Hyperuricemia and its relation to type 2 diabetes mellitus and insulin resistance: A review

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■ **Abstract:**

In recent years, there has been an increase in the prevalence of hyperuricemia, and the latter has attracted attention as an lifestyle-associated disease, together with diabetes, and insulin resistance. The data regarding of plasma uric acid levels in insulin resistance; type 2 diabetes mellitus; their role in the development and progression of diabetic complications have been observed by many studies. In this review we attended to explain cause of hyperuricemia and the associations between hyperuricemia, insulin resistance, and type 2 diabetes mellitus based on the latest published evidence.

● **Keywords:** insulin, insulin resistance, type 2 diabetes mellitus, uric acid, hyperuricemia.

المستخلص:

مرض فرط حمض بوليك الدم ازداد بشكل كبير في السنوات الأخيرة، وقد جذب الانتباه باعتباره مرضاً مرتبطاً بنمط حياة البالغين، إلى جانب مرض السكري ومقاومة الأنسولين. حيث لوحظ من قبل العديد من الدراسات ارتباط البيانات المتعلقة بمستويات حمض البوليك في البلازما مع مرض السكري ومقاومة الأنسولين ودورها في تطور مرض السكري ومضاعفاته. سيتعرض هذا البحث إلى أسباب فرط حمض بوليك الدم ومن ثم علاقته بمقاومة الأنسولين ومرض السكري من النوع الثاني استناداً على أحدث الدراسات المنشورة.

● **الكلمات المفتاحية:** الأنسولين، مقاومة الأنسولين، مرض السكري من النوع الثاني، حمض البوليك، ارتفاع حمض البوليك في الدم.

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■ Introduction:

Hyperuricemia is a condition in which the subject has increased serum uric acid levels(1). Hyperuricemia was defined as the fasting serum UA concentrations are above 7.2 mg/dl in males and6.2 mg/dl in females according to the reference ranges(2). Studies have noted that an elevated level of uric acid predicts the development of diabetes, obesity, hypertension and the metabolic syndrome. Uric acid levels tend to decrease with increasing plasma glucose levels in patients with type 2 diabetes mellitus (T2DM)(1). Hyperuricemia, the precursor of gout, is strongly associated with insulin resistance syndrome, an established risk factor for Type II diabetes, cardiovascular disease and also play a role in the development of renal and metabolic diseases in diabetic patients(3).

Uric acid (UA) in serum is the final oxidation product of purine metabolism in human(4) generated during enzymatic degradation by hypoxanthine and xanthine(1), which they are produced by the liver and excreted by the kidneys, with recognized antioxidant action when its blood levels are within physiological limits. However, the increase in its serum levels, called hyperuricemia(5). Serum uric acid (SUA) is an excretory metabolite produced by the metabolism of the purines. It can be elevated as a result of the low renal filtration rate, overproduction of purine precursors, and diet(6).The SUA level reflects the balance between UA production and excretion. The production of UA depends on the intake of dietary protein and the breakdown of endogenous purines by xanthine oxidase. The kidneys are the major site of UA excretion and the small intestines are the secondary sites(7). Excessive UA production or low excretion can increase the SUA levels, leading to hyperuricemia. Approximately 90 % of hyperuricemia is associated with reduced UA excretion and only 10 % is caused by increased UA production(7).

Some studies reported that there is a positive association between high serum uric acid levels and diabetes, whereas other studies reported no association, or an inverse relationship. Few studies show that reduced clearance of uric acid is associated with hyperinsulinemia that causes insulin resistance in type 2 diabetes(8). A positive correlation between uric acid and fasting blood glucose levels leads to the causation of type 2 diabetes. Furthermore, certain

studies indicate that uric acid functions as pro-oxidant and antioxidant according to their concentration levels. Blood uric acid has a role of pro-oxidant properties that causes oxidative stress in the cells and results in the resistance of the cells to the insulin. Studies showed hyperuricemia is associated with excess risk for development of type 2diabetes.Whether the hyperuricemia causes type 2diabetes, or is it one of the complications of diabetes(8).

