REVIEW ARTICLE

ASSOCIATION OF SERUM URIC ACID WITH DIABETES MELLITUS TYPE-2: A NARRATIVE REVIEW

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Diabetes mellitus type 2 (T2DM) is a disease which imposes a great burden on the health resources of the emerging and developing world. It is a global pandemic which leads to chronic complications. Serum uric acid (SUA) is a biomarker that could be of value in detection of early complications and better prognosis in diabetic patients. SUA serves both as a causal factor and disease progression marker in DM, having a causal relationship with diabetic complications. This narrative review aims to determine the association between SUA and T2DM. Research articles from the year 2005 to 2023 were selected for this review. Literature search was conducted from PubMed and Google Scholar which resulted in short listing of 15 articles. It also reflects upon the diabetic complications associated with Hyperuricemia (HUA) and focuses on the health implications of HUA in T2DM patients. SUA and T2DM were negatively associated in 8 research studies and positively associated in 6 studies in which one revealed a partial association, one was prevalent in the female gender only, and one was negatively associated in uncontrolled DM. Another study was associated with both hypouricemia and HUA. SUA levels were moderately increased in moderately elevated glycaemic control and declined in uncontrolled DM with HbA1c levels above 7%.

Keywords: Uric Acid, Glycated haemoglobin, HbA1c, Diabetes mellitus type 2, Biomarker, Complications

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INTRODUCTION

Diabetes mellitus (DM) is a disease which imposes a great burden on the health resources of the emerging and developing world.[1] It is a global pandemic which leads to chronic complications including neuropathy, retinopathy, nephropathy, dyslipidemia, infections, diabetic foot, cardiovascular complications such as stroke and myocardial infarction. The targets of management of diabetes include optimum glycaemic control, which is correlated with HbA1c and is achieved through hypoglycaemic agents. However, a large number of patients are unable to achieve the required target glycaemic control, resulting in progression to chronic complications.[2]

For the purpose of detection of progression of diabetic complications a clinical biomarker is required which could be prognostic in nature. These complications eventually lead to morbidity and mortality in diabetic patients. Hyperuricemia (HUA) is considered as an evolving and rising metabolic disorder, associated with T2DM and obesity. Hence, there is a significant relationship between insulin resistance and HUA. SUA is a biomarker that could assist in detection of early complications and better prognosis in diabetic patients.[3] It could be considered as a predictive marker for renal and cardiovascular complications and as an indicative marker for acute myocardial infarction and chronic coronary syndrome. It could also be considered a therapeutic target in diabetic patients for prevention of disease progression as long term HUA leads to multiple organ damage.[4] Thus SUA serves as both a causal factor and disease progression marker in DM, having a causal relationship with diabetic complications. There is a bidirectional causal effect between HUA and Insulin.[5] It can be used as both a diagnostic and prognostic marker of complications in diabetic patients.[6] It could be recommended as an additional clinical biomarker in all T2DM patients.[7] This could possibly improve patient management in DM. It could also identify potential diabetic patients who could possibly benefit with uricosuric drugs for treatment of HUA. SUA lowering drugs could help prevent diabetic complications, such as diabetic kidney disease (DKD) which leads to the eventual cause of mortality in diabetics.

This narrative review aims to determine the association between SUA and T2DM. It also reflects upon the diabetic complications associated with HUA, and focuses on the health implications of HUA in T2DM patients. Research articles from the year 2005 to 2023 were selected for this review. Articles in English, with abstracts and full texts available, and open accessible were included.

Prevalence of HUA:

According to a systematic review the prevalence of HUA was reported to be 19.01% in T2DM patients.[8] The prevalence of HUA varies in different countries; in India it was found to be 25.8%, 18% in Indonesia, 6% to 25% in China and 10% to 52% in Taiwan. In Uganda, the prevalence of HUA was found to be 38.57%.[3] In a Chinese study the frequency was reported as 35.3%. Another study revealed that the prevalence of HUA ranged from 13.1% to 13.3% in China, 11.9% to 25% in Europe and 11.3% to 47% in USA.[8] In a study

conducted in T2DM patients in Pakistan, HUA was found to be 36.04%, with 47.5% and 52.5% prevalence in females and males respectively.[6]

Primary, secondary and hereditary causes of HUA:

Primary or hereditary causes of HUA include Lesch Nyhann Syndrome and Kelley Seegmiller Syndrome. Secondary causes of HUA include high cell turnover in cancers and myeloproliferative disorders such as lymphomas and leukaemias, tumour lysis syndrome, chemotherapy and radiotherapy, excessive intake of alcohol, fructose and purine rich diet. These account for 10%, while renal insufficiency accounts for 90% of HUA.[9,10]

Role of Uric Acid in Type 2 Diabetes mellitus:

HUA is linked with pancreatic beta (β) cell dysfunction and insulin resistance. The mechanism which is involved in T2DM includes inflammation, oxidative stress and nitric oxide (NO) induced stress of β cells produced by HUA. Glucose transporter 9 (GLUT 9) is considered to be a carrier which is responsible for β cell function and urate transportation.[11] HUA is a major contributing factor in the development of DM and it also contributes independently to diabetic complications.[3]

One of the major complications of diabetes is DKD which comprises of Chronic Renal Failure (CRF) and End-Stage Renal Disease (ESRD). Elevated blood pressure, proteinuria and decrease in estimated Glomerular Filtration Rate (eGFR) are the hallmarks of diabetic nephropathy (DN). The pathogenesis of HUA associated DN involves activation of Renin-Angiotensin-Aldosterone system and oxidative stress. The risk of DN increases with rise in SUA in diabetic patients. SUA not only serves as a potential biomarker but also independently contributes in the development of Chronic Kidney Disease (CKD) and later cardiovascular complications. Therefore it is a predictor of diabetic complications.[12] It has a pathogenic role in their development. These in turn contribute to morbidity and mortality in diabetic patients.[13] A large majority of deaths in diabetic patients is attributed to CRF.[14] Other nephropathies associated with SUA are polycystic kidney disease, immunoglobulin A (Ig A) nephropathy and renal transplantation.

Genetic predisposition of uric acid disturbances:

Several genes encode the uric acid transporters and play a possible role in maintenance of uric acid homeostasis. SLC2A9 (GLUT9) is a transporter gene which if mutated is responsible for derangement of uric acid levels. Epigenetic modification and the role of genetic and environmental factors play a role in SUA levels.[15]

Theories related to HUA and DM:

There are several research studies in terms of uric acid induced DM and elevated SUA levels in DM which are suggestive of a temporal association between HUA and T2DM. There are two central theories that interplay. Firstly SUA secretion is inhibited by insulin resistance and hyperinsulinemia in turn leads to HUA through increased SUA reabsorption. Secondly, HUA leads to oxidative stress and inflammation and decreased levels of NO causing dysfunction of pancreatic β cells. Both are associated with diabetic complications subsequently.[11,16] Some animal studies are also suggestive that insulin secretion is inhibited by HUA.[14]

Pancreatic β cells and insulin resistance:

Through Insulin Receptor Substrate 2/Ak strain transforming or Kinase B protein (IRS2/Akt) signalling pathway in pancreatic β-cells, HUA induces insulin resistance by impairing mitochondrial function. There is also apoptosis of pancreatic β-cells.[17] Insulin contributes in 75% of glucose uptake in skeletal muscles. This is inhibited by HUA in myoblast cell line (C2C12) skeletal muscles.[18] There is a correlation between HUA and adipose induced insulin resistance, which is related to IRS/PI3K/Akt signalling pathway phosphorylation.[19]

Complications of DM related to elevated uric acid:

Oxidative stress:

Excessive production of reactive oxygen species (ROS) is termed as oxidative stress. Elevated levels of uric acid lead to up-regulation of oxidant producing enzymes and thus increased oxidative stress.[20] This leads to vascular inflammation and endothelial dysfunction and cellular damage, and affects insulin gene expression through loss of transcription factors, thus causing decreased secretion of insulin hormone. This eventually results in excessive Xanthine Oxide (XO) production and ROS formation, and diabetes with its complications.[21]

Endothelial dysfunction:

Endothelium releases vasoconstrictors and vasodilators which regulate oxidation, inflammation, vascular tone and thrombosis. Vasoconstrictors include endothelin-1, angiotensin-II and thromboxane A_2, while vasodilators include prostaglandin I_2 and NO. An imbalance between these vasodilators and vasoconstrictors results in endothelial dysfunction.[22] A deficiency of endothelial derived NO results in vascular endothelial dysfunction. This eventually leads to vascular disease and hypertension.[21]

Inflammation:

The expression of CRP, tumour necrosis factor-α (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6) is enhanced by HUA, thus leading to inflammation.[23] The proinflammatory cytokines are released from adipose tissue, pancreatic β-cells, cardiomyocytes, vascular endothelial cells, skeletal muscles, liver, and macrophages. Intracellularly uric acid acts as a pro-oxidant agent while it acts as an antioxidant extra-cellularly.[22] These inflammatory markers are present in much higher urinary concentration in hyperglycaemia as compared to normoglycaemia.[21]

SUA activates several signalling pathways which include mitogen-activated protein kinase (MAPK) pathway. This pathway results in the activation of extracellular signal-regulated kinase (ERK) and p38 group of mitogen-activated protein kinase (p38 MAPK) which release inflammatory cytokines. Another pathway which SUA activates is phosphatidylinositol-3 kinase-Protein kinase B (PI3K)-Akt pathway which also promotes inflammation. Adenosine monophosphate-activated protein kinase (AMPK) pathway which when suppressed by SUA also leads to inflammation.[24]

Renin-Angiotensin-Aldosterone System:
Elevated SUA levels lead to activation of the Renin-Angiotensin-Aldosterone System which results in renal and cardiovascular complications because of increased glomerular pressure and vascular endothelial dysfunction.[23]

Thrombus formation:
Uric acid also gives rise to thrombus formation in vessels through platelet adhesion and aggregation.[23]

Macroangiopathy in DM:
The macrovascular complications in DM include peripheral arterial disease, ischemic heart disease, peripheral vascular disease and cerebrovascular disease.[25] This is caused as a result of hyperglycaemia, altered metabolism and insulin resistance. Macroangiopathy is characterised by angiogenesis, capillary permeability and oedema which give rise to atherosclerosis and rupture of plaques.[26]

Association of uric acid with other diseases:
HUA is also found to be associated with other clinical entities including ischemic heart disease, stroke, hypertension, renal insufficiency, urolithiasis, primary gout, inflammatory arthritis, nephropathy and metabolic syndrome.[27] Neurologic disorders include Alzheimer's disease, Parkinson's disease and Multiple sclerosis. Other conditions also associated with HUA include vitamin D deficiency, cardiac failure, dyslipidemia and obesity. There is involvement of organ systems with the interplay between cell signalling and metabolism.[28] A correlation of HUA also exists with other comorbidities of DM which include neuropathy, retinopathy, nephropathy and Non-alcoholic Fatty Liver Disease (NAFLD). Neovascularization, exudates and microaneurysm are suggestive of retinopathy of both proliferative and non-proliferative types. Diabetic nephropathy determined by eGFR, and microalbuminuria later result in CKD. Diabetic neuropathy included sensory deficit, numbness, tingling and peripheral arterial disease.[29] Hypouricemia is found to be associated with chronic obstructive pulmonary disease (COPD), Parkinson's and Alzheimer's disease. Both fasting blood sugar (FBS) and SUA are associated with loss of renal function.[30] Diabetic complications are also classified as macrovascular (cerebrovascular disease, peripheral arterial disease and coronary heart disease) and microvascular (retinopathy, nephropathy, and neuropathy) respectively. Other life threatening emergencies include diabetic ketoacidosis (DKA) and hyperosmolar non-ketotic coma for diabetes mellitus Type-1 and Type-2 respectively. Atrial fibrillation and severe cardiac failure are also considered as diabetic complications of HUA.[31]

Theoretical application of research to clinical practice:
The recommendations regarding dosage, titration, and effective target SUA levels take into consideration the adverse effects and weigh the potential benefits and risks of initiating an HUA lowering therapy in asymptomatic HUA patients. This decision-making rests with the consulting physicians. Some research studies are suggestive of treatment only in the presence of severity of HUA and symptoms. There are also certain medications which when discontinued result in normal SUA levels such as Thiazide and loop diuretics.[32] A study suggested that SUA lowering drugs in diabetics with DN resulted in controlled glycaemic levels.[14]

Guidelines for management of hyperuricemia:
According to the 3rd edition of Japanese Guidelines on the Management of Asymptomatic HUA, treatment of asymptomatic HUA or HUA with complications is not recommended through pharmacological therapy.[33] There are different criteria for the management of HUA, and research is suggestive of treatment following only urate nephrolithiasis, arthropathy, tophi, and recurrent flares of gout and in patients with several comorbidities. However, guidelines recommend that asymptomatic HUA should remain untreated.[24] Thus the treatment of asymptomatic HUA through urate lowering drugs is still inconclusive. The recommendations of the Japanese Society of Gout are initiation of therapy at SUA levels of 8 mg/dL; while asymptomatic HUA should remain untreated according to the recommendations of the 2020 American Society of Rheumatology Guidelines.[34]

