World Journal of Diabetes

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DOI: 10.4239/wjd.v5.i6.787

World J Diabetes 2014 December 15; 5(6): 787-795
ISSN 1948-9358 (online)

REVIEW

Linking uric acid metabolism to diabetic complications

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Received: August 31, 2014 Revised: October 22, 2014

Accepted: November 7, 2014

Published online: December 15, 2014

Abstract

Hyperuricemia have been thought to be caused by the ingestion of large amounts of purines, and prevention or treatment of hyperuricemia has intended to prevent gout. Xanthine dehydrogenase/xanthine oxidase (XDH/XO) is rate-limiting enzyme of uric acid generation, and allopurinol was developed as a uric acid (UA) generation inhibitor in the 1950s and has been routinely used for gout prevention since then. Serum UA levels are an important risk factor of disease progression for various diseases, including those related to lifestyle. Recently, other UA generation inhibitors such as febuxostat and topiroxostat were launched. The emergence of these novel medications has promoted new research in the field. Lifestyle-related diseases, such as metabolic syndrome or type 2 diabetes mellitus, often have a common pathological foundation. As such, hyperuricemia is often present among these patients. Many in vitro and animal studies have implicated inflammation and oxidative stress in UA metabolism and vascular injury because XDH/XO act as one of the major source of reactive oxygen species Many studies on UA levels and associated diseases implicate involvement of UA generation in disease onset and/or progression. Interventional studies for UA generation, not UA excretion revealed XDH/XO can be the therapeutic target for vascular injury and renal dysfunction. In this review, the relationship between UA metabolism and diabetic complications is highlighted.

Key words: Uric acid; Xanthine dehydrogenase/xanthine oxidase; Diabetes mellitus; Diabetic complications; Xanthine oxidase inhibitor; Metabolism

Core tip: Uric acid (UA) is derived from essential metabolism, and UA metabolism is becoming a novel risk and interventional factor of lifestyle-related diseases in this obesity-prone era. The relationship between UA metabolism and diabetic complications is highlighted in this review and supposed molecular mechanisms are mentioned.

Kushiyama A, Tanaka K, Hara S, Kawazu S. Linking uric acid metabolism to diabetic complications. *World J Diabetes* 2014; 5(6): 787-795 Available from: URL: http://www.wjgnet.com/1948-9358/full/v5/i6/787.htm DOI: http://dx.doi.org/10.4239/wjd.v5.i6.787

URIC ACID METABOLISM

Gout, which is caused by increased serum uric acid (SUA) levels, is becoming one of the most prevalent lifestyle-related diseases. According to the National Livelihood Survey in Japan, 874000 people go to hospital for gout in 2004. This constitutes an increase of 3.4 times compared with 1986. Higher prevalence of metabolic syndrome (MetS) is one possible cause for this increase in gout cases, as both the reduced excretion and increased production of UA have been suggested to be associated with MetS. Increased visceral adiposity also causes MetS. In mice, evidence exists that UA is secreted from bloated adipocytes[1]. No studies in humans have confirmed this finding yet.

Uric acid (UA) (2,6,8-trihydroxypurine, C5H4N4O3) is a purine derivative. UA metabolism is a type of nucleic acid metabolism metabolizing purine and its derivatives (adenine, and guanine). Phosphorus oxidation of adenine and guanine (resulting in ATP and GTP) and UA production are essential for many physiological functions. For example, high fructose consumption cause hyperuricemia.

FACTORS THAT DEFINE SERUM URIC ACID LEVELS

SUA levels are determined by a balance between UA production and excretion. At present, no method for detecting the UA production rate is available in humans. Instead, UA production are indirectly speculated through SUA level and urine excretion. The rate-limiting step of UA production is an enzymatic reaction of the xanthine dehydrogenase/xanthine oxidase (XDH/XO) enzyme that oxidizes hypoxanthine-xanthine into UA. Human XDH/XO was cloned in 1993 by Richard[2]. It is expressed in the liver and small intestine of XDH/XO-rich parenchyma cells[3] and is thought to be the major source for SUA. The enzyme is also expressed in adipose tissue, the vascular endothelium, and macrophages, all of which are implicated in lifestyle-related diseases[4]. The UA production rate is based on the amount of substrate and/or XO activity. Since the generation of reactive oxygen species (ROS) depends on XO activity, XO is one of the major sources of oxidative stress in cells along with nicotinamide adenine dinucleotide phosphate oxidase, myeloperoxidase, lipoxygenase, and nitric oxide synthase[5].

