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Hyperuricemia is Equivalent to Type 2 Diabetes - Transforming Myth into Reality

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ABSTRACT

Hyperuricemia is a metabolic disorder characterized by a high level of uric acid in the blood and was commonly thought to be associated with gout and nephrolithiasis. While hyperuricemia and T2D (Type 2 diabetes) are distinct medical conditions, they share certain similarities, and both have significant detrimental effects on humans. The prevalence of hyperuricemia and T2D has been alarmingly rising in the past two decades, and the development of these two conditions among young adults is worrisome for healthcare professionals. Research and debates have recently focused on a possible link between hyperuricemia and T2D. Individuals with persistent hyperuricemia are more likely to develop T2D. The underlying mechanisms contributing to these associations may involve chronic systemic inflammation, oxidative stress, and endothelial dysfunction. They are almost identical in etiology, pathophysiology, complications, and management. Recent studies have revealed an intricate relationship between these two conditions, suggesting hyperuricemia may be equivalent to T2D. Screening for hyperuricemia at an early stage can prevent the development of prediabetes and later overt T2D. This review article aims to explore the concept of hyperuricemia as an equivalent of T2D and shed light on the transforming perception of this association.

Key Words: Uric acid, prehyperuricemia, hyperuricemia, type 2 diabetes, metabolic disorder, non-communicable disorder, endothelial dysfunction, systemic inflammation, oxidative stress, and preventive measures.

INTRODUCTION

The onset of gout, one of the oldest diseases, can be traced back to the early BCs. Two hundred years ago, scientists discovered that high SUA (serum uric acid) levels cause gout. Past knowledge of HU (hyperuricemia) was limited to gout and nephrolithiasis, which are painful forms. Back then, we knew nothing about the pathophysiology of HU. Recently, HU has been recognized as a metabolic disorder. A wide range of diseases, especially T2D, has been linked to HU, making it a significant topic of research and discussion. Accumulating clinical evidence supports that HU is a causal factor for T2D and authenticates that these two diseases go hand in hand. In the modern metabolic era, HU and T2D are common in the rich and the poor. The critical factors linking HU and T2D are insulin resistance (IR) - a hallmark of T2D, systemic inflammation, and endothelial dysfunction. We were previously unaware of an invisible link between the two diseases. However, these two diseases have many similarities concerning their causes, pathophysiology, complications, and management.

To date, few metabolic diseases are reversible, especially T2D. Preventing T2D is more feasible if the possibility of reversal exists. To build on this preventive program, screening for HU is an essential initial step since the modern lifestyle leads to prehyperuricemia (PHU)(SUA between 6-7mg/dL in men and 5-6 in women) [(1)], HU, prediabetes, and later overt diabetes. Thus,

understanding this diversity in the association between HU and T2D may strengthen HU controlling measures and diabetes prevention, improving quality of life.

SEARCH STRATEGY

Articles were referred in Google search and Pub Med from 1975 to 2022 using keywords uric acid, prehyperuricemia, hyperuricemia, type 2 diabetes, metabolic disorder, non-communicable disorder, systemic inflammation and stress, molecular mechanism, and preventive measures. This review article highlights the concept of HU as an equivalent of T2D and sheds light on the preventive measures in the development of T2D.

HISTORICAL SIMILARITIES OF HU AND T2D

Gout has been known since antiquity. Historically, it was referred to as the `king of diseases`, the `disease of kings`, or `rich man's disease`. When we praise gout as king's disease, how can we ignore a `princess disease` – hyperuricemia, which is on the way to ascending the throne by becoming a key contributor to the development of T2D. Sir Alfred Baring Garrod first discovered HU in 1848, and it has been identified with or thought to be the same as gout for centuries. However, HU has been identified as a marker for several metabolic and hemodynamic abnormalities in the past few decades. In 1552 BC, an Egyptian physician, Hesy-Ra, described diabetes as one of the ancient diseases. The importance of insulin in diabetes was determined only in the 1920s [(2)]. Sushruta, the father of surgery, around the 5th century BC, mentioned that diabetes affects predominantly the rich castes [(3)]. In contrary to the past, T2D and HU are ordinary people's disorders in modern-day society, regardless of their age, gender, or income status.

Between these two earliest metabolic conditions, there is considerable overlap. Both diseases have multisystem implications and are characterized by similar pathophysiological mechanisms, such as oxidative stress, endothelial dysfunction, and end-organ damage. One of these conditions can make the other worse.

PREVALENCE OF HU AND T2D.

