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Original article:

Uric acid in relation to Type 2 diabetes

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Abstract:

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia associated with disturbance of carbohydrate, fat and protein metabolism due absolute or relative deficiency of insulin secretion or its action. Uric acid (UA) is the end product of the purine metabolism. The association between the blood glucose and the serum uric acid levels has been known for quite some time. A positive association between the serum uric acid levels and the development of type 2 diabetes mellitus (T2DM) has been found by many studies. In individuals with an impaired glucose tolerance, an elevated Serum Uric Acid (SUA) level was found to increase the risk for developing type2 diabetes mellitus. Hyperuricemia has been also added to the set of metabolic abnormalities which are associated with insulin resistance and/or hyperinsulinaemia in the metabolic syndrome. It has been observed that serum uric acid levels are higher in case of prediabetic as compared to patients suffering from type 2 diabetes. The reason is considered to be the nephropathy due to increased glucose level in type 2 diabetes. Hyperuricemia induces endothelial dysfunction which results in nephropathy in type 2 diabetes mellitus patients. Study done by Tseng also says even mild hyperuricemia will result in kidney injury(1). The study showed the negative correlation between serum blood glucose type 2 diabetes mellitus. The mean serum uric acid level in diabetic patients was 4. 065 and 5.505 in the controls showing a clear negative correlation.

Introduction:

Diabetes a hyperglycemic chronic disorder which is mainly caused due to either insufficiency or inefficiency of a pancreatic hormone insulin**.** International diabetic federation shows that world Diabetes and pre-diabetes prevalence in 2007 is 5.7% and 7.5% respectively (1) .Diabetes causes long term dysfunction of various organs like heart, kidneys, eyes, nerves and blood vessels. Age adjusted mortality rates among diabetes is 1.5 to 2.5 times higher than general population. Much of this higher mortality is attributed to cardiovascular diseases (2). Serum uric acid an end product of purine metabolism is observed to be in lower ranges in diabetic patients which reflects the initiation of nephropathy due to type 2 diabetes. Serum uric acid an end product of purine metabolism is observed to be in lower ranges in diabetic patients which reflects the initiation of nephropathy due to type 2 diabetes. The role of uric acid in the progression of prediabetes to diabetes has been know(3) .However, conflicting data exist as regards the serum uric acid (UA) levels in type 2 diabetes mellitus, which are associated with risk factors and complications. The present study was done to see the association of serum uric acid with hypertension in type 2 diabetes mellitus, taking into consideration the relevant clinical and biochemical data. Uric acid was first isolated from kidney stones by Swedish chemist Carl Welhelm Scheele in 1776(3). It is an aromatic and heterocyclic compound of carbon , nitrogen, oxygen and hydrogen having the molecular formula C5H4N4O3. It forms ion and salts known as urates. Uric acid is the by product of purine nucleotides metabolism and is excreated through urine. In humans, about 70% of daily uric acid disposal occurs via the kidneys and 5- 25% of humans impaired

renal(kidney) excretion leads to hyperurecemea(4). High blood concentration of uric acid can lead to gout and are associated with other medical conditions including diabetes and the formation of ammonium acid urate kidney stones. The enzyme xanthine oxidase catalyses formation of 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(5). Within cells, xanthine oxidase can exist as xanthine dehydrogenase and xanthine oxireductase, which has also been purified from bovine milk and spleen extracts(6).

Causes of higher uric acid

- Diet may be a factor. Higher intake of dietary purine, high fructose com syrup and table sugar can cause increased levels of uric acid(7)(8).
- Serum uric acid can be elevated due to reduced excretion by the kidneys(9).
- Certain drugs, such as thiazide diuretics, can increase uric acid levels in the blood by interfering with renal clearance(10).