The kidney is an important regulator of circulating UA levels and is responsible for 60%-70% of total body UA excretion[6]. The remaining UA is secreted into the intestine, followed by bacterial uricolysis[6]. UA excretion in the kidney consists of urate secretion and reabsorption, and earlier research suggests the involvement of hyperfiltration[7]. UA apical transporters [uric acid transporter 1, organic anion transporter 4 (OAT4), OAT10, sodium-coupled monocarboxylate transporters 1/2, and Na^+-dicarboxylate cotransporter (NaDC1)], which are expressed in the nephron lumen are implicated in the reabsorption process. The role of basolateral transporters in proximal tubular cell is not clarified except for glucose transporter type 9 (GLUT9). During the secretion process, UA is transported into proximal tubular cells *via* OAT1/3 and/or NaDC3 and then secreted by human uric acid transporter, Na^+-phosphate cotransporter (NPT), ATP-binding cassette sub-family G member 2 (ABCG2), and/or ATP-binding cassette sub-family C member 4. Ninety percent of UA filtered by the kidney is reabsorbed[6]. In the intestine, ABCG2 is responsible for about 50% of UA efflux[8-10].

There are many studies about genetic variations exhibiting hyperuricemia. Among genes introduced above, variants of GLUT9 (SLC2A9)[11,12], NPT (SLC17A1)[13], ABCG2 (BCRP) variant[14], are well established and proved to be important in hyperuricemia as a result of decreased extra-renal urate excretion. Genome-wide association study is applied for detecting loci affecting serum UA level. Recent report identified 18 new loci (18 new regions in or near TRIM46, INHBB, SFMBT1, TMEM171, VEGFA, BAZ1B, PRKAG2, STC1, HNF4G, A1CF, ATXN2, UBE2Q2, IGF1R, NFAT5, MAF, HLF, ACVR1B-ACVRL1 and B3GNT4) associated UA concentrations[15]. Not only transporters, but also transcriptional factors, signaling receptors, enzymes are involved in serum UA level.

UA LEVELS IN TYPE 2 DIABETES MELLITUS AND METS

Table 1 shows association between life-style related diseases and UA metabolism[16-24]. Distinguishing cause and effect is difficult; some diseases raise SUA level, but UA affect disease onset or progression.

In patients with diabetes, the SUA level is low due to increased urate clearance[20,25]. In these patients, hypouricemia is associated with glycosuria[26], decreased metabolic control, hyperfiltration, and a late onset of disease, while elevated SUA is a feature of hyperinsulinemia or insulin resistance[7]. Type 2 diabetes mellitus (T2DM) is a risk factor for nephrolithiasis and has been associated with UA stones[27]. It has been suggested that patients with UA stones, especially if overweight, should be screened for T2DM or MetS[28]. The rate of obesity is increasing in Asia as well as in Western countries[29], and hyperuricemia will increase in patients with T2DM. Novel class of anti-diabetic agent, sodium glucose cotransporter 2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria[21,30].

T2DM ONSET AND UA LEVELS

Besides age, race, family history of diabetes, body mass index (BMI), glucose intolerance, and MetS, SUA levels have been suggested to be associated with T2DM risk[31]. If elevated SUA levels play a causal role in T2DM, SUA might also indirectly affect the prevalence of diabetic complications. The diabetogenic action of UA was reported in 1950[32]; however, its physiological mechanism is not yet known. SUA levels affect insulin resistance[19] and show a significant correlation with risk factors for MetS (high BMI, blood pressure, fasting plasma glucose, and triglyceride levels) and low HDL cholesterol values[19,31,33,34]. Moreover, high SUA levels were shown to predict MetS in a Japanese cohort[35]. We previously reported an association between inflammation, macrophage activation, and SUA production *via* XDH/XO activation in an animal model[36]. In summary, a link between SUA and insulin resistance has repeatedly been shown, and UA itself reportedly plays an important role in the exacerbation of insulin resistance[37].