■ **Hyperuricemia and regulation of uric acid**

Uric acid (2,6,8 trioxypurine-C5H4N4O3) is an organic compound that is endogenously produced by animals as a purine metabolite. It is formed by the liver and mainly excreted by the kidneys (65-75 %) and intestines (25-35 %) (9). UA is the end product of purine metabolism in humans (9). Uric acid is synthesized from xanthine by xanthine oxidoreductase as well as from guanosine. The free purine bases, yielded by nucleoside cleavage are adenine, guanine, hypoxanthine and xanthine. Since purine nucleoside phosphorylase acts with relatively higher affinity on inosine and guanosine, the major bases generated are hypoxanthine and guanine. Hypoxanthine is oxidized to xanthine by xanthine oxidoreductase (XOR) and then further oxidized to uric acid by the same enzyme, while guanine is oxidized to xanthine. Uric acid synthesis happens mainly in the liver, where XOR is richly expressed(10).

Briefly, inosine monophosphate (IMP) is derived from de novo purine synthesis and from purine salvage. Hypoxanthine from IMP is catalyzed to xanthine and then to uric acid by xanthine oxidase (XO). De novo nucleotide synthesis generates IMP via ribose-5-phosphate, catalyzed to 5-phosphoribosyl-1-pyrophosphate (PRPP). In the salvage pathway, hypoxanthine-guanine phosphoribosyl transferase (HGPRT) plays an important role in generating IMP, thereby inhibiting UA generation. Since humans are unable to catabolize UA to the more soluble compound allantoin due to lack of urate oxidase or uricase, the serum UA concentration is higher in humans than almost all other mammals. However, this high UA level in humans has been regarded as being beneficial in the presence of elevated oxidative stress. UA is oxidized to allantoin and other metabolites via nonenzymatic oxidation and, thus, UA can function to neutralize prooxidant molecules, such as hydroxyl radicals, hydrogen peroxide, and peroxynitrite(11). The resulting xanthine, through ad-

enine and guanine pathway, under the action of xanthine oxidase, is oxidized to uric acid, which in the normal human body's physiological conditions, exists as urate, with the following normal range of levels, which are different for men and women: 2.5–7.0 mg/dL in male gender and 1.5–6.0 mg/dL in female gender, respectively. Furthermore, the urate is easily transformed to allantoic acid and ammonia, allowing its renal excretion (almost 200–300 mg/day)(12).

Most UA is filtered from glomerular, while renal tubules reabsorption and secretion regulate the amount of urate excretion. The proximal tubule is the site of UA reabsorption and excretion. About 90 % UA is reabsorbed into blood. Urate transporters are mostly located in the proximal tubules of the kidney and play key roles in reabsorption and excretion of UA(13). However, UA is a polar molecule and, thus, cannot freely pass through the cell membrane. Therefore, the process of UA reabsorption depends on ion channels. A genome-wide association study has revealed numerous genes (encoding for UA transporters) that are associated with hyperuricemia and gout(7).

Excretion of nitrogenous waste from the body can manifest in three forms: urea, ammonia, and uric acid. Uric acid (UA) is the final product of purine metabolism(adenine and guanine degradation), mostly derived from endogenous synthesis and only a minor part from exogenous sources(12). The kidney is the main organ for the excretion of uric acid. About 75 % of the uric acid in the body is excreted by the kidneys and finally excreted in the form of urine (14). Uric acid metabolism is regulated by secretion and reabsorption transporters. Among the secreted proteins, the dysfunction of adenosine triphosphate binding cassette subfamily G member 2 ABCG2 (an ATP-driven efflux pump) has become one of the major factors in human hyperuricemia; organic anion transporter 1 OAT1 (encoded by solute carrier family 22, organic anion / urate transporter, member 6 gene SLC22A6)/ organic anion transporter 3 OAT3 (encoded by solute carrier family 22, organic anion / urate transporter, member 8 gene SLC22A8) driven by α-ketoglutarate (α-KG) leads to uric acid being secreted from the basolateral side of the cells to the renal tubular cells, and finally excreted in the urine. Uric acid transporters coordinate with each other in structure, function, and location to regulate the balance of uric

acid in the human body(15). The uric acid reabsorption transporter URAT1 encoded by the hyperuricemia-related gene (Solute carrier family 22, organic anion / urate transporter, member 12 gene SLC22A12) reabsorbs urate from filtered urine(15). The gut also plays an important role in the excretion of uric acid, with about a quarter of uric acid being excreted into the gut. As the main site of digestion and absorption, the small intestine is also the main site of uric acid metabolism in the intestinal tract. ABCG2 is the main transporter of uric acid excretion in the intestine(15). In adults, approximately 30 % of the uric acid that is produced daily is excreted through the biliary and gastrointestinal tract and degraded by gastrointestinal bacteria by a process called uricolysis(14).