Over the past few decades, the prevalence of HU and T2D worldwide has seen a noticeable increase. To date, next to T2D, HU is the most prevalent metabolic disorder. Rapid urbanization and changes in lifestyle and food habits may contribute to this. High fructose-containing food, alcohol, and red meat are essential factors in nutritional behaviour. By evolution, the mean SUA level is increased from 4.5 mg/dL to 6.5 mg/dL. The prevalence of HU varies widely from 2.6% to 47.2% in different populations globally and is on the surge. In some populations, its prevalence has increased to 85% (Marshal Island) [(4)]. It has been estimated that 21% of the general population and 25% of hospitalized patients have HU [(5)]. Observing together, there are about 9 million people with gout in the United States, and one in four people with gout have T2D, according to experts. Around 530 million adults worldwide have diabetes, with a global prevalence of 10.5% among adults aged 20 to 79. T2D represents approximately 98 % of global diabetes diagnoses, and the number of people diagnosed with T2D in the United States could rise by nearly 70% by 2060, according to a recent report by `The Centers for Disease Control and Prevention. Additionally, there was an increase in hospitalizations of adults above 18 years with diabetes, from 17.1% in 2000 to 27.3% in 2018[(6)]. In the last two decades, the average age of T2D onset has decreased dramatically from 40-60 years to 30-40 years. A similar increase in prediabetes has also been noted in the younger age group of 20-30 years. The rising incidence of T2D at an earlier age warrants closer attention. Several clinical-based studies have demonstrated an increased prevalence of

T2D in young adults who are obese and hyperuricemic [7].

Researchers forecasted that the number of people under age 20 with T2D in the US may increase by nearly 675% by 2060 if the modern lifestyle trends continue. Those worrisome data and projected numbers should be a wake-up call for all healthcare professionals. These numbers are alarming, and it is concerning that the incidence of HU and T2D has been increasing in recent years, especially among younger age groups.

ETIOLOGICAL SIMILARITIES

Several factors, like rapid urbanization and unhealthy eating habits, may increase the chances of getting either HU or T2D, or both - particularly with the early age of onset. Overconsumption of high fructose-containing food and an inactive lifestyle are the two essential causes of HU, high triglycerides, systemic inflammation, insulin resistance, and later T2D. Furthermore, it is well-recognized that diabetes and HU run in some families.

PATHOPHYSIOLOGICAL SIMILARITIES OF HU AND T2D

The end product of both endogenous and exogenous purine metabolism is UA, of which the kidney excretes 70% and the gastrointestinal tract 30%. UA enters cells at high serum levels, exhibiting as a pro-oxidant and triggering the development of T2D. The possible biological mechanisms underlying this relationship have yet to be fully elucidated. Research indicates that a high level of SUA can lead to oxidative stress, systemic inflammation, and endothelial dysfunction, which results in IR and, thus, T2D [8, 9]. High levels of UA can trigger an inflammatory response by releasing pro-inflammatory cytokines. Low-grade chronic inflammation has been implicated in IR and T2D. The HU initiates oxidative stress by producing reactive oxygen species (ROS), which interfere with insulin signaling, create an inflammatory state, and increase IR. Also, HU reduces insulin production by suppressing pancreatic beta cells.

A few experimental studies indicate that 75 grams of glucose consumption induces acute oxidative stress and inflammation. As glucose levels rise, it becomes pro-inflammatory. In this context, normal-range insulin is anti-inflammatory, whereas hyperglycemia is pro-inflammatory [10]. Conversely, UA exhibits pro-oxidant properties at higher serum levels while functioning as an anti-oxidant at normal levels. In turn, hyperglycemia, hyperinsulinemia, and HU promote inflammation. Epidemiological research findings suggest that hyperinsulinemia and high-dose exogenous insulin enhance the risk of cardiovascular disease by inducing inflammation, similar to HU [11].

DISCUSSION

The field of metabolism still confronts many challenges, particularly with the remarkable progress made in recent years, even after bringing metabolomics to research on hyperuricemia and related disorders. In fact, HU and T2D are two of the most prevalent lifestyle-related diseases and are closely linked to oxidative stress, systemic inflammation, and IR. These two metabolic disorders are preventable and reversible with healthy lifestyle measures.

HU and T2D are different metabolic conditions, yet researchers have found certain common risk factors. Some of these risk factors include rapidly changing eating habits and being sedentary. Therefore, identifying and modifying these factors are beneficial in preventing the disease in high-risk patients. Many risk factors of T2D have been identified, and one of them during this obesity-prone era is HU; both share a common risk relation with an unhealthy lifestyle [12]. Persistently high SUA levels, regardless of other risk factors, increase the risk of T2D, especially in younger people.