Table 1 Association between life-style related diseases and uric acid metabolism

Diseases/status	SUA level	UA production	Focus 1	UA excresion	Focus 2
T2DM	High/low				
Glucosuria	Low			Up	Glomerulus
Insulin resistance	High			Down	Proximal tubule cell
Use of SGLT2 inhibitor	Low			Up	
Retinopathy		Up	Vitreus		
MetS	High	Up	Adipocyte/liver?	Down	Proximal tubule cell
CKD	High	Up	Vascular endothelial cell/inflammatory cell	Down/up	Kidney/intestine
Hypertension	High	Up			
Atherosclerosis		Up	Vascular endothelial cell/inflammatory cell		
Reperfusion injury		Up	Vascular endothelial cell		
Heart failure		Up	Inflammatory cell		
Fructose intake	High	Up	Liver	Down	
Sodium intake	High			Down	
Thiazide administration	High			Down	Proximal tubule cell

UA: Uric acid; SUA: Serum uric acid; T2DML: Type 2 diabetes mellitus; CKD: Chronic kidney disease; MetS: Metabolic syndrome.

DIABETIC COMPLICATIONS AND UA LEVELS

SUA independently predicted the development of vascular complications, both retinopathy and nephropahy and coronary artery calcification in type 1 diabetes study by Bjornstad *et al*[38]. The following section discusses the relationship between SUA levels and each diabetic complication.

Neuropathy

Diabetic neuropathy is occasionally the initial manifestation of disease in T2DM patients[39]. It leads to chronic pain, numbness, and substantial loss of quality of life. The prevalence of diabetic peripheral neuropathy shows a significant correlation with increased UA levels[40]. Several studies demonstrated that, when controlled for confounding factors such as age, gender, BMI, renal function, and/or diabetic duration, SUA levels were high in patients with diabetic polyneuropathy and sudomotor dysfunction[41-43].

The pathophysiology of diabetic neuropathy is not completely understood, and multiple metabolic imbalances underlie the development of diabetic neuropathy[44]. Hyperglycemia, dyslipidemia, and cardiovascular dysfunction are all independent risk factors for neuropathy. Probable etiologic factors include the polyol pathway, non-enzymatic glycation, free radicals, oxidative stress, and inflammation. Oxidative stress and inflammation are involved in XDH/XO activity. It is therefore speculated that UA generation by XDH/XO plays a role in diabetic neuropathy.

Diabetic retinopathy

The presence of diabetic retinopathy (DR) is associated with visceral fat accumulation and insulin resistance in T2DM patients[45]. An earlier report found no significant difference in UA levels between patients with or without retinopathy[46], but several recent studies showed a significant increase of UA-related metabolites levels in DR compared to T2DM[47]. SUA concentration was shown to be associated with an increased severity of DR over a three-year period in patients with T2DM. Cox regression analysis showed that patients with SUA levels in the third (5.9-6.9 mg/dL) and fourth ($\geq$ 7.0 mg/dL) quartiles had increased hazard ratios for DR when compared with patients with SUA in the first quartile ($<$ 4.9 mg/dL)[48]. Furthermore, vitreous UA and glucose concentrations were higher in proliferative than in non-proliferative DR. Focal UA production in the vitreous is thought to be involved in the pathogenesis and progression of DR[49].

Nephropathy

Shichiri *et al*[50] showed that glomerular hyperfiltration also occurs in non-insulin-dependent diabetes mellitus (NIDDM) and that it lowers SUA levels by increasing the renal clearance of urate during the hyperfiltration phase[50]. They suggested that hypouricemia can predict the future progression of incipient nephropathy in NIDDM[50]. However, other reports have implied that high (and not low) SUA levels define the prognosis of chronic kidney disease (CKD)[51]. SUA is also associated with known risk factors for kidney disease progression[52], including hypertension[53], cardiovascular disease[54-56], and atherosclerosis[55]. SUA is an independent risk factor for CKD, even without diabetes[57].

