Evaluation of uric acid excretion as an early marker of renal dysfunction in diabetic patients type 2

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Contents

List of Abbreviations

ADMA : asymmetric dimethyl arginine
APO : apolipoprotein
AT : angiotensinogen
CRP : c reactive protein
CVD : CardioVascular Diseases
DM : diabetes mellitus
ESRD : End Stage Renal Disease
GFR : glomerular filtration rate
GFR : Glomerular Filtration Rate
GLUT 9 : glucose transporter 9
HCV : Hepatitis C Virus
HD : Hemodialysis
HDL : high density lipoprotein
HGPRT : hypoxanthine guanine phosphoribosyltransferase
IR : insulin resistance
MET S : metabolic syndrome
MFFIT : multiple risk factor intervention trial
NO : Nitric Oxide
PAH : p-amino hippourate
PNP : purine neuclosidephosphorylase
PRPS : phosphoribosyl pyrophosphate synthetase
PZA : pyriazinzmide
RAAS : rennin angiotensin aldosterone system
RAS : rennin angiotensin system
RRF : Residual Renal Function
SIADH : syndrome of inappropriate antidiuretic hormone
TLR : toll like receptor
UA : uric acid
UAE : urinary albumin excretion
URAT-1 : urate transport -1
VEGF : Vascular Endothelial Growth Factor
DN : Diabetic nephropathy

CL : Chloride
OH : Hydroxl
RST : Renal specific transporter
TLR : Toll like receptor
NSAIDs : Non steroidal ant inflammatory drugs
PNP : Purine nucleoside phosphorylase
SIADH : Syndrome of inappropriate anti diuretic hormone
AKI : Acute kidney injury
ATN : Acute tubular necrosis
ATP : Adenosine triphosphate
METs : metabolic syndrome
CKD : Chronic kidney disease
APO E : Apolipoprotein e
TGF : Tumor growth factor
IR : Insulin resistance
HUS : hemolytic uremic syndrome

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Introduction

Urate secretion does appear to correlate with the serum urate concentration because a small increase in the serum urate concentration results in a marked increase in urate excretion. **(Johnson RJ. et al., 2005)**

Uric acid is handled by the kidney through many modes including filtration, reabsorption, secretion and post secretory reabsorption. **(School Werth and Sica, 2000)**

It has been shown that serum uric acid level may be lower than normal in diabetic patients with poor glycemic control. (**Bo, et al., 2001)**

The underlying mechanism of hypouricemia in diabetic patient is controversial. Some authors have attributed enhanced uricosuria to the concomitant elevated glomerular filtration rate. **(Schichiri, et al., 1990)** others have attributed that to increased tubular secretion of uric acid **(Erdberg, et al., 1992)**

Persistent hypouricemia was observed prior to the initial appearance of proteinuria and sometimes normalization of uric acid level occurs after appearance of persistent proteinuria. Thus persistent hypouricemia may be predictive of future nephropathy. **(Schichir, et al., 1990)**

The pathogenesis of diabetic nephropathy is complex and still not fully elucidated. Uric acid has been associated with renal disease, even though hyperuricemia may be a marker of or by itself be responsible for microvascular disease in diabetes. In patients with diabetes, serum uric acid early in the course of diabetes is significantly, and independent of confounders, associated with later development of persistent macroalbuminuria. Therefore, uric acid maybe a novel and important player in the pathogenesis of microvascular complications in diabetes.**(Hovind P.et al.,2011)**

Conflicting data exist about uric acid levels in type 2 diabetes mellitus, as low levels were found in diabetic patients, while elevated serum uric acid is a feature of hyperinsulinemia and impaired glucose tolerance. In type 2 diabetes, hyperuricemia seems to be associated with the insulin-resistant syndrome and with early onset or increased progression to overt nephropathy, while hypouricemia is associated with worse metabolic control, hyperfiltration and a late onset or decreased progression to overt nephropathy.**(Cavallo-Perin P.,et al.,2001).**

Despite advances in the management of patients with diabetes, diabetic nephropathy (DN) remains the most common cause of end-stage renal disease in the world, Inflammation and endothelial dysfunction appear to play a central role in the onset and the progression of DN. Recent evidence has emerged in the past decade to suggest uric acid is an inflammatory factor and may play a role in endothelial dysfunction. **(Jalal DI., 2011)**

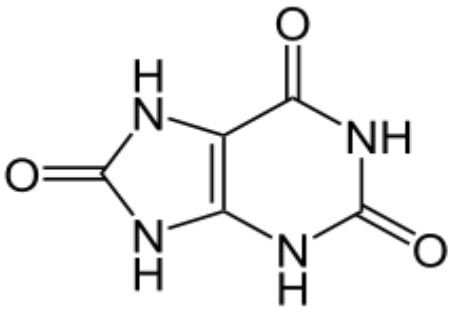
Aim of the work

This study aims to evaluate **uric acid** excretion as an early marker for **renal dysfunction** in patients with type 2 diabetes.

