/day failed to affect eGFR (10), but this finding in a short-term study is not in line with some recent more extended studies also with more statistical power; e.g. Ito (27) found a significant difference of loss of GFR in patients treated with Losartan: patients in whom the decrease of serum uric acid was > 0.5 mg/dl compared to individuals with a decrease < 0.5 mg/dl the loss of eGFR was only 2.1 ± 17.2 ml/min/1.73 m² versus 6.3 ± 21.5 , $p < 0.001$. Currently the limited but best evidence is provided by the study of Goicoechea (28), a prospective controlled study in patients with chronic kidney disease who received Allopurinol (or who continued on treatment not impacting on serum uric acid). Treatment with Allopurinol was associated with significantly ($p = 0.018$) less decrease of eGFR and with a decrease of albuminuria ($p = 0.000$); there was also a reduction of cardiovascular events by 71% compared to standard therapy. The study is certainly underpowered, but the difference achieved is impressive and calls for further studies.

Currently, the main pharmacological interventions to lower serum uric acid concentrations are Allopurinol and Febuxostat.

Allopurinol (a xanthine-oxidase inhibitor) – the problem is that in rare, but dramatic cases, a Stevens-

-Johnsons syndrome may develop. The pre-disposition to this syndrome is mediated by the HLA-system (HLA-B*58:01) (29).

Febuxostat, a further xanthine-oxidase inhibitor has so far not been associated with the Stevens-Johnsons syndrome; it is more effective in patients with CKD as shown by Naoyuki (30).

The information on Febuxostat on renal function is still incomplete. More effective lowering of serum uric acid concentration has been documented by Becker (31) and the study of Schumacher (32) showed that in patients with normal as well as reduced renal function, a goal of < 6 mg/dl was achieved more frequently with Febuxostat than in patients treated with Allopurinol. In a multi-center open label comparative but extremely short-term study (33) no significant side effects were seen in patients with impaired renal function. In a randomized 12-week study of Hirawa compared Febuxostat with Allopurinol in patients with CKD 3-5; after two weeks the decrease of serum uric acid was similar with the two medications, but after 12 weeks, uric acid was 6.8 mg/dl on Febuxostat versus 8.1 mg/dl on Allopurinol ($p < 0.025$). No side effects were seen with Febuxostat. Unfortunately, dose response curves are not available.

In a post-hoc analysis of the “Febuxostat Urate Lowering Efficacy and Safety Study” (34) 116 hyperuricemic patients on Febuxostat were observed for 5 years. By mathematical modeling, the effect on serum uric acid concentration was related to the change in eGFR: The result showed that lowering of serum uric acid by 1 mg/dl increased on average eGFR by 1 ml/min in patients with – as opposed to patients without – treatment with Febuxostat. Whether lowering of serum uric acid is indeed efficacious to attenuate loss of GFR is still a matter of discussion. In patients with hereditary hyperuricemia, e.g. mutations of the uromodulin chain, loss of GFR was not affected by Allopurinol in hereditary hyperuricemia (35).

Three large trials comparing Febuxostat with Allopurinol are currently available (31, 32, 36). In the FACT trial Febuxostat was more effective in lowering uric acid concentration with no effect on tophi (31), in the APEX trial on patients with normal or moderately reduced renal function (eGFR > 30 ml/min/1.73 m²) again Febuxostat was more powerful in lowering s-uric acid concentrations and provoked no adverse effects in CKD patients. The CONFIRMIS trial (36) included specifically 65% patients with CKD; in patients with reduced renal function the target of < 6 mg/dl uric acid was reached more frequently (72%) with Febuxostat 80 mg/dl compared to Allopurinol 200 mg/day ($p < 0.001$). No major side effects were seen in CKD patients.

Hyperuricemia – beyond renal complications

We restrict this discussion to patients with CKD. In a brilliant overview, Johnson (37) had summarized the evidence that – in addition to the known role in renal disease – uric acid plays a pathogenetic role in the

genesis of hypertension and cardiovascular disease in general and specifically predicts cardiovascular events in advanced nephropathy (38): in 303 patients with CKD 3-5 in a 39-months study, lethal or non-lethal CV events were related by multivariate Cox regression analysis apart from diabetes and smoking also to uric acid. Both fatal (32 of 214 vs. 1 of 89 subjects) and combined fatal and nonfatal (100 of 214 vs. 13 of 89 subjects). Ito (27) showed that in patients with CKD and lowered eGFR cardiovascular events were significantly more frequent in individuals with serum uric acid > 7 mg/dl compared to < 7 mg/dl; at a eGFR 45-59 ml/min the relative risk was higher by a factor of 3.43.