SUA is known to be associated with disease progression in the early stage of diabetic nephropathy[17,58]. We found that the progression of renal dysfunction in patients with type 2 diabetic overt nephropathy with an SUA concentration of $\geq$ 6.3 mg/dL carries a poor prognosis, even though their SUA range is considered high-normal[59]. Our data shows the association between UA and disease progression is independent of diabetic control in multivariate analysis. Another report provided evidence for a clear dose-response relationship between SUA levels and early glomerular filtration rate (GFR) loss in patients with T1DM. The progression and regression of urinary albumin excretion were not associated with UA levels[60]. These studies show that UA is an in-

dependent risk factor for renal dysfunction, even after adjustments for confounding factors. Furthermore, even high-normal SUA levels accelerated renal dysfunction in T2DM patients[17,59-62].

UA is lowered in diabetes mellitus (DM) due to hyperfiltration[50], but decreased UA excretion during renal dysfunction raises SUA levels. Our previous study showed that UA levels in the patients who doubled Cr in the observation period (Cr doubling group) were higher than in the non-doubling group at the same estimated GFR (eGFR) level, suggesting that UA production was increased in the Cr doubling group[59]. These data suggest that higher levels of UA production are involved in the pathophysiology of nephropathy progression.

Several recent studies have been investigating therapeutic interventions to delay nephropathy progression[63-65]. Allopurinol therapy significantly decreases SUA levels in hyperuricemic patients with mild to moderate CKD. Its use is safe and has been shown to help preserve kidney function when used for a duration of 12 mo[63]. Febuxostat has a higher renoprotective effect than allopurinol, inhibits oxidative stress, has anti-atherogenic activity, reduces blood pressure, and decreases pulse wave velocity and left ventricular mass index, most likely due to a strong SUA lowering effect[65]. In an animal diabetic nephropathy model, allopurinol attenuated transforming growth factor-beta1-induced Smad pathway activation in tubular cells[66].

Diabetic foot

There are a few reports regarding the relationship between diabetic foot and UA levels. One study states that elevated UA levels are a significant and independent risk factor for diabetic foot ulcer in female Chinese patients with T2DM[67].

Macrovascular complication

A relationship between SUA levels and the development of atherosclerotic disease has been suggested[68-70]. Moreover, there is epidemiological evidence of an association between hyperuricemia and mortality in patients undergoing percutaneous coronary intervention or presenting with acute myocardial infarction[71-73]. Our study showed that SUA is an independent risk factor for vascular complications, even when adjusted for several confounders, including eGFR[56].

Macroangiopathy includes stroke, peripheral artery disease, and ischemic heart disease. In stroke, SUA levels are higher in patients with cardiac syndrome X, and elevated SUA levels are associated with carotid atherosclerosis[74]. A U-shaped relationship was shown for this correlation, as both the upper and bottom quintiles of SUA were associated with a higher risk of fatal stroke[75]. Besides, our study, a link between peripheral artery disease and UA has been rarely reported[56].

Several interventional studies have proven the efficacy of hyperuricemia treatments. A randomized controlled study showed that allopurinol prolongs exercise capacity (especially exercise time until ST depression) when a high dose of 600 mg/d of allopurinol was administered to patients with chronic stable angina[76]. Allopurinol treatment also protects the heart from ischemic reperfusion[77], and oxypurinol, an allopurinol derivative, improves the left ventricular ejection fraction (LVEF) in congestive heart failure patients with low LVEF[22]. Despite the numerous aforementioned studies, several studies have indicated that no association between UA and ischemic stroke[78] or heart disease[79] exists.

OXIDATIVE STRESS, ISCHEMIA/REPERFUSION, AND VASCULAR ENDOTHELIAL XDH/XO

UA itself reportedly functions as an anti-oxidant[80]. For example, XDH-null mutant Drosophila melanogaster have increased vulnerability to oxidative stress[81]. Uric acid administration improved endothelial function in the forearm vascular bed of patients with type 1 diabetes and smokers[82]. However, UA synthesis is accompanied by the generation of ROS.

XDH/XO in the vascular endothelium is associated with ischemia reperfusion injury. It has also been suggested that XO inhibitors improve endothelium-dependent vascular relaxation in blood vessels of hyperlipidemic rabbits[83]. XO as the source of ROS in ischemia/reperfusion injury has been discovered 30 years ago[84,85], and this injury is preventable with XO inhibitors[86]. XOR inhibition reverses endothelial dysfunction in heavy smokers[87,88]. XO inhibitors have the potential to act as free radical scavengers. Febuxostat, however, does not have this activity but can improve organ changes induced by ischemia/reperfusion[23].