Research has shown that prediabetes is linked to a substantial decline in beta-cell glucose sensitivity and a 40% reduction in whole-body insulin sensitivity; this typically

develops into diabetes [13]. The Framingham Heart Study, conducted in two generations, revealed a positive correlation between HU and an increased likelihood of developing T2D in the future[14]. Furthermore, an American retrospective cohort study revealed a significant association with HU and an increased likelihood of developing T2D [15]. The Atherosclerosis Risk in Communities Study also found a correlation between UA levels and a higher risk of T2D after adjustment for other risk factors [16]. These remarkable findings suggest a substantial correlation between a high-increasing HU trajectory and a greater likelihood of T2D [17]. Moreover, the high prevalence of HU and T2D places an alarmingly heavy burden on patients and healthcare systems [18].

Targeted lifestyle modifications may prevent diabetes in high-risk patients, but early identification is challenging. HU plays a significant role in this scenario. A research analysis found a quantitative relationship between SUA level and T2D risks, showing that for every 1 mg/dl increase in SUA, the risk of T2D increased by 17% [19]. To support this, another study observed that the risk of T2D increased by 6% to 17% for every 1 mg/dL increase in SUA concentration [20]. Few other studies found that baseline HU was associated with an increased risk of diabetes by 48% [21]. The population-attributable risk of HU for T2D was 24%, according to another analysis [23].

According to research conducted three decades ago, individuals with prediabetes obviously have higher levels of SUA than individuals with T2D, whereas people with normal glucose tolerance have lower levels of SUA [22]. Studies have shown that SUA plays a crucial role in developing IR, a vital factor in the pathophysiology of T2D [19, 23]. A high dose of allopurinol may have a beneficial role in lowering blood glucose levels and increasing insulin sensitivity. Evidence suggests that some of this effect may be explained by a decrease in SUA, but suppression of xanthine oxidase activity may also be significant [24]. In hyperglycemia, xanthine oxidase activity has been associated with elevated reactive oxygen species (ROS) formation; allopurinol may mitigate this impact [25]. Interestingly, endothelial dysfunction might occur before T2D. In this regard, healthy individuals without diabetes with a first-degree relative with T2D exhibit reduced endothelium-dependent vasodilation and elevated markers of endothelial cell activation.

INSULIN RESISTANCE

Research revealed that the likelihood of developing IR increased by 91% with each 1 mg/dL elevation in SUA levels [26]. It has been widely recognized that SUA and IR are closely related, which could be one mechanism to explain how SUA contributes to the emergence of T2D in obese people. It has been discovered that people with high HOMA-IR (Homeostatic Model Assessment of insulin resistance) had a higher SUA level and that SUA was also an independent risk factor for HOMA-IR. Based on an analysis, SUA played a part in mediating IR, which suggests that an obesity → SUA → IR direct pathway exists in obese children and adolescents [27].

Additionally, SUA-induced IR has been reported to be caused by increased tissue NADPH oxidase or hs-CRP levels [28]. Another possible mechanism by which UA (uric acid) mediates IR and impairs insulin secretion is by increasing mitochondrial oxidative stress and decreasing insulin-dependent stimulation of nitric oxide [29]. Raising the level of SUA can cause increases in monocyte chemoattractant protein-1, which plays a critical role in inflammatory reactions in fat cells [30]. The direct inhibition of insulin signaling by UA and the subsequent development of IR has been identified as the primary mechanism behind hepatic steatosis [31]. IR certainly plays a vital role in the causal link between Mets, T2D, and HU. Furthermore, there is a significant possibility that HU and IR have a bidirectional causal relationship [32]. Research has demonstrated that HU directly

induces IR by inhibiting IRS1 and Akt insulin signaling [33, 34]. The relationship between HU and T2D is not fully understood, but being diagnosed with one can increase the risk of the other and worsen insulin resistance.