Excess serum accumulation of uric acid in the blood can lead to a type of arthritis known as gout(11). This painful condition is the result of needle-like crystals of uric acid precipitating in joints, capillaries , skin, and other tissues(12)'.Kidney stones can also form through the process of formation and deposition of sodium urate microcrystals(13)(14). A study found that men who drink two or more sugar-sweetened beverages a day have an 85% higher chance of developing gout than those who drank such beverages infrequently(15). Gout can occur where serum uric acid levels are as low as 6 mg/dL (~357 μMol/L), but an individual can have serum values as high as 9.6 mg/dL (~565 μmol/L) and not have gout(16)**.**

Low uric acid

Lower uric acid level in serum is known as hypourecemea**.**

Causes of low uric acid

Low dietary zinc intakes cause lower uric acid levels. This effect can be even more pronounced in women taking oral contraceptive medication(17). **Relationship between Type 2 diabetes and uric acid:-** Diabetes mellitus is a clinical syndrome which is characterized by hyperglycaemia due to an absolute or a relative deficiency of insulin. It may be associated with a number of complications which include macro and microvascular diseases. Uric acid (UA) is the end product of the purine metabolism. The association between the blood glucose and the serum uric acid levels has been known for quite some time (18). A positive association between the serum uric acid levels and the development of type 2 diabetes mellitus (T2DM) has been reported(19). In individuals with an impaired glucose tolerance, an elevated Serum Uric Acid (SUA) level was found to increase the risk for developing T2DM (20).Studies have shown that uric acid is significantly elevated in prediabetic stages and low in diabetes, and rises again after the development of renal insufficiency(21). Hyperuricemia has been found to be associated with obesity and insulinresistance, and consequently with type2 diabetes. Further potentially important biological effects of uric acid relate to endothelial dysfunction by inducing antiproliferative effects on endothelium and impairing nitric oxide production and inflammation, through increased Creactive protein expression, although these issues are considered controversial. Uric acid may play a role in immune activation with subsequent increased chemokine and cytokine

expression(22). Some studies reported that there is a positive association between elevated serum uric acid levels and diabetes (23)(24). whereas some other study reported no positive association between serum uric acid and diabetes mellitus (25). Also, some studies reported that serum uric acid is inversely associated with diabetes mellitus (26)(27). Hyperuricaemia has been also added to the set of metabolic abnormalities which are associated with insulin resistance and/or hyperinsulinaemia in the metabolic syndrome (28). While an increase in the uric acid levels in prediabetes and diabetes was demonstrated by some studies, a declining trend of the serum uric acid levels . Hyperuricaemia has been also added to the set of metabolic abnormalities which are associated with insulin resistance and/or hyperinsulinaemia in the metabolic syndrome (29). While an increase in the uric acid levels in prediabetes and diabetes was demonstrated by some studies, a declining trend of the serum uric acid levels with increasing blood glucose levels was observed by other research workers with increasing blood glucose levels was observed by other research workers(30). in the proximal tubule by high glucdiabetes is not clear. Most of these studies were limited by small sample sizes, including either men or women and not both, not having data on confounding factors, or were from selected populations such as industrial workers as opposed to general population samples. The exact reason for why previous studies found a positive relation between uric acid and e mechanism for the observed results of an inverse association between increasing serum uric acid and diabetes mellitus may be related to the inhibition of uric acid reabsorption levels in diabetic individuals (31)(32). This is supported by findings that fructose-induced hyperuricemia in rats leads to insulin resistance along with other components of metabolic syndrome, and these conditions are improved by decreasing uric acid levels(33)(34).However, it is also conceivable that elevated serum acid levels may reflect prediabetes status, particularly at the renal level, although our observed association was independent of fasting glucose, triglycerides, and serum creatinine. Higher insulin levels associated with prediabetes can reduce renal excretion of uric acid,(35)(36) as insulin can stimulate the urate-anion exchanger(37) and/or the Na+-dependent anion co-transporter in brush border membranes of the renal proximal tubule(38) and increase renal urate reabsorption. Thus, although our study provides support for the independent association between serum uric acid levels and the risk of incident type 2 diabetes, any causal inference remains to be clarified by future studies.Various mechanisms have been suggested through which uric acid may be implicated in the atherosclerotic process and its clinical complications. Uric acid can act as a prooxidant, particularly at increased concentrations, and may thus be a marker of oxidative stress, but it may also have a therapeutic role as an antioxidant. It is unclear whether increased concentrations of uric acid in diseases associated with oxidative stress, such as atherosclerotic coronary heart disease, stroke, and peripheral arterial occlusive, disease, are a protective response or a primary cause(39). In humans, uric acid is the most abundant aqueous antioxidant, accounting for up to 60% of serum free radical scavenging capacity and is an important intracellular free radical scavenger during metabolic stress. Serum uric acid concentrations are reduced in patients with type 1 diabetes and in regular smokers, which could increase susceptibility to oxidative damage and account for the excessive free radical production characteristically found in both groups. In type 1 diabetes, low serum uric acid underlying the bell-shaped relation between blood glucose levels and serum uric acid levels is thought to be due to the uricosuric effect of glycosuria, which occurs when the blood glucose level is greater than 180 mg/dl(40). Higher insulin levels are known to reduce renal excretion of urate. Insulin may enhance renal urate reabsorption via stimulation of the urate-

