

**IMPORTANCE OF HYPERURICEMIA IN DIABETES MELLITUS AND
HYPERTENSION-A REVIEW**

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ABSTRACT

Uric acid is a heterolytic Carbon compound and is the end product of Purine metabolism. It is catalyzed by the enzyme Xanthine Oxidoreductase (XO). It is an antioxidant which is known to cause gout and kidney calculi but emerging evidence, recently, has suggested that hyperuricemia may also have a role in the development and progression of many metabolic syndromes like Type 2 Diabetes Mellitus, Chronic Kidney Disease (CKD), Cardiovascular manifestations (hypertension etc.,). Uric acid and Type 2 Diabetes Mellitus are closely related, Hyperuricemia and Type 2 Diabetes Mellitus have higher risk factors together than Type 2 Diabetes Mellitus alone. T2DM or, non insulin- dependent diabetes mellitus accounts for over 90% of the total cases of Diabetes worldwide. Type 2 diabetes mellitus is due to insulin resistance and can cause serious long- term complications if left untreated. It develops due to insufficient secretion of insulin from the beta cells of pancreatic islet cells. Causes of adult- onset diabetes is mostly genetic or due to obesity. It is characterized by polyuria, polydipsia and weight loss. In severe or untreated cases it may cause serious complications like cardiovascular

diseases, chronic kidney disease, retinopathy etc. In case of hypertension, many epidemiological and experimental studies have suggested that Hyperuricemia might have a direct role in causing Hypertension (Uric acid induced- hypertension). It is presumed that the renal microvasculature and tubulointerstitial injury play a major role in Uric Acid induced hypertension. There are several proposed mechanisms and clinical trials going on to assess whether uric acid plays an important role in the progression of such manifestations.

Keywords: Uric acid, Hyperuricemia, Diabetes mellitus, Hypertension

INTRODUCTION

Hyperuricemia is defined as an increased concentration of serum uric acid (> 6.8 mg/dL) [1]. Uric acid is produced in the liver, intestines and muscles by purine metabolism by enzyme Xanthine Oxidoreductase (XO) [2]. It is mainly

associated with gout and kidney stones [3]. Increased uric acid can be due to hypoxic conditions or due to exogenous sources like fatty meat, seafood, fructose etc. Fructose is the main source of exogenous Uric acid [2].

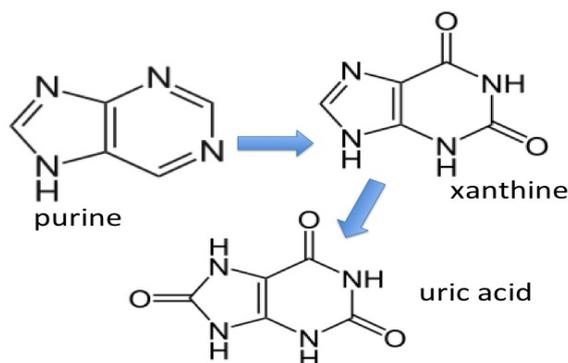


Figure 1

Fructose is converted into uric acid by the enzyme fructokinase. It takes up Adenosine Triphosphate (ATP) and forms Adenosine Monophosphate (AMP) which is further converted into Uric acid [2]. Hyperuricemia is considered an important risk factor in case of DM and Hypertension. So to establish its role in these manifestations, several epidemiological and experimental studies

have been carried out over the period of time. A few studies suggest that Hyperuricemia affects the Albumin- Creatinine ratio (ACR) which may be responsible for early pathological changes in Type 2 DM [4]. Some other studies suggest that the urate clearance in kidney decreases due to increased secretion of insulin in insulin resistance, to maintain glucose metabolism

[1]. In case of hypertension, it is proposed that increased uric acid concentration causes decrease in NO, therefore, causing vasoconstriction which results in hypertension.

Uric Acid Homeostasis

Ribose-5- Phosphatase combines with ATP to form 5'- Phosphoribosyl 1- Pyrophosphate (PRPP) in the presence of PRPP synthetase enzyme. The purine bases are utilized through the salvage pathway. There is simultaneous conversion of Hypoxanthine to Inosine Monophosphate (IMP) and Guanine to Guanosine Monophosphate mediated by the enzyme Hypoxanthine- Guanine Phosphoribosyl transferase (HPRT). Many factors like presence of ethanol, fructose intolerance, glycogen storage diseases and severe tissue hypoxia may accelerate the conversion of ATP to AMP which rapidly converts into uric acid. Inborn errors of metabolism can cause increased PRPP and decreased HPRT [5]. The kidney eliminates about 70% of daily uric acid produced [6]. URAT-1 is the urate transporter which is responsible for the efficient reabsorption of glomerular filtrated uric acid and it is present in the brush border epithelium of the Proximal Convoluted Tubule (PCT).

