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Research Article

IMPORTANCE OF HYPERURICEMIA IN DIABETES MELLITUS AND HYPERTENSION

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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.

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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].

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]

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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 Phosphoribosyltransferase (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).[2]

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- κB, TNF α, CRP, IL-6.
3. Endothelial dysfunction- Decrease bioavailability of NO.
4. Inhibiting Insulin Pathway- Inhibits the insulin signalling pathway by ENPP 1 (Etonucleotide pyrophosphatase/ phosphodiesterase 1). [7]

(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 ß 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 ↔ Hepatic insulin resistance and Uric acid ↔ 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].

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Fig. 1.

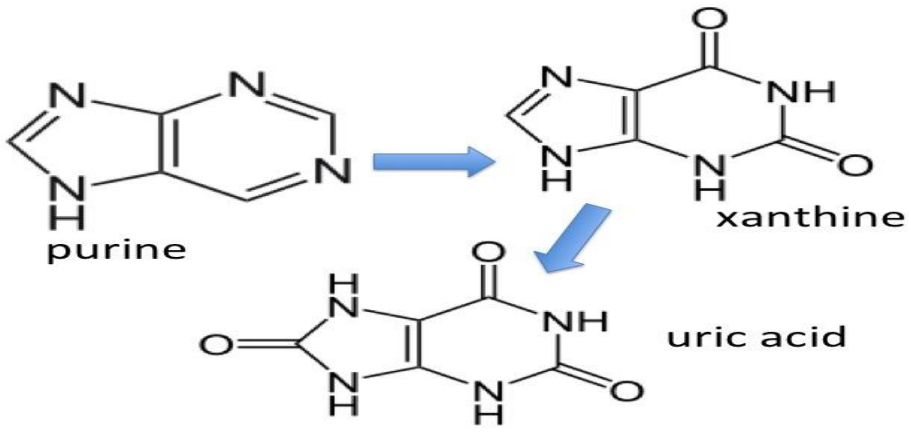


Fig 2: (NO- Nitric Oxide; FMD- Flow mediated dilation).

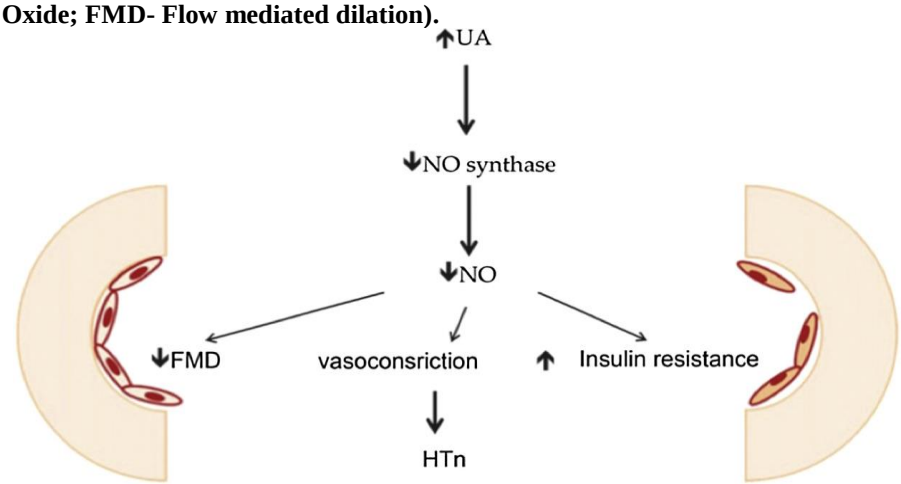


Fig. 3

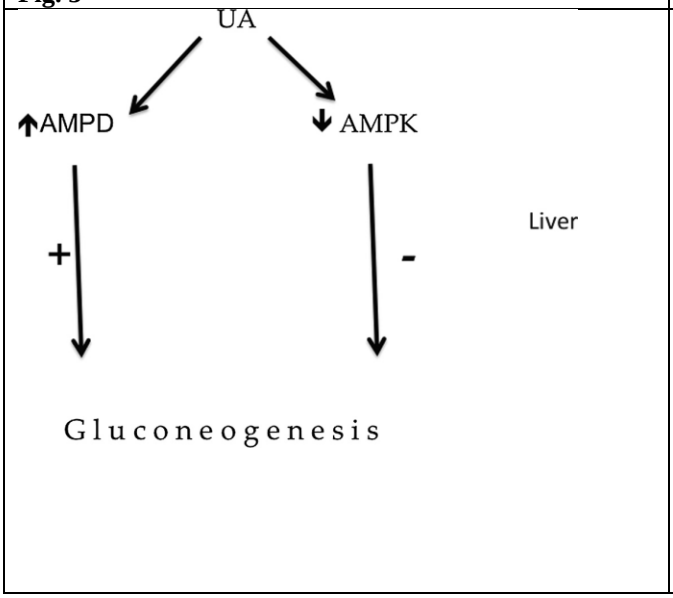
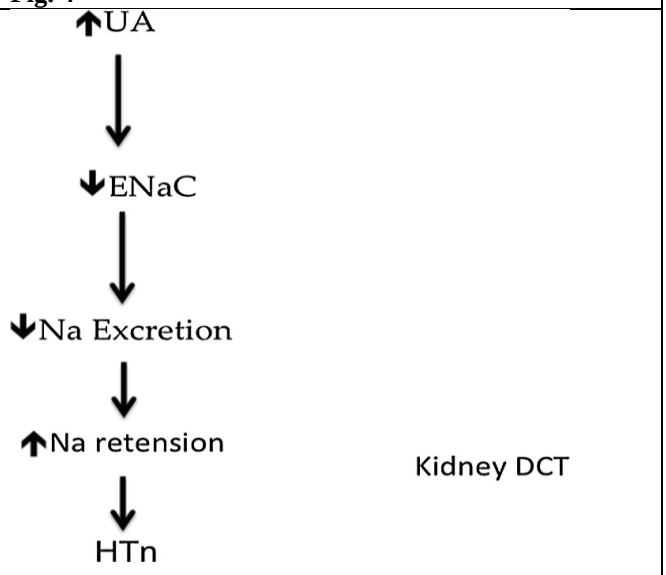


Fig. 4



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.

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