Treatment of HUA:
Hypouricemic drugs aim at lowering the SUA levels. There are two categories of drugs used for the treatment of HUA. These are called uricostatic and uricosuric drugs. The former category includes allopurinol and febuxostat and the later includes benzbromarone, probeneceid and sulphinpyrazone. Uricostatic drugs function by decreasing production of uric acid while uricostatic drugs increase excretion of uric acid.[35] Other classes of drugs include recombinant uricases. Along with xanthine oxidase inhibitors, Lesinurad is also being used for the treatment of HUA.[4] Uric acid lowering drugs such as xanthine oxidase inhibitors used for the treatment of asymptomatic HUA also improve insulin resistance and systemic inflammation. This is because it is hypothesized that SUA lowers NO production and

causes down regulation of insulin sensitisers, thus contributing to insulin resistance.[36]

METHOD

Literature search was done in PubMed and Google Scholar. Initial search revealed 17,500 results of published articles using the terms association of SUA and T2DM, out of which 6,930 (39.6%) articles were found relevant, 276 (4%) were selected for evaluation of title and abstract while 15 (5.4%) were assessed for full-text and subsequently these 15 articles fulfilling the required criteria of original articles were included. Systematic and narrative reviews were excluded from the analysis. (Figure-1)

RESULTS

Literature did not reveal many review articles based on association between SUA and HbA1c in T2DM patients. Literature search conducted from PubMed and Google Scholar resulted in short-listing of 15 articles which revealed the themes of correlation and association of SUA with T2DM. Out of these 15 articles, 8 were consistent with a negative association while 6 were suggestive of a positive association between SUA and T2DM. However in these 6 studies, 1 suggested a partial association of SUA with T2DM, 1 was found prevalent in the female gender only and one explained negative association of SUA with uncontrolled T2DM. One study revealed association of SUA with both hypouricemia and HUA. Thus, SUA was found to be negatively associated with HbA1c and T2DM. These findings are summarized in Table-1.

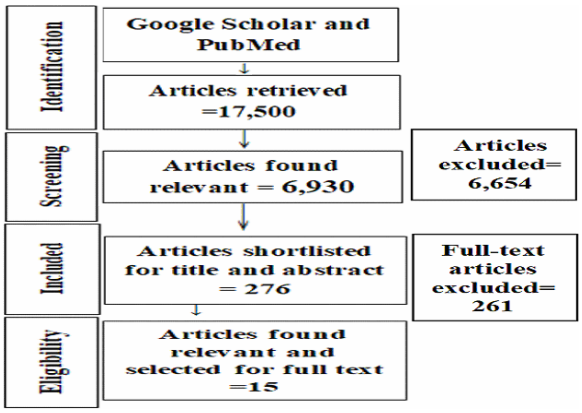

Figure-1: Flowchart based on literature search on association between SUA and T2DM

Table-1: Summary of selected research articles based on association of SUA with T2DM

No.	Authors	References	Results
1.	Yuan *et al*	37	SUA levels decreased with higher glycaemic levels in T2DM patients in comparison with normoglycaemic and impaired glucose intolerance individuals
2.	Hidayat *et al*	38	A negative correlation between SUA and HbA1c and thus T2DM
3.	Xue *et al*	39	Levels of SUA were found to be lower in newly diagnosed or already diagnosed T2DM patients
4.	F. Wei *et al*	40	SUA was found to be inversely related with HbA1c and FBS in T2DM patients
5.	Neupane *et al*	41	SUA and HbA1c were positively associated
6.	Cui *et al*	42	The correlation between SUA and HbA1c is negative in newly diagnosed T2DM patients
7.	Hussain *et al*	43	There was a significant association between SUA and T2DM
8.	Kawamoto *et al*	44	SUA and HbA1c were significantly associated with the female gender
9.	Donkeng *et al*	45	A positive correlation was found between HUA and HbA1c in both controlled and uncontrolled T2DM; while no association was found between HUA and uncontrolled T2DM. HUA was found in female patients >45 years of age
10.	Samin *et al*	46	There was a significant association of SUA with T2DM, however HbA1c was not taken into consideration
11.	Y. Wei *et al*	47	There was an inverse relationship between SUA and HbA1c in T2DM patients
12.	Dhungana *et al*	48	Negative correlation between SUA and HbA1c
13.	Singh *et al*	49	In newly diagnosed patients both hypouricemia and hyperuricemia was found prevalent
14.	Ali *et al*	6	The relationship between SUA and T2DM was found to be linear
15.	Beniwal *et al*	7	No association between SUA and HbA1c