When there is hyperuricemia, urate crystals may get deposited in the kidney which deteriorates kidney function [1]. Also, in case of Insulin Resistance, there may be, "Insulin Induced Urinary Na⁺ Retention" which occurs due to increased insulin secretion to maintain glucose metabolism. In this case, kidney decreases the urate clearance which causes increased serum uric acid levels [1].

Pathological Mechanism

Several mechanisms have been proposed to link hyperuricemia with metabolic syndromes. Some of them are as follows-

1. Oxidative stress- high serum uric acid levels cause an increase in Reactive Oxygen Species (ROS) which causes vessel dysfunction and inflammation.
2. Inflammation- Causes release of NF- κ B, TNF α , CRP, IL-6.
3. Endothelial dysfunction- Decrease bioavailability of NO.
4. Inhibiting Insulin Pathway- Inhibits the insulin signalling pathway by ENPP1 (Etonucleotidepyrophosphatase/ phosphodiesterase 1) [7].

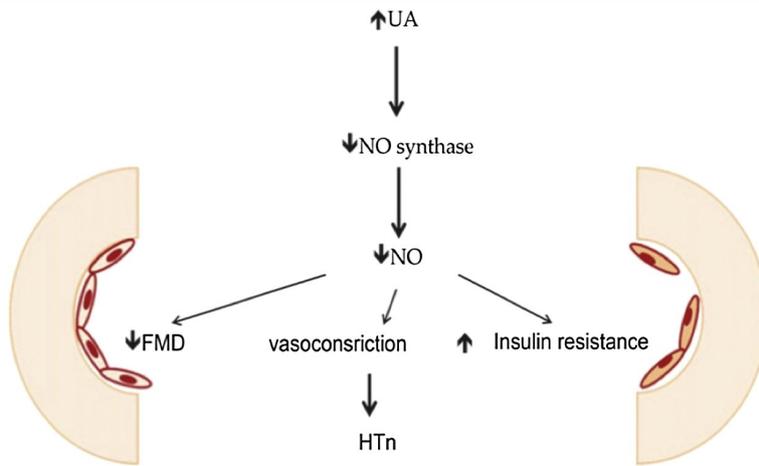


Figure 2: (NO- Nitric Oxide; FMD- Flow mediated dilation)

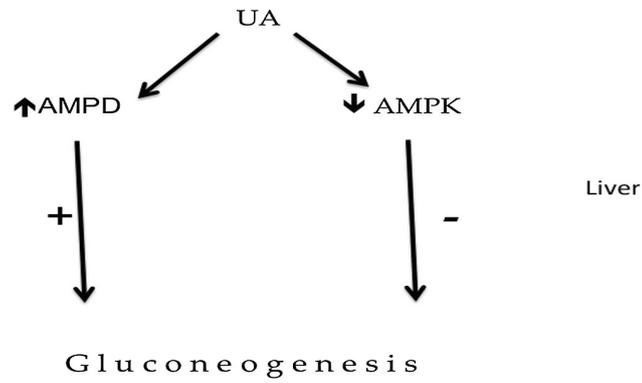


Figure 3

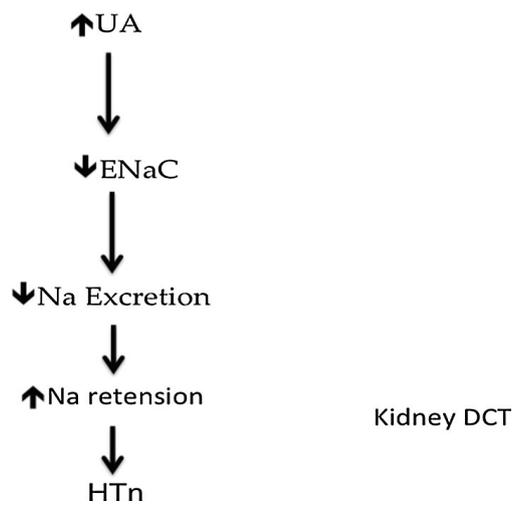


Figure 4

(AMPD- Adenosine monophosphate dehydrogenase; AMPK- Adenosine monophosphate protein kinase; ENaC- Epithelial Sodium channels)

Effect of Intracellular UA on NO synthesis within vascular endothelium- When there is increased uric acid concentration, bioavailability of NO is decreased which causes decreased flow mediated dilation, vasoconstriction and increases insulin resistance.