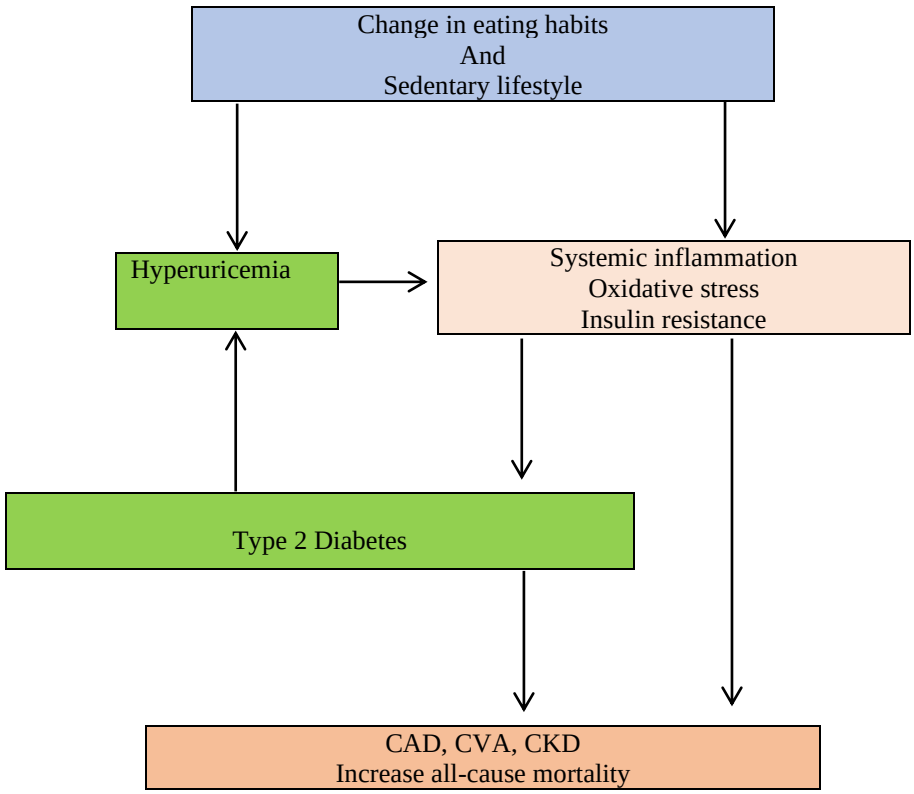

Figure-1. Flowchart: Metabolic equivalence of Hyperuricemia and T2D in Human

HU AND T2D ARE NOT PARALLEL THROUGHOUT.

HU may have a metabolic influence on the progression of T2D; however, this relationship is not consistent throughout the disease. The interaction between UA and blood glucose appears to differ based on the stages of diabetes, such as prediabetes, overt diabetes, and diabetic kidney disease (DKD).

According to epidemiologic studies, prediabetes has significantly higher SUA levels than non-diabetes [35]. SUA gradually increases in prediabetes and decreases as glucose levels increase from prediabetes and T2D [36]. Also, it has been documented that SUA levels decrease as the duration of T2D progresses [37]. In patients with T2D, the SUA level is low due to increased urate clearance [38]. In these diabetes patients, glucosuria exhibits a complimentary uricosuria as a coexisting manifestation [39]. This leads to a transient stage of normal SUA level, and finally, UA increases as DKD develops. Compared with non-diabetes people and T2D, prediabetes subjects have a higher SUA level, which is related to hyperinsulinemia [40]. Viewed separately, a reduction in fasting blood sugar levels associated with a drop in SUA has been observed in non-diabetic people but not in diabetes patients [41]. The mechanisms underlying these changes are raising blood glucose, increasing glucose concentration in the lumen of the proximal convoluted tubule, and inhibiting UA reabsorption, which lowers SUA [39]. In T2D, glucose competitively inhibits UA reabsorption at the same proximal tubule, lowering SUA levels [42]. Hence, due to an urbanized lifestyle, people initially may develop HU, and this triggers inflammation

and hyperinsulinemia, which leads to the first stage of hyperuricemia–hyperinsulinemia–euglycemia; classical prediabetes. In this stage, blood sugar may become normal. If this HU continues for a long duration and preventive measures have not been adopted, these high-risk people develop a prolonged second stage of hyperinsulinemia–hyperglycemia–normouricemia; an uncomplicated T2D that is commonly come across. This is because of the uricosuric effect of hyperglycemia and glucosuria; the SUA level gradually reduces to a normal value. Finally, when DKD develops, the SUA level again slowly increases, leading to the third and final stage of hyperinsulinemia–hyperglycemia–hyperuricemia. These mechanisms may explain the question: why aren't all individuals with T2D hyperuricemic?

RENAL MECHANISMS IN ASSOCIATION WITH T2D AND HU

Under normal conditions, UA is completely filtered in the renal glomeruli and reabsorbed in the proximal tubules. About 5 to 10 percent is secreted into the distal tubules and excreted in the urine. Hyperglycaemia and glucosuria are associated with glucose-competitive inhibition of UA reabsorption in the proximal tubules. Through this process, SUA will gradually decline due to the increased excretion of UA. Therefore, UA-lowering drugs may not significantly affect fasting blood glucose in patients with diabetes since their SUA is obviously lower. Yet, limited pharmacological research shows that administering high doses of UA-lowering drugs, particularly with lifestyle modifications, may positively impact blood glucose levels. This potential benefit is likely attributed to decreased insulin resistance (IR) and inflammation.