Chapter 1
Uric acid metabolism

Chemistry:

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula $C_5H_4N_4O_3$. It forms ions and salts known as **urates** and **acid urates** such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purine nucleotides**.(McCrudden, Francis H.2008).**



Uric acid is a diprotic acid with pKa_1=5.4 and pKa_2=10.3**(*McCrudden, et al .2008).*** Thus in strong alkali at high pH, it forms the dually charged full urate ion, but at biological pH or in the presence of carbonic acid or carbonate ions, it forms the singly charged hydrogen or acid urate ion as its pKa_1 is lower than the pKa_1 of carbonic acid. As its second ionization is so weak, the full urate salts tend to hydrolyze back to hydrogen urate salts and free base at pH values around neutral. It is aromatic because of the purine functional group. **(Scheele, V. Q.1776)**

As a bicyclic, heterocyclic purine derivative, uric acid does not protonate like carboxylic acids. X-Ray diffraction studies on the hydrogen urate ion in crystals of ammomium hydrogen urate, formed *in vivo* as gouty deposits, reveal the keto-oxygen in the 2 position of a tautomer of the purine structure exists as a hydroxyl group and the two flanking nitrogen atoms at the 1 and 3 positions share the ionic charge in the six membered pi-resonance-stabilized ring***(European Powder Diffraction Conference.2009)***

Solubility:

Generally, the water solubility of uric acid and its alkali metal and alkaline earth salts is rather low. All these salts exhibit greater solubility in hot water than cold, allowing for easy recrystallization. This low solubility is significant for the

etiology of gout. The solubility of the acid and its salts in ethanol is very low or negligible. In ethanol water mixtures, the solubilities are somewhere between the end values for pure ethanol and pure water.**MERK Index, Ninth Ed**

Biology:

The enzyme xanthine oxidase makes uric acid from xanthine and hypoxanthine, which in turn are produced from other purines. Xanthine oxidase is a large enzyme whose active site consists of the metal, molybdenum, bound to sulfur and oxygen. ***(Hille R, et al. 2004)***.Within cells, xanthine oxidase can exist as xanthine dehydrogenase and xanthine oxireductase, which has also been purified from bovine milk and spleen extracts.***(Hor, N,et al. 1992)***.Uric acid is released in hypoxic conditions***(Baillie, J.K.et al 2009).***

In humans, about 70% of daily uric acid disposal occurs via the kidneys, and in 5-25% of humans, impaired renal (kidney) excretion leads to hyperuricemia**(Vitart V, et al., 2008).**

Renal Urate Transport:

Several recent developments have created a renaissance of sorts for uricacid homeostasis. In particular, there have been major advances in the molecularunderstanding of renal urate transport. These developments include the molecularcharacterization of urate transporter-1 (URAT1), the urate exchanger inthe proximal tubule that reabsorbs the bulk of filtered urate from the glomerularultrafiltrate***,(Enomoto A, et al. 2002)***. More recently, two candidates have emerged for the sodiumdependentanion transporters that collaborate with URAT1 in urate reabsorptionby the proximal tubule***. (Zandi-Nejad K, et al. 2004)***.

The physiologic relationships between these apicaltransporters are relevant particularly for the pathogenesis of hyperuricemia andgout. There also is an increasing interest in the role of uric acid in hypertension,***(Johnson RJ, et al. 2003)***, and progressive renal disease***(Nakagawa T, et al. 2003)***.

Novel, provocativeroles for uric acid have also been proposed in inflammation, ***(Shi Y,et al, 2003),***cardiovascular disease, ***(Waring J, et al. 2000),*** heart failure***,(Hare JM, et al.2001),*** and the metabolic syndrome, ***(Fam AG. 2002)***.

Urate transporter-1 is the reabsorptive urate-anion exchanger:

This anion exchangeraccepts various monovalent organic anions, including urate, p-aminohippurate(PAH), and lactate, in addition to chloride (Cl) and hydroxyl (OH); divalentanions are not substrates. Apical urate-anion exchange activity evidently isabsent in species with net urate secretionWerner **(D,**

Martinez F, et al.,1990), although it is present andhighly sensitive to uricosuric agents in urate-reabsorbing species **(Kahn AM, et al.,1983)**; theseobservations suggest a significant role for urate exchange in proximal reabsorption.

A similar urate exchanger has been demonstrated in BBMV from humankidneys, albeit with some important distinctions; notably, PAH and OH_ are notsubstrates for the human exchanger **(Roch-Ramel F, et al., 1994)**. This is reflected in the modest effectofPAH infusion on urate excretion in humans; PZA, furthermore, is withouteffect on PAH homeostasis, suggesting that the absorptive mechanism for PAHand urate are distinct in this species **(Boner G, et al.,1973).**

The recent molecular identification of URAT1 as the dominant apical urateexchanger of human proximal tubule was a landmark event in the physiologyof urate homeostasis. The URAT1 protein is encoded by the SLC22A12 gene, partof the rapidly expanding SLC22 family of organic ion transporters.

URAT1primarily is homologous to members of the organic anion transporter (OAT)branch of this gene family; other subgroups include organic cation transportersand organic cation transporter novel type/carnitine transporters**(Koepsell H, et al., 2004).**Althoughnot acknowledged initially, URAT1 is the human ortholog of renal-specifictransporter (RST), cloned from murine kidney several years ago **(Mori K, et al, 1997).** URAT1/RST is in point of fact not renal specific, with detectable transcript in lung andbrain **(Zandi Nejad, unpublished data, 2004).** Regardless, immunohistochemistryreveals the URAT1 protein at the apical membrane of proximal tubules in humanand mouse **(Hosoyamada, et al.. 2004)**kidney.

Patients whohave homozygous loss-of-function mutations in SLC22A12 do not respond topyrazinamide and benzbromarone loading with urate retention and uricosuria,respectively. A very modest response to probenecid suggests,however,that anion transporters other than URAT1 may participate in the luminalreabsorption of urate from the glomerular ultrafiltrate **(Ichida K, et al., 2004).**

<u>The secondary sodium dependency of urate reabsorption:</u>

URAT1 reabsorbs urate from the glomerularultrafiltrate by exchanging luminal urate with monovalent intracellular anions,such as PZA. The intracellular concentration of these anions is determined largelyby sodium-dependent