On the other hand, AMPD is increased which promotes hepatic gluconeogenesis while AMPK is decreased which inhibits gluconeogenesis [2].

Uric acid increases Sodium retention which may result in hypertension.

Therefore, to sum up, Uric acid causes increased gluconeogenesis, increased lipogenesis, decreased NO and various other effects by several different pathways [2].

There is evidence based on gender as well. According to a study conducted in India and Nigeria, estrogen promotes uric acid excretion [9]. Also, men drink more alcohol which contains purine (especially beer), so the ATP binding cassette transporter subfamily G member 2 (ABCG2) expression is more in men. This protein causes increase in uric acid levels [10, 11].

However, incidence of CV manifestations in case of hyperuricemia is higher in women than men. A possible explanation being women's sensitivity to the effects of uric acid, for example, inflammatory and oxidative changes, endothelial function [1].

Causes of increased serum uric acid levels- Purine rich food (seafood, fatty food), fructose, Lesch- Nyhan syndrome and certain drugs like antihypertensives (diuretics etc) [1, 8].

Hyperuricemia and Insulin Resistance

The mechanism and behaviour of Uric acid is closely related to β cell function [12]. Some studies specify that insulin resistance and type 2 diabetes mellitus can be predicted by hyperuricemia [13]. It is not yet clear as to which one of these (hyperuricemia or insulin resistance) is the precursor [14], since some studies showed that hyperinsulinemia due to decreased renal uric acid excretion results in hyperuricemia while other studies oppose it and specify that insulin resistance is preceded by hyperuricemia [13]. According to a study conducted in China, hyperuricemia and insulin resistance have 2 unidirectional relationships which are- Uric acid \leftrightarrow Hepatic insulin resistance and Uric acid \leftrightarrow Peripheral insulin resistance [14]. These incidences

were found to be higher in patients with history of hypertension. Three mechanisms were proposed to correlate between Insulin resistance, uric acid and their influence on blood pressure:- 1) Stimulation of renal Na⁺ reabsorption directly by uric acid and insulin. 2) Activation of RAAS. 3) Decreased bioavailability of NO due to endothelial dysfunction [15, 16]. Consequently, Insulin resistance can be deduced to have a role in the development of hypertension [14].

It is also suggested that hyperinsulinemia causes decreased uric acid renal clearance which results in hyperuricemia [17, 18].

Apart from Insulin resistance and hyperuricemia, obesity also plays a significant role in development of Type 2 Diabetes Mellitus [13]. Non esterified fatty acids, hormones and pro inflammatory cytokines are released by adipose tissues in obese individuals [19, 20]. Cytokines like Leptin, visfatin and TNF- α are directly related to insulin resistance. Also, Adiponectin (anti inflammatory cytokine) levels are decreased in obese individuals; Adiponectin is inversely proportional to Insulin resistance [19].

Allopurinol and SGLT-2 Inhibitors

Hyperuricemia, if caught early, can be helpful in prevention of Type 2 diabetes

mellitus, hypertension and other metabolic syndromes. Therefore, people having hyperuricemia can be treated for it using drugs like uric acid lowering agents (allopurinol) and Sodium Glucose Co-transporter- 2 Inhibitors (canagliflozin, dapagliflozin). Allopurinol is a xanthine oxidase inhibitor therefore, blocking production of uric acid [21]. According to a study by Takir M *et al* [22] allopurinol decreases serum uric acid as well as improves insulin resistance therefore reducing the chances of development of type 2 diabetes mellitus [22]. SGLT-2 Inhibitors (Sodium Glucose co- transporter 2 inhibitors) *Gliflozins* are used to decrease glucose reabsorption in kidney causing decreased serum glucose levels.^[23] Some studies indicate that the renal SLC2A9 (GLUT9) transporter is implicated in the mechanism by which it decreases serum uric acid levels. This SLC2A9 gene is expressed in the proximal tubule which is the main site of uric acid transportation. This causes liberation of uric acid from blood into urine therefore decreasing the serum concentration of uric acid [24].

CONCLUSION

The evidence from these studies point toward a role for hyperuricemia as an independent risk factor for Hypertension and

DM. Uric acid decreases the bioavailability of NO and various other effects which may, directly or indirectly, result in DM or hypertension or both. Insulin resistance may also play an important role in the development of these conditions. Therefore, the use of uric acid lowering agents could be a novel treatment to prevent these manifestations.