Uric acid is primarily a purine metabolic waste product. About 70 % of uric acid is excreted by the kidneys, and decreased excretion is one of the main causes of hyperuricemia(1). Under physiological conditions, UA synthesis and excretion are balanced in the body. Once this balance is disturbed, it leads to hyperuricemia(16). Normally, male UA levels greater than 7 mg/dL or female UA levels greater than 6 mg/dL are considered to be hyperuricemia(16). Hyperuricemia is caused by a disturbance of uric acid metabolism, a complex physiological process involving multiple organs (liver, kidney, and intestine). Uric acid is formed in the liver by purine dehydrogenase or oxidase degrading purines, and 2/3-3/4 of the totaluric acid produced by the body every day is excreted through the kidneys in the urine, andthe rest is excreted into the intestines through the hepatobiliary system(15).

Hyperuricemia is the major and primary risk factor of symptomatic gout, coronary artery disease and type 2 diabetes(17). Elevated serum UA levels can result from a number of factors, including both acute and chronic causes. Acute causes of hyperuricemia include the intake of large amounts of alcohol, tumor lysis syndrome (a complication of cancer chemotherapy), and a diet that is high in purines or proteins. Alternatively, chronic hyperuricemia can result from conditions that cause a reduction in the glomerular filtration rate, a decrease in the excretion of UA, or an increase in overall tubular absorption(18). Hyperuricemia has been shown to be linked to a number of diseases and conditions, including gout, hypertension, cardiovasculardisease,

myocardial infarction, stroke, and renal disease. However, it remains unclear whether an increased UA level is the cause or a consequence of some of these conditions(18).

A number of studies reported significant associations between serum uric acid levels and individual components of the metabolic syndrome, but the scope of prevalence of the metabolic syndrome using recent definitions among individuals with hyperuricemia is unknown. Renal clearance of urate is inversely related to the degree of insulin resistance. Thus, the reduced renal excretion of urate among patients with the metabolic syndrome may explain the increased frequency of hyperuricemia. On the basis of these data, hyperuricemia has been suggested as a simplemarker of the metabolic syndrome(19).

Metabolic syndrome is a cluster physiological and anthropometric abnormalities of nutrients metabolism, such as hyperglycemia, hyperuricemia and hyperlipidemia. The metabolism of three major nutrients are closely linked. Hyperuricemia could contribute to abnormal glucose metabolism, insulin resistance (IR),even pancreatic β-cell death. Substantial data from epidemiologic and experimental studies indicate an emerging association between hypruricemia, type 2 diabetes mellitus (T2DM), and cardiovascular-related diseases. Several studies revealed that hyperuricemia may be an independent risk factor for the development of T2DM, which suggest a substantial implication for a correlation between uric acid concentration and insulin resistance (or insulin sensitivity). Also, hyperuricemia is substantially implicated in cardiovascular risks, vascular complications, the further long-term cardiovascular events and mortalityin T2DM patients(20).

■ Type 2 diabetes mellitus and insulin resistance

Diabetes mellitus is a non-communicable metabolic disorder. It is a genetically multifactorial disease characterized by abnormally elevated blood glucose and dysregulation of carbohydrate, protein and lipid metabolism. In diabetes mellitus, homeostasisof carbohydrate and lipid metabolism is altered due to defects in insulin production, secretion or action. The global prevalence of diabetes mellitus in 2019 is estimated to be about 9.3 % of the population and was responsible for about 4 million deaths globallyin 2017(21).

Type 2 diabetes, the most common form of diabetes, is mainly caused by insulin resistance(22) and relative insulin deficiency(23). Type 2 accounts for 90-95 % of cases of diabetes. The chronic hyperglycemia that characterizes diabetes mellitus results from defects in insulin secretion, insulin action, or both(24). Insulin resistance can be defined as a condition in which the pancreas is required to secrete more insulin than normal in order to achieve normal blood glucose levels due to reduced sensitivity or responsiveness of tissues to insulin biologic activity. The prevalence of insulin resistance varies across countries(22).