In patients without renal impairment, the recent analysis of Loeffler (39) showed that in the NHANES survey in 6.036 juveniles (!) the odds ratio for elevated blood pressure per 0.1 mg/l uric acid was 1.38 (1.16-1.6;

$p < 0.01$); from the first to the fifth uric acid quintile, the odds ratio increased from 1.00 to 3.19 ($p < 0.001$). This finding indicates that uric acid, apart from being a well documented risk factor for CKD, is also a powerful cardiovascular risk factor.

CONCLUSIONS

While much information on the role of uric acid in kidney disease and potential underlying pathogenetic mechanisms has recently been provided by experimental studies and clinical observations, we still do not know whether the extremely suggestive relations in CKD patients are causal. This issue might certainly have important implications for patient management so that there is definitely an urgent need for proof of the concept by controlled clinical intervention studies in CKD patients.

BIBLIOGRAPHY

1. Ichida K, Matsuo H, Takada T et al.: Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 2012; 3: 764.
2. Warren DJ, Simmonds HA, Gibson T et al.: Familial gout and renal failure. *Arch Dis Child* 1981; 56(9): 699-704.
3. Gibson T: Hyperuricemia, gout and the kidney. *Curr Opin Rheumatol* 2012; 24(2): 127-131.
4. Kang DH, Nakagawa T, Feng L et al.: A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002; 13(12): 2888-2897.
5. Mok Y, Lee SJ, Kim MS et al.: Serum uric acid and chronic kidney disease: the Severance cohort study. *Nephrol Dial Transplant* 2012; 27(5): 1831-1835.
6. Wang S, Shu Z, Tao Q et al.: Uric acid and incident chronic kidney disease in a large health check-up population in Taiwan. *Nephrology (Carlton)* 2011; 16(8): 767-776.
7. Yamada T, Fukatsu M, Suzuki S et al.: Elevated serum uric acid predicts chronic kidney disease. *Am J Med Sci* 2011; 342(6): 461-466.
8. Jolly SE, Mete M, Wang H et al.: Uric acid, hypertension, and chronic kidney disease among Alaska Eskimos: the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. *J Clin Hypertens (Greenwich)* 2012; 14(2): 71-77.
9. Zhang L, Wang F, Wang X et al.: The association between plasma uric acid and renal function decline in a Chinese population-based cohort. *Nephrol Dial Transplant* 2012; 27(5): 1836-1839.
10. Shi Y, Chen W, Jalal D et al.: Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. *Kidney Blood Press Res* 2012; 35(3): 153-160.
11. Ohno I: Relationship between hyperuricemia and chronic kidney disease. *Nucleosides Nucleotides Nucleic Acids* 2001; 30(12): 1039-1044.
12. Sulikowska B, Johnson RJ, Odrowąż-Sypniewska G, Manitius J: Uric acid, renal vasoconstriction and erythropoietin relationship in IgA nephropathy revealed by dopamine-induced glomerular filtration response. *Kidney Blood Press Res* 2012; 35(3): 161-166.
13. Kohagura K, Kochi M, Miyagi T et al.: An association between uric acid levels and renal arteriopathy in chronic kidney disease: a biopsy-based study. *Hypertens Res* 2013; 36(1): 43-49.
14. Hovind P, Rossing P, Tarnow L et al.: Serum uric acid as a predictor for development of diabetic nephropathy in type 1 diabetes: an inception cohort study. *Diabetes* 2009; 58(7): 1668-1671.
15. Bhole V, Choi JW, Kim SW et al.: Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med* 2010; 123(10): 957-961.
16. Krishnan E, Pandya BJ, Chung L et al.: Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. *Am J Epidemiol* 2012; 176(2): 108-116.
17. Zoppini G, Targher G, Chonchol M et al.: Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. *Diabetes Care* 2012; 35(1): 99-104.
18. Haririan A, Metireddy M, Cangro C et al.: Association of serum uric acid with graft survival after kidney transplantation: a time-varying analysis. *Am J Transplant* 2011; 11(9): 1943-1950.
19. Lapsia V, Johnson RJ, Dass B et al.: Elevated uric acid increases the risk for acute kidney injury. *Am J Med* 2012; 125(3): 302.e9-17.
20. Ejaz AA, Kambhampati G, Ejaz NI et al.: Post-operative serum uric acid and acute kidney injury. *J Nephrol* 2012; 25(4): 497-505.
21. Zhou Y, Fang L, Jiang L et al.: Uric acid induces renal inflammation via activating tubular NF-kappaB signaling pathway. *PLoS One* 2012; 7(6): e39738.
22. Barlow KA, Beilin LJ: Renal disease in primary gout. *Q J Med* 1968; 37(145): 79-96.
23. Krishnan E, Lingala B, Bhalla V: Low-level lead exposure and the prevalence of gout: an observational study. *Ann Intern Med* 2012; 157(4): 233-241.
24. Busse FP, Fiedler GM, Leichtle A et al.: Lead poisoning due to adulterated marijuana. *N Engl J Med* 2008; 358(15): 1641-1642.
25. Miao Y, Ottenbros SA, Laverman GD et al.: Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. *Hypertension* 2011; 58(1): 2-7.
26. Wang H, Wei Y, Kong X, Xu D: Effects of Urate-Lowering Therapy in Hyperuricemia on Slowing the Progression of Renal Function: A Meta-Analysis. *J Ren Nutr* 2012; pii: S1051-2276(12)00172-0 (e-pub ahead of print).
27. Ito S, Naritomi H, Ogihara T et al.: Impact of serum uric acid on renal function and cardiovascular events in hypertensive patients treated with losartan. *Hypertens Res* 2012; 35(8): 867-873.