anion exchanger URAT1 and/or the sodium-dependent anion cotransporter in brush border membranes of the renal proximal tubule.(41)

Unique effect 0f fructose on uric acid and diabetes:-

The uptake of fructose by cells is largely mediated by Glut 5 and Glut 2 transporters, followed by metabolism by fructokinase(ketohexokinase, KHK) . Fructokinase may exist in two isoforms, of which KHK-C appears to be the principal isoform involved in fructose metabolism (42). The dominant sites of KHK-C expression include the liver, the intestinal epithelium, the proximal tubule of the kidney, the adipocyte, and possibly the vascular endothelium (43)(44). Fructose may also be metabolized by hexokinase (glucokinase); however, the Km for fructose is much higher than glucose, and hence minimal amounts of fructose are metabolized via this pathway (45).Fructose differs from glucose primarily due to its different transporters and the first three enzymes involved in its metabolism . A key enzyme is fructokinase, which uses ATP to phosphorylate fructose to fructose-1-phosphate. Unlike enzymes involved in glucose metabolism (glucokinase and phosphofructokinase), in which downstream metabolites prevent excessive phosphorylation, fructokinase is poorly regulated and will phosphorylate all fructose rapidly with the depletion of ATP (46). The administration of fructose rapidly depletes ATP in human liver (47)(48). Similarly, concentrations of fructose as low as 1.0 mm (similar to that observed postprandially in plasma after a fructose-enriched meal) can significantly reduce ATP levels in vascular endo-thelial cells (49) and human proximal tubular cells (50). The effect of fructose to cause ATP depletion acts like a type of ischemia and can cause transient arrest of protein synthesis (51)(52) and the production of inflammatory proteins, endothelial dysfunction, and oxidative stress (53).

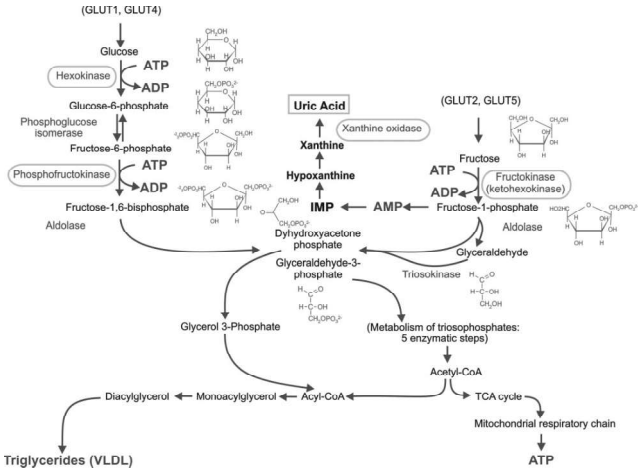

FIG. 1. Fructose metabolism. Fructose enters cells via a transporter (typically Glut 5, Glut 2, or SLC2A9) where it is preferentially metabolized by fructokinase (KHK) to generate fructose-1-phosphate. Unlike phosphofructokinase, which is involved in glucose metabolism, fructokinase has no negative feedback system to prevent it from continuing to phosphorylate substrate, and as a consequence ATP can be depleted, causing intracellular phosphate depletion, activation of AMP deaminase, and uric acid generation. In addition, fructose is lipogenic and can generate

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both glycerol phosphate and acyl coenzyme A, resulting in triglyceride formation that is both secreted and stored in hepatocytes. IMP, Inosinemonophosphate; TCA, trichloroacetic acid.(54)