Insulin secretion and insulin sensitivity are regulated by pancreatic β-cells in a very definite manner to maintain homeostatic concentrations of plasma glucose in healthy individuals(25). Insulin is the most important biological hormone that regulates energy metabolism, including carbohydrates, lipid, and protein. Insulin promotes the absorption of glucose from the blood into liver and skeletal muscle cells. Insulin resistance is defined as a metabolic state in which insulin sensitivity is abnormally low at physiological insulin concentrations, eventually leading to hyperinsulinemia. Insulin resistance has been thought to be a strong determinant for the development of some components of metabolic syndrome including dyslipidemia, diabetes mellitus, and hypertension (26).

In insulin resistance, tissues have a diminished ability to respond to the action of insulin. To compensate for resistance, the pancreas secretes more insulin. Insulin-resistant persons, therefore, have high plasma insulin levels. The syndrome can be defined as a cluster of abnormalities, including obesity, hypertension, dyslipidemia and type 2 diabetes, that are associated with insulin resistance and compensatory hyperinsulinemia. However, a cause and-effect relationship between insulin resistance, these diseases and the mechanisms through which insulin resistance influences their development has yet to be conclusively demonstrated(27). Insulin resistance state is associated with diabetes mellitus and metabolic syndrome (MS)(8). During IR, the body's compensatory release of excess insulin to maintain blood sugar stability causes hyperinsulinemia that can progress to type 2 diabetes mellitus (T2D). Prospective studies have highlighted the importance of IR in the pathogenesis of T2D

and suggest that IR is the best predictor of future T2D diagnosis(28). In the insulin sensitivity assays, insulin resistance has following characteristics: hyperinsulinemia and hyperglycemia in fasting condition, increased glycosylated haemoglobin (HbA1c), postprandial hyperglycemia, hyperlipidemia, impaired glucose tolerance, impaired insulin tolerance, decreased glucose infusion rate, increased hepatic glucose production, loss of first phase secretion of insulin, hypoadiponectinemia, and increased inflammatory markers in plasma(29).

The disturbances in insulin pathway are responsible for the development of insulin resistance. Insulin, by the control of numerous enzymes and kinases during feeding and fasting periods, is a major regulator of energy homeostasis. Thereby, the decline of insulin capability to elevate the uptake of glucose by adipose tissue, liver, and muscle, contributes to the development of insulin resistance. It was found that inhibitory effect of insulin on lipolysis is diminished during decreased insulin sensitivity(30). Abnormalities of insulin signalling account for insulin resistance. Insulin mediates its action on target organs through phosphorylation of a transmembrane-spanning tyrosine kinase receptor, the insulin receptor (IR). The binding of insulin to the α subunit of its receptor activates the tyrosine kinase of the β subunit of the receptor, leading to autophosphorylation, as well as tyrosine phosphorylation of several IR substrates (IRS), including IRS-1 andIRS-2. These, in turn, interact with phosphatidylinositol3-kinase (PI3K). Activation of PI3K stimulates the main downstream effector Akt, a serine/theronine kinase, which stimulates the glucose uptake through the translocation of the major glucose transporter GLUT-4 to the plasma membrane. Abnormalities of the IR function that may contribute to insulin resistance include the defects of receptor structure, number, binding affinity, and/or its signaling capacity. It is noteworthy that hyperglycaemia, accounts for the development of insulin resistance through the generation of reactive oxygen species (ROS), which abrogate insulin-induced tyrosine autophosphorylation of IR. In addition, several mechanisms have been described as responsible for the inhibition of insulin-stimulated tyrosine phosphorylation of IR and the IRS proteins, including proteasome-mediated degradation, phosphatase-mediated dephosphorylation, and kinase-mediated serine/threonine phosphorylation. In particular, phosphorylation of IRS-1 on serine Ser612causes dissociation of the p85 subunit of PI3-K, inhibiting fur-

ther signalling. In addition, phosphorylation of IRS-1 on Ser307 results in its dissociation from the IR and triggers proteasome-dependent degradation, also impairing insulin signaling (31).