FAT DIFFERENTIATION, INSULIN RESISTANCE, AND XDH/XO IN FAT CELLS

Adipose tissue has a high xanthine oxidoreductase activity in mice[1], and UA is secreted from adipocytes. XDH/XO is a novel regulator of adipogenesis and peroxisome proliferator-activated receptor gamma (PPARγ) activity and is essential for the regulation of fat accretion[89]. In addition, UA and adipose tissue XOR mRNAs are increased in ob/ob mice, and fat mass is reduced by 50% in $XOR^{-/-}$ mice.

ATHEROSCLEROSIS AND XDH/XO IN MONOCYTES/MACROPHAGES

XDH/XO is localized to CD68 positive macrophages in the pathological state[36,90]. Inhibition of XDH/XO in inflammatory mononuclear phagocytes inhibits the migration of neutrophils during acute lung injury[91]. Through inhibition of XDH/XO activity, cytokine-induced neu-

trophil chemoattractant secretion from mononuclear phagocytes is reduced, and small ubiquitin-like modifier of PPARγ and hypoxia-inducible factor 1α levels are increased[92]. Febuxostat activates mitogen-activated protein kinase phosphatase-1 and inhibits inflammation by lipopolysaccharide stimulation through the inhibition of ROS generation[93]. Tungsten, acting as a xanthine oxidase inhibitor, prevents the development of atherosclerosis in ApoE knockout mice fed a Western-type diet[94].

XDH/XO activity is also important for lipid accumulation[36]. XDH/XO knockdown or allopurinol administration inhibited foam cell formation in macrophage J774.1 cells. The production of inflammatory cytokines associated with foam cell formation was reduced by allopurinol and febuxostat, and these medications also significantly improved calcification and lipid accumulation in the aortic plaque of ApoE-KO mice[36,95]. It should be noted that the expression of XDH/XO and the deposition of UA are seen in macrophages in arteriosclerotic lesions[96]. *In vitro*, febuxostat inhibited cholesterol crystal-induced ROS formation[95].

Some reports describe XDH/XO as an endogenous regulator of cyclooxygenase (Cox)-2[97] in the inflammatory system, and XDH/XO is central to innate immune function[98]. XDH/XO is thought to be upstream of PPARγ in lipid retention[89] and also induces Cox-2 to induce inflammation, forming a potential feedback loop. In our study, administration of allopurinol to J774.1 cells inhibited secretion of inflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1β, and IL-6[36]. Gout-associated uric acid crystals activate the NALP3 inflammasome[99]. UA crystals can injure organelle such as lysosomes, and damaged organelle selectively sequestered by autophagy[100]. If mitochondria is damaged, autophagosome is driven *via* microtubule to NLRP3 inflammasome[101]. Colchine treatment expresses the anti-inflammatory effect for gout by inhibiting microtubule-driven spatial arrangement, not by inhibiting UA crystallization. Therefore uric acid crystal in inflammatory cells of atherosclerosis lesion might activate inflammation, while solvent uric acid acts as antioxidant. Microtubule-driven spatial arrangement might be a possible target for diabetic complication derived from UA crystals.

SIGNIFICANCE OF FUTURE UA METABOLISM RESEARCH FOR THE TREATMENT OF PATIENTS WITH DIABETES

XDH/XO has been studied for more than a century, and allopurinol has been used before enzyme inhibition therapy was established. In recent years, the various roles of XDH/XO in diverse pathological conditions have been revealed using a wide variety of research techniques, particularly in the field of molecular biology. This progress in research is related to the global demand to target lifestyle-related diseases such as T2DM, coronary artery disease, CKD, and MetS. Novel research has also led to the development of new powerful and safe UA lowering agent.

Obesity rates are increasing rapidly, and consequently, the pathophysiology of T2DM will be increasingly correlated with fat accumulation, chronic inflammation, and oxidative stress. UA metabolism (involving XDH/XO) is thought to play a central role in the pathogenesis of these conditions. Hence, the need for novel research will increase in the future.

CONCLUSION

The incidence of hyperuricemia has been on the increase since decades. The condition seems to be associated with increased insulin resistance and onset and progression of diabetic complications. UA might thus be suitable marker for both risk evaluation and intervention.

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P- Reviewer: Isaka Y **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

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