28. Goicoechea M, de Vinuesa SG, Verdalles U et al.: Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2011; 5(8): 1388-1393.
29. Jung JW, Song WJ, Kim YS et al.: HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant* 2011; 26(11): 3567-3572.
30. Naoyuki K, Shin F, Toshikazu H et al.: Placebo-controlled, double-blind study of the non-purine-selective xanthine oxidase inhibitor Febuxostat (TMX-67) in patients with hyperuricemia including those with gout in Japan: phase 3 clinical study. *J Clin Rheumatol* 2011; 17 (4 Suppl. 2): 19-26.
31. Becker MA, Schumacher HR Jr, Wortmann RL et al.: Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005; 353(23): 2450-2461.
32. Schumacher HR Jr, Becker MA, Wortmann RL et al.: Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008; 59(11): 1540-1548.
33. Tatsuo H, Iwao O: A repeated oral administration study of febuxostat (TMX-67), a non-purine-selective inhibitor of xanthine oxidase, in patients with impaired renal function in Japan: pharmacokinetic and pharmacodynamic study. *J Clin Rheumatol* 2011; 17 (4 Suppl. 2): 27-34.
34. Whelton A, Macdonald PA, Zhao L et al.: Renal function in gout: long-term treatment effects of febuxostat. *J Clin Rheumatol* 2011; 17(1): 7-13.
35. Schäffer P, Gombos E, Meichelbeck K et al.: Childhood course of renal insufficiency in a family with a uromodulin gene mutation. *Pediatr Nephrol* 2010; 25(7): 1355-1360.
36. Becker MA, Schumacher HR, Espinoza LR et al.: The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010; 12(2): 63.
37. Johnson RJ, Kang DH, Feig D et al.: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension* 2003; 41(6): 1183-1190.
38. Kanbay M, Yilmaz MI, Sonmez A et al.: Serum uric acid independently predicts cardiovascular events in advanced nephropathy. *Am J Nephrol* 2012; 36(4): 324-331.
39. Loeffler LF, Navas-Acien A, Brady TM et al.: Uric acid level and elevated blood pressure in US adolescents: National Health and Nutrition Examination Survey, 1999-2006. *Hypertension* 2012; 59(4): 811-817.

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