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Fructose is also highly lipogenic, stimulates triglyceride synthesis, and increases fat deposition in the liver, likely mediated in part by increasing fatty acyl coenzyme A and diacylglycerol (55). Splanchnic perfusion studies have shown that hepatic production of triglycerides is much greater with fructose compared with equimolar concentrations of glucose (56). Fructose administration results in greater postprandial hypertriglyceridemia than that observed with isocaloric glucose, and it can also result in higher apolipoprotein B levels (57)(58). Fructose feeding is also an effective way to induce fatty liver (59)(60) and may be preferentially used by hibernating mammals as a means to increase fat stores (61). One of the more striking aspects of its ability to stimulate uric acid production (62). As ATP is consumedAMP accumulates and stimulates AMP deaminase, resulting in uric acid production (63). Serum uric acid can increase rapidly after ingestion of fructose, resulting in increases as high as 2 mg/dl within 1 h (64)(65). Although initially the rise in uric acid is transient, studies in which high fructose (or sucrose) diets have been administered have found that even fasting uric acid levels will increase after several weeks (66)(67). Choi *et al.* have reported a dose-dependent relationship between fructose ingestion and serum uric acid levels in both men and women, although in another study this relationship could not be confirmed in women (68).

Material and methods:-

This case control study was carried out at Shere-i-kashmir Institute of medical sciences college Bemina, Srinagar in the department of Biochemistry. The study included a total of 53 subjects. All were the cases of type 2 diabetes millitus, they were diagnosed on the basis of GTT (Glucose tolerence test). Both the fasting and post prandial glucose levels. the whole medical history of the patients were taken. the normal blood glucose level for fasting sample was taken in range i-e between 75- 115 mg/dl(4.1-6.4mmol/l).The serum uric acid level was measured in the random sample.

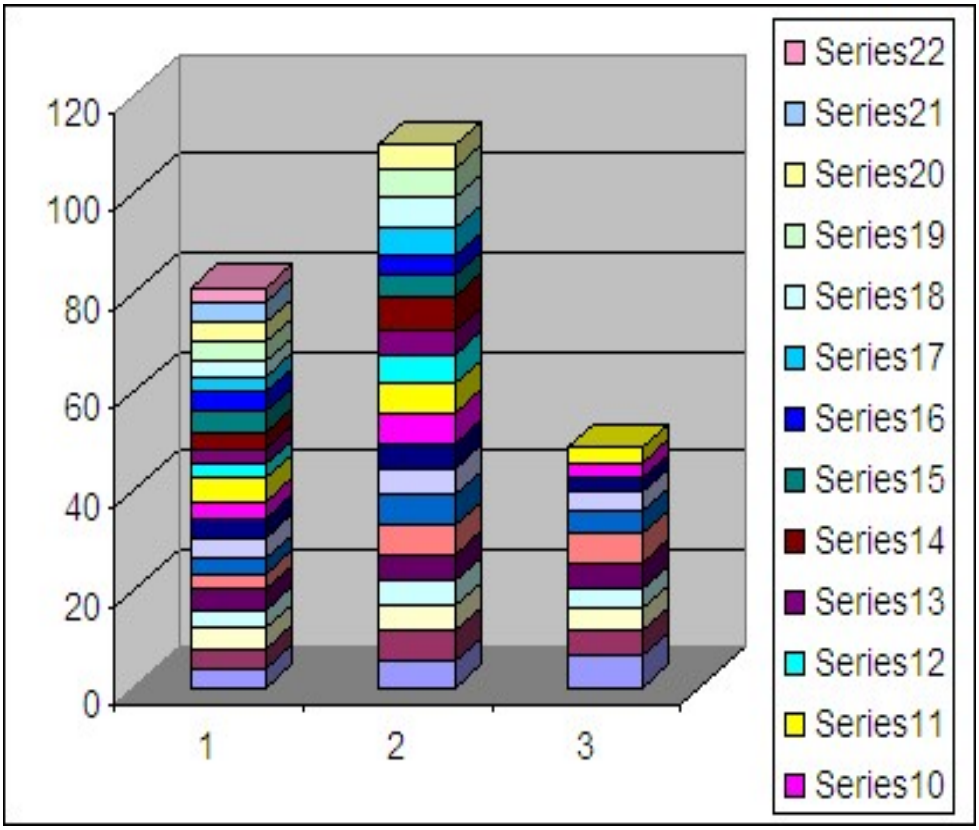
All the serum samples were determined using Beckman Coulter AU 680 autoanalyser. The analyser was calibrated at regular intervals and quality control was also maintained before sample analysis was performed.