■ A review of the relationship between hyperuricemia, type 2 diabetes mellitus and insulin resistance

Serum uric acid (SUA) is usually overlooked as a potential marker of diabetic metabolic status and insulin secretion estimation. In the medical literature, there are some studies which have proved a positive association between serum uric acid and development of type-2 diabetes. Type 2diabetes mellitus patients have insulin resistance. Higher levels of serum insulin may decrease uric acid clearance by kidneys causing hyperuricemia, the mechanisms behind this association remains obscure. The most conceivable hypothesis is that this occurs at the renal level. Renal tubular function is influenced by hyperinsulinemia, and urinary uric acid clearance decreases with decreasing insulin mediated glucose disposal. Thus, decreased uric acid excretion leads to hyperuricemia(3).

SUA is an antioxidant metabolite that maintains the stability of the vascular endothelium. High levels produce a pro-oxidant environment, endothelial dysfunction, and mitochondrial damage(6). Additionally, the increase of reactive oxygen species (ROS) and inflammatory proteins (interleukin-1, interleukin-6, and TNF-α) are involved in the development of IR and MetS. Previous studies have shown that elevated SUA levels predispose to IR and MetS. Some studies infer that high SUA levels may be both a risk factor and an outcome of some metabolic disorders(6).

Uric acid may also induce mononuclear cells to produced interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), but the most important pro-inflammatory mediators involved in inflammation are IL-6 and TNF-α. The IL-6 activates Src (proto-oncogene tyrosine-protein kinase)-homology 2 domain (SH2)-containing: SHP-2, and signal transducer and activator of transcription 3 (STAT3) resulting in increased expression of cytokine signalling 3 (SOCS3). The IL-6 also activate several serine/threonine kinases such c-Jun N-terminal kinases (JNK), p38MAPK, and PKC-δ which contributes in reducing insulin sensitivity and glucose metabolism.

The TNF-α causes insulin resistance by suppressing IRS- 1 associated insulin signalling and glucose transport in skeletal muscle(32).

Hyperuricemia, hyperlipidemia and inflammation are associated with the development and progression of diabetic kidney injury. Uric acid contributes to the secretion of proinflammatory cytokines such as interleukin 1b (IL-1b) and IL-18. The elevated IL-1band IL-18 levels are observed in diabetic patients with nephropathy. The NOD-like receptors (NLRs) are a family of intracellular sensors of danger-associated molecular patterns. NLR protein 3 (NLRP3, also known as NALP3/Cryopyrin) interacts with the bridging molecule apoptosis-associated speck-like protein(ASC) to activate caspase-1, which is essential for mature IL-1b and IL-18 production. The NLRP3 inflammasome activation promotes kidney injury process with up-regulation ofIL-1b and IL-18 and enhances IL-1b levels in the type 2 diabetes. It is noted that high uric acid level is a causative factor of the NLRP3 inflammasome-mediated inflammation in lung injury. Dyslipidemia is involved in the retarded urateclearance, causing the elevated serum uric acid level. Free fatty acids synergistically enhance urate to activate the NLRP3 inflammasome, being responsible for obesity-induced inflammation and insulin resistance in fat depots of mice. Therefore, serum level of uric acid is suggested as a new player in the development of diabetic nephropathy(33).

Uric Acid may stimulate receptor for advanced glycation end products (RAGE) as a transmembrane multiligand receptor of the immunoglobulin superfamily which has been implicated in many chronic diseases and also inflammation. After the RAGE signaling pathway is stimulated, then the nuclear factor kappa B (NF-κB) will be activated, resulting in the production and release of pro-inflammatory cytokines, and also increasing the expression and extracellular release of high mobility group box chromosomal protein 1 (HMGB1) that causes the amplification of inflammatory response(32).

Uric acid also may decrease glucose-stimulated insulin secretion from pancreatic two main transcription factors, pancreatic and duodenal homeobox-1 (PDX-1) and musculoaponeurotic fibrosarcoma oncogene homologue A (MafA) which bind to their promoter region. It is known that p38 mitogen activated protein kinasee (p38 MAPK) and c-Jun N-terminal kinases (JNK)

which are activated by reactive oxygen species (ROS), are also available in pancreatic islet cells and the amount and activity of c-Jun phosphorylated by JNK are also raise in number by ROS. The c-Jun may interfere the insulin transcription process at the promotor region by translocating PDX-1 from nucleus into cytoplasm and decrease of posttranslational mafA protein level. The mafA is also degradated using proteosomal system and it is enhanced in the uric acid-treated cells, and makes the decreased of insulin gene expression, insulin production, and insulin secretion(32).