Factors associated with variation in SUA levels:

There are several factors responsible for variation in the prevalence of HUA; these include environmental, geographic, and genetic variations, as well as food preferences and life styles. It is also dependent on the cut-off values taken into consideration for normal SUA values for both the genders separately. Thus patients with HUA are more prone to develop complications in T2DM as compared to normouricemic patients.[3] There are also other modifiable risk factors which could possibly affect SUA levels such as diuretics, alcohol, Dietary Approaches to Stop Hypertension (DASH) style diet and Body Mass Index (BMI). The DASH-diet is based on less sodium intake, beverages, red meat, and higher intake of legumes, nuts, fruits and vegetables, whole grains and low dairy products. The variance in SUA is also based on common genome wide genes. However, several times it is observed that prevalence, exposure or causal effect and variance do not correspond.[50] HUA is also significantly associated with dietary factors such as consumption of seafood and red meat however it was not associated with total protein intake. An inversely related association with cheese, eggs, skimmed milk and non-citrus fruits was also found. However some studies are suggestive of genome wide single nucleotide variance contributing to 23.9% variation in SUA levels. Other factors contributing to renal clearance of SUA are genetic and clinical variants. It also varies with respect to different population distribution. Fractional Excretion of Uric Acid (FEUA) may also have a role to play in the

renal control of SUA excretion related to population specific differences in individuals.[51]

There is a gender variation with relatively lower SUA levels in females as compared to males. This is because of the differences in renal handling of urate in either gender and the uricosuric acid effects of the reproductive hormone oestrogen in the female gender. Therefore the mechanisms involved include higher uric acid fractional excretion and lower uric acid tubular postsecretory reabsorption. Thus it is suggested that a higher level of oestrogen caused higher clearance of SUA levels. A study conducted in premenopausal and postmenopausal females revealed that the SUA levels were found to be higher in postmenopausal women as compared to premenopausal women.[52]

According to a study conducted in China it was revealed that SUA levels increased when HbA1c levels were >5.7%; however they decreased with a further increase in HbA1c levels. Thus SUA levels were moderately elevated with moderate rise in HbA1c. The mechanism by which SUA results in the inhibition of insulin signalling is the recruitment of ectonucleotide pyrophosphatase/phosphodiesterase-1 (ENPP1). SUA genes have a role to interplay in the differences in either gender; SUA in women is lowered by the gene SLC2A9, while in men by ABCG2.[41]

A study revealed that SUA was inversely related with HbA1c but only when insulin levels were high, however there was no correlation when the levels were low. This could possibly be because hexose monophosphate shunt increases both biogenesis and uricogenesis under the influence of hyperinsulinemia. Insulin also promotes reabsorption of SUA in the proximal convoluted tubule. Thus both SUA and HbA1c levels are regulated by insulin.[42] There is a variation and fluctuation in SUA levels with respect to glycaemic control and gender. Studies are suggestive of a bell-shaped relationship between SUA and HbA1c which explain that the levels of SUA are elevated moderately when HbA1c levels are <7% and decline when >7%.[38] Several other reasons have been proposed for lower SUA levels in diabetics; these are low calorie intake, increase in extracellular volume, glycosuria, hyperfiltration and osmotic diuresis.[14] Glycosuria further results in decreased reabsorption of sodium ions in the proximal convoluted tubule, thus further decreasing tubular SUA reabsorption.[48]

CONCLUSION

Several relationships have been developed between the association of HUA and T2DM, which are bi-directionally related. Both are considered as metabolic disorders and either T2DM leads to the development of HUA or HUA is a causative factor in the incidence of T2DM. Our findings are suggestive that SUA and T2DM were negatively associated. Some studies are suggestive of a positive association between SUA and T2DM and development of complications in T2DM. SUA levels have a pathogenic role in the development of diabetic complications of nephropathy. The levels of SUA could possibly be investigated for early detection of diabetic complications, specifically in T2DM patients with moderately controlled glycaemic control. SUA and T2DM were negatively associated in 8 research studies and positively associated in 3 studies. However, one study revealed that SUA was associated with both hypouricemia and HUA.

DISCLOSURE

A part of this narrative review article is based on the M. Phil. (Physiology) thesis submitted to Bahria University Health Sciences Campus, Karachi as a requirement for postgraduate degree.

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