The enzymatic colour test method was used for the estimation of serum uric acid and blood glucose on Beckman Coulter AU 680 analysers.

Results:

The serum uric acid level was observed negatively correlated with type 2 diabetes mellitus. The average serum uric acid level in male diabetic patients (n=22) was 3.686, in female diabetic patients (n=11) was 4.445 and in controls (n=20) was 5.505.

Fig 1.1 Serum uric acid level 1. Male diabetic patients 2.Controls 3.Female diabetic patients

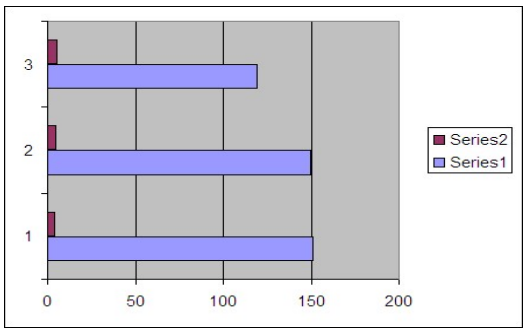


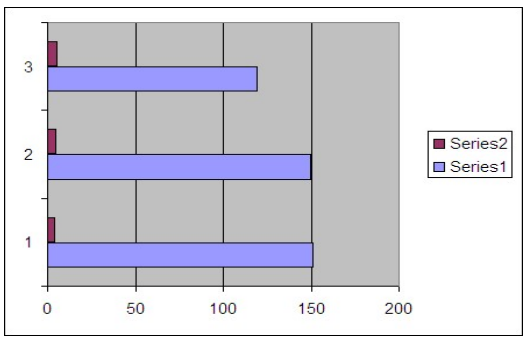
The serum uric acid level is also in negative correlation to blood glucose level. The higher blood glucose is observed to minimize the reabsorbtion of uric acid in proximal tubules the reason behind this is uncertain.

PARAMETERS	FBS	PPBS	URIC ACID
MALES	124.5	151	3.686
FEMALES	123.3	149.7	4.445
CONTROLS	84	119	5.505

Table 1. shows the mean of parameters

Fig 1.2Series 1: Blood glucose, series 2: Serum uric acid





Discussion:-

In this study we observed that higher serum uric acid levels are inversely associated with type 2 diabetes. This inverse association is independent of other factors such as hypertension, obesity, gender etc. Some studies reported that there is a positive association between elevated serum uric acid and diabetes (74). While as some studies reported no positive association between serum uric acid and diabetes . Also some studies reported that serum uric acid is inversely associated with diabetes. The exact reason why the previous studies found the positive association is not clear. A plausible mechanism for the observed results of an inverse association between serum uric acid and diabetes mellitus may be related to the inhibition of uric acid reabsorption in proximal tubules by higher levels of glucose in diabetic patients. The elevated levels of serum uric acid are responsible to cause insulin resistance, impaired renal function, albuminuria, nephropathies, stimulates the production of cytokines from leukocytes etc. The study also shows that serum uric acid is inversely associated to serum glucose level but the reason behind this is not clear.

Conclusion

The serum uric acid was closely associated with type 2 diabetes mellitus showing a negative correlation with serum blood glucose. Hyperuricemea is known to be responsible for various complications such as insulin resistance leading to type 2 diabetes, kidney stones, nephropathies etc. Some studies have found that serum uric acid is elevated in prediabetic patients. The elevated levels of serum glucose level reduce the reabsorbtion of uric acid in proximal tubules causing decrease in its serum levels. Higher uric acid also induces the metabolic syndrome due to oxidative stress on mitochondrial electron transport chain and induce oxidative stress resulting in insulin resistance leading to type 2 diabetes.

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