Elevated uric acid causes a series of pathophysiological changes through inflammation, oxidative stress and activation of the renin-aldosterone-angiotensin system (RAAS), which subsequently promotes the initiation and progression of multiple diseases including metabolic syndrome(34). Uric acid can lead to the activation of the renin-angiotensin-aldosterone System (RAAS), through increasing the production of juxta glomerular renin. UA-induced ROS stimulated the increase of plasma angiotensin II which induced aldosterone release, leading to activation of RAAS. RAAS activation induced afferent renal arteriolopathy and tubulointerstitial fibrosis in rodent models. In diabetes, RAAS activation causes a range of pathological changes including vascular dysfunction, high intraglomerular pressure, inflammation, and so on, leading to cardiovascular and renal complications (35).

Current studies confirm that oxidative stress and inflammation may be the pathophysiological basis of insulin resistance. Hyperuricemia can promote oxidative stress in many cell lines. The rise of reactive oxygen species (ROS) level can induce insulin resistance. Oxidative stress may be the cause of insulin resistance–related cardiovascular complications because overgenerated ROS and insulin resistance may lead to cardiac dysfunction(16).

A biological mechanism 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. Higher insulin levels are known to reduce renal excretion of urate. Insulin may enhance renal urate reabsorption via stimulation of the urate-anionexchanger URAT1 and/or the sodium-dependent anion cotransporter in brush border membranes of the renal proximal tubule(36).

Variations in uric acid levels have been increasingly associated with insulin resistance, hyperinsulinemia, and diabetes(37). High UA level is found in patients with metabolic syndrome. Insulin resistance can elevate UA by reducing renal urate clearance. Increasing studies verify that insulin resistance is usually accompanied by an increased UA and high UA could induce insulin resistance. While insulin resistance leads to a significant increase in the expression of urate transport-related proteins, an increase in urate reabsorption and an increase in SUA levels. Therefore, hyperuricaemia and insulin resistance may promote each other. Reducing the expression of UA transporter proteins in the setting of insulin resistance downregulates blood UA levels(13).

Uric acid is the end product of purine metabolism and is secreted by the kidney. Elevated levels of SUA can result from decreased renal clearance. Hyperinsulinemia has been postulated to decrease uric acid clearance by the kidneys and to increase serum uric acid. Nitric oxide (NO) is the major endothelium-derived relaxing factor associated with oxidative stress and insulin resistance. Uric acid impairs endothelial function and enhances nitric synthase deficiency, which reduces NO, a known mechanism for inducing insulin resistance(38). Several studies also reported that there is a two-way relationship between insulin resistance and hyperuricemia. Increasing serum uric acid can cause insulin resistance through depressed bioavailability of Nitric Oxide (NO) and eventually creates oxidative stress in mitochondria(39). IR also can cause hyperuricemia through increased sodium reabsorbtion mechanism which caused the increasing absorption of uric acid. Elevation of serum uric acid negatively correlated with insulin sensitivity. This data indicated that hyperuricemia is an important component in MetS and can predict IR(39). One of the possible links between hyperuricemia and insulin resistance seems to be endothelial dysfunction. Hyperuricemia induction in animals resulted in reduced nitric oxide bioavailability, vasoconstriction and the development of microvascular disease and, according to Park *et al*., (2013) (40) uric acid is responsible for attenuating the production of nitric oxide by reducing the interaction between *NOS* (endothelial nitric oxide synthase enzyme), and calmodulin (40). In fact, clinical studies have shown that elevated levels of uric acid are associated with impaired vascular function in children and adolescents. Thus, the hyperuricemia-mediated endothelial dysfunction could result in lower insulin uptake by

reduced blood flow in peripheral tissues (less nitric oxide supply)(5). In addition to interfering with nitric oxide production, uric acid may also be responsible for its degradation. Although, at physiological concentrations, uric acid has antioxidant effects, thus being an endothelial protective factor, the increase in serum levels causes it to play a pro-oxidant role, as its formation pathway through xanthine oxidase produces reactive oxygen species and hydrogen peroxide, which, in excess, will react with the endothelial nitric oxide and create peroxynitrite, an important oxidizing agent(5).