REFERENCES

- [1] Woldeamlak B *et al*; Oct 2019 “Hyperuricemia and its Association with Cardiovascular Disease Risk Factors in Type Two Diabetes Mellitus Patients at the University of Gondar Hospital, Northwest Ethiopia” The journal of International federation of clinical chemistry and laboratory medicine.
- [2] El Din S *et al*, Dec 2016 “Uric acid in the pathogenesis of metabolic, renal and cardiovascular diseases: A review” Journal of Advanced Research.
- [3] Mortada I, 2017 Sep “Hyperuricemia, Type 2 Diabetes Mellitus, and Hypertension: an Emerging Association”. *Curr Hypertens Rep*. doi: 10.1007/s11906-017-0770-x. PMID: 28770533.
- [4] Li G-, Jiao H, Cheng B; 2018 “Correlations between blood uric acid and the incidence and progression of type 2 diabetes nephropathy” *European review for Medical and pharmacological sciences*.
- [5] Mandal A, Mount D; Oct 2016 “The molecular Physiology of uric acid homeostasis” *Annual review of physiology*
- [6] Maesaka JK, Fishbane S. “Regulation of renal urate excretion: a critical review” *Am J Kidney Dis* 1998; 32: 917–33 (Kidney and uric acid).
- [7] Xiong Q *et al*; Oct 2019, “Effects of uric acid on diabetes mellitus and its chronic complications” *International Journal of Endocrinology*. <https://doi.org/10.1155/2019/9691345>
- [8] Nanagiri, Apoorva; Shabbir, Nadeem (2020), "Lesch Nyhan Syndrome", Stat Pearls, Treasure Island (FL): Stat Pearls Publishing, PMID-32310539, retrieved 2020-09-03
- [9] Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. “Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia”. *The Lancet*. 1999; 354(9179): 650.

- [10] Li Z, Guo X, Liu Y, Chang Y, Sun Y, Zhu G, *et al*. “The Relation of Moderate Alcohol Consumption to Hyperuricemia in a Rural General Population”. *International journal of environmental research and public health*. 2016; 13(7): 732.
- [11] Dehghan A, Köttgen A, Yang Q, Hwang S-J, Kao WL, Rivadeneira F, *et al*. “Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study”. *The Lancet*. 2008; 372(9654): 1953-61.
- [12] Robles-Cervantes J.A. *et al*; Nov 2011, “Relationship between serum concentration of uric acid and Insulin secretion among adults with Type 2 Diabetes Mellitus” *International journal of Endocrinology*. doi:10.1155/2011/107904
- [13] Miranda J.A. *et al*; August, 2015 “The role of uric acid in the insulin resistance in children and adolescents with obesity” Elsevier.
- [14] Han T *et al*; Aug 2017, “Temporal relationship between hyperuricemia and insulin resistance and its impact on future risk of hypertension” *Hypertension* vol. 70 issue 4.
- [15] Kanellis J, Kang DH; 2005 “Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease.” Elsevier; 2005; 25: 39–42
- [16] Feig DI, Kang DH, Johnson RJ; 2008 “Uric acid and cardiovascular risk.” 2008; 359: 1811–1821. doi: 10.1056/NEJMra0
- [17] Li C, Hsieh MC, Chang SJ; 2013 “Metabolic syndrome, diabetes, and hyperuricemia.” *Curr Opin Rheumatol*. 2013; 25: 210---6.
- [18] Feig DI, Kang DH, Johnson RJ; 2008 “Uric acid and cardiovascular risk.” *N Engl J Med*. 2008; 359: 1811---21.
- [19] Van Gaal LF, Mertens IL, De Block CE; 2006, “Mechanisms linking obesity with cardiovascular disease.” *Nature*. 2006; 444: 875---80.
- [20] Balagopal PB, de Ferranti SD, Cook S, Daniels SR, Gidding SS, Hayman LL, *et al*; 2011, “Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific

- statement from the American Heart Association." *Circulation*. 2011; 123: 2749---69.
- [21] Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM (2007). "Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol". *Clinical Pharmacokinetics*.
- [22] Takir M *et al*; Dec 2015, "Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia" *Journal of Investigative medicine*.
- [23] Shubrook, Jay; Baradar- Bokaie, Babak; Adkins, Sarah (2015). "Empagliflozin in the treatment of type 2 diabetes: Evidence to date" *Drug Design, Development and Therapy*.
- [24] Xin Y, Guo Y, Li Y, Jiang H *et al*; Feb 2019, "Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: A systematic review with an indirect comparison meta-analysis" *Saudi journal of Biological Sciences*.