UA is considered to be an antioxidant in human blood, though UA induces oxidative stress in cells. UA raised NADPH oxidase activity and ROS production in mature adipocytes. The stimulation of NADPH oxidase-dependent ROS by UA resulted in the activation of MAP kinase p38and ERK1/2, a decrease in NO bioavailability, and increases in both protein nitrosylation and lipid oxidation. Increased UA production, in turn, generates mitochondrial oxidants. Mitochondrial oxidative stress inhibits aconitase in the Krebs cycle, resulting in citrate accumulation and the stimulation of ATP citrate lyase and fatty acid synthase, ultimately leading to de novo lipogenesis(11).

In hepatocytes treated with high UA, oxidative stress is increased, which activates serine (rat Ser307 and human Ser312) phosphorylation of IRS-1. This activity impairs Akt phosphorylation, thereby resulting in acute hepatic insulin resistance after exposure to high UA levels. Therefore, UA-induced lipid accumulation and oxidative stress are responsible for the development of insulin resistance and diabetes(11).

Most studies of the effect of fructose on serum or urine urates have been limited to a few hours duration(41).Fructose is widely used intravenously as a carbohydrate nutrient. Fructose infusion is indicated in patients requiring fluid replacement and caloric feeding. It is metabolized more rapidly than dextrose without requiring insulin and thus is used in diabetic patients. It is significantly metabolized to fructose-1-phosphate by fructokinase with an abrupt consumption of adenosine triphosphate (ATP) and phosphate, and increased activity of AMP deaminase suppressed by phosphate, consequently, degradation of adenine nucleotide is accelerated, hence increasing the synthesis of uric acid. Fructose also inhibits the excretion of uric acid, apparently

by competing with uric acid for access to the transport protein GLUT-9 (42).

Animal experiments and few intervention studies in human have shown that reducing SUA might improve insulin resistance, which raises great interest in the relation between SUA and DM. In recent decades, a number of prospective observational studies reported a positive association between SUA levels and incident DM risk. In contrast, some indicated a negative association or supported by stander role of SUA in the development of DM(43). Clinical studies have shown a link between hyperuricemia and diabetes; however, it is controversial whether hyperuricemia plays a causal role in diabetes(16). Study by Zafar *et. al*., (2021) (44)aimed to check the correlation of serum uric acid and the indices associated with insulin resistance in metabolic syndrome and healthy male subjects. It was an observational and correlational study; including 200 subjects 120 with MetS and 80 healthy controls. The results observed that serum insulin, glucose, uric acid were higher considerably in the cases than the controls. This study concluded that the correlation of serum uric acid and study variables incriminates the role of uric acid in insulin resistance and associated conditions such as metabolic syndrome, central obesity and altered glycemic metabolism. Raised levels of uric acid can be targeted as a curable risk element in the control of cardiovascular and metabolic derangements (44). In another study by Galindo-Yllu *et. al*., (2021) (6) evaluated the association of serum uric acid (SUA) to Metabolic syndrome (MetS) and insulin resistance in a sample of 292 participants with an average age of 46.2±10.6 years. This study concluded that SUA is strongly associated with MetS in women, and SUA increases hypertriglyceridemia and IR in both sexes(6).

Study by de Miranda *et. al*., (2015) (5) investigated the association between serum uric acid levels and insulin resistance in children and adolescents with obesity. Cross-sectional study with 245 children and adolescents (134 obese and 111 controls), aged 8-18 years. The results demonstrated that prevalence of insulin resistance was 26.9 % . The logistic regression model that included age, gender and obesity, showed an odds ratio of uric acid as a variable associated with insulin resistance of 1.91 (95 % CI 1.40-2.62; $p<-0.001$). This study concluded that the increase in serum uric acid showed a positive statistical correlation with insulin resistance and it is associated with and increased risk of insulin resistance in obese children and adolescents (5).

Additionally, Study by Gil-Campos *et. al*., (2009) (45) evaluated plasma uric

acid in 34 obese and 20 normal-weight children exclusively at prepubertal stage and its relationship with anthropometric measurements, intake, and features of insulin resistance syndrome. The results demonstrated that plasmauric concentration was significantly higher in the obese group than in the control group and when adjusted by sex, age and BMI was positively associated with tricipital skinfold and insulin resistance, and negatively with adiponectin. This study concluded that elevated levels of uric acid in obese children, compared with lean subjects, at the prepubertal period, seems to be an early metabolic alteration that is associated with other features of insulin resistance syndrome(45).

Recently, serum uric acid (SUA) has been regarded as a risk factor for T2DMsince hyperuricemia stimulates insulin secretion and aggravates insulin resistance (34). Hyperuricemia was reportedly found to be related to insulin resistance in several clinical analyses (11). Study by Yu *et. al*., (2021) (46) investigated the association between SUA levels and insulin resistance in individuals without diabetes, thus explicating the role of uric acid in the early stage of the natural history of type 2 diabetes(46).Study by Solanki *et. al*., (2021) (8) reported that there is a positive association between high serum uric acid levels and diabetes. A positive correlation present between SUA and duration of type 2 diabetes is statistically significant. As the duration of diabetes increases than there is an increase in the serum uric acid concentration in type 2 diabetes patients. Average uric acid level elevated from 6.80 ± 0.89 in people with the duration of diabetes 2 to 6 years to 7.72 ± 2.90 in people with the duration of diabetes 7 to 10 years. This studyhas shown a positive correlation existing between SUA and duration of diabetes in the type 2 diabetics (8). In study was conducted to determine the magnitude of hyperuricemia and associated factors among type 2 diabetes mellitus patients. The prevalence of hyperuricemia and metabolic syndrome among type 2 diabetic patients in the study area were 33.8 % (n = 106) and 70.1 % (n = 220) respectively. There was high prevalence of hyperuricemia among type 2 diabetic patients with high prevalence of metabolic syndrome. Therefore, regular health information about life style modification, early diagnosis and treatment for hyperuricemia and metabolic syndrome are essential to reduce hyperuricemia and metabolic syndrome in type 2 diabetic patients(47). Hu *et. al*., (2021) (23) aimed to investigate the association between plasma uric acid and insulin resistance in newly diagnosed type 2 diabetes (T2D). The adjusted b coefficients for Ln-transformed Matsuda index and HOMA2-IR per1 mg/dL uric

acid increment were - 0.070 (95 % CI: - 0.089, -0.052) and 0.057 (95 % CI: 0.039,0.075). These associations were more pronounced among women than men. This study concluded elevated plasma uric acid was associated with higher risk of insulin resistance, along with observation of gender difference in such association (23).

In addition, study by Elizalde-Barrera *et. al*., (2017) (48) aimed to evaluate whether there is a correlation between serum uric acid levels with homeostatic model assessment (HOMA) 1 in non-diabetic patients. The study evaluated 88 non-diabetic patients, in whom uric acid levels were measured, in all of them HOMA of β-cell function (HOMA 1B) and HOMA of insulin resistance (HOMA 1IR)scores were performed. Uric acid and the HOMA 1 values were correlated using the Pearson coefficient. The results suggest that serum uric acid levels seem to be associated with insulin resistance in women, and in obese patients, but not in non-obese men. Uric acid also modifies β-cell function in men and in obese patients(48). Study by Adnan *et. al*., (2019) (39) assessed the relationship between insulin resistance and metabolic syndrome components with the level of serum uric acid. This study found that serum uric acid range in IR between 2.6 and 11 mg/dL compared to non IR 3.4-10.6. The mean value of serum uric acid in IR tended to be higher than in non IR(39). Also, study by Foster *et. al*., (2020) (38) conducted that patients with hyperuricemia demonstrated significant elevations in markers of metabolic syndrome including higher blood pressures, serum glucoses, insulin resistance and triglycerides(38). Study X. Tian *et. al*., (2022) (43) demonstrated that incident DM risk depends on cumulative exposure of SUA and time course of SUA accumulation. Early SUA accumulation resulted in a greater risk increase compared with later accumulation, emphasizing the importance of optimal SUA control early in life (43).

■ Conclusion:

In conclusion, the previous studies demonstrated that hyperuricemia is associated with type 2 diabetes mellitus and insulin resistance. Furthermore, the serum uric acid is also found to be associated risk factors for diabetic complications. Hence, timely diagnosis and management of diabetes is vital to control the complications related to diabetes.

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