OBESITY AND ADIPOSE TISSUE IN HU/T2D

In the present obesity-prone era, HU is becoming one of the most prevalent lifestyle-related conditions like T2D. Recent studies show that adipose tissue is another major organ responsible for UA production [(43, 44, 45)]. Hyperuricemia-induced endothelial dysfunction and direct oxidative changes in adipocytes may be the mechanism underlying the association between HU and metabolic syndrome (Mets), leading to T2D [(46)]. The final step in the production of UA is carried out by the enzyme xanthine oxidoreductase (XOR). Adipose tissue is another vital organ with significant expression and activities of XOR, in addition to the liver and small intestine [(47)]. Obesity is associated with elevated activity of xanthine oxidase and increased UA production by the adipose tissue [(48)].

Hypoxia in obese adipose tissue could be another contributing factor in the development of inflammation. It has been shown that obese adipose tissue is hypoxic, which induces adipose tissue dysfunction involving adipocytokine deregulation and chronic low-grade inflammation [(49)]. Local tissue hypoxia enhances UA synthesis by 3T3-L1 mature adipocytes and up-regulates intracellular XOR activity. Therefore, local hypoxia may be an upstream factor causing high UA synthesis in adipose tissue of obese individuals [(50)].

Furthermore, UA can decrease the synthesis of adiponectin, the specific insulin action enhancer of adipose tissue, and a medium against inflammatory reactions. Hence, HU may lead to endocrine disorders of fat cells by generating low-grade inflammatory responses and IR [(40)].

Since obese individuals have reduced renal clearance of UA, their SUA and IR increase gradually, and later, T2D develops [(51)]. Increased SUA may result from hyperinsulinemia in Mets since high serum insulin reduces UA excretion by the kidneys [(52)]. However, HU is usually detected before hyperinsulinemia in most individuals [(53)]. Euglycemic hyperinsulinemia by administration of exogenous insulin infusion has been observed to reduce urinary excretion of UA [(54)].

Obese children may over-secrete insulin in response to high IR to maintain the fasting blood sugar within the normal range. However, this condition is strongly associated with changes that indicate an increased likelihood of developing HU and T2D in adulthood. People with HUA have a higher chance of developing MetS and T2D, particularly in the young age group. Using UA as a metabolic biomarker may help healthcare professionals detect early and prevent MetS and T2D [(55)]. Furthermore, Doshi et al. identified that the urate reabsorption transporter URAT1 protein has been involved in obesity/MetS-associated hyperuricemia [(56)].

PANCREATIC BETA CELL.

The pancreatic β cells might be affected by elevated SUA levels and contribute to insulin resistance. HU directly inhibits insulin signaling, induces IR and secretion, and leads to T2D [(57)]. Evidence suggests that HU induces pancreatic β cell dysfunction, inhibiting glucose uptake, insulin secretion, glycolysis, and reduction of MMP. Urate crystals have the potential to separate and precipitate in pancreatic islets when HU exists, thereby impairing the function of pancreatic islet B cells and resulting in T2D.

HU/ T2D IN CARDIAC AND RENAL DISEASES: PATHOPHYSIOLOGICAL LINKS

HU and T2D share a common risk factor for cardiovascular complications. Research has shown that individuals with HU are more likely to develop hypertension, CAD, dyslipidemia, and CVA, which are also prevalent among people with T2D. These cardiovascular complications further emphasize the potential metabolic equivalence between HU and T2D. DKD occurs in approximately 40% of individuals with T2D, and this percentage is projected to grow because of the increasing incidence of T2D [(58)].

T2D and HU have a significant association with increased all-cause mortality. Furthermore, the co-occurrence of T2D and HU significantly amplifies the chances of all-cause mortality; one may increase the risk of the other [(59)].

TREATMENT IMPLICATIONS

A prospective study demonstrated the predictive abilities of HU changes for T2D. Consequently, in the clinical guidelines for preventing T2D, individuals with HU deserve greater attention, particularly those with persistent HU [(60)]. Currently, HU, PHU, and prediabetes are not considered an indication for pharmacotherapy. Still, as a metabolic disorder, this needs non-pharmacological measures like lifestyle modification to prevent the development of T2D and other HU/T2D-associated diseases. A five-year study observed that, after adjusting for significant covariates, a 10% drop in SUA was linked to a 16% lower risk of T2D. These crucial observations suggest that lowering SUA may prevent the onset of T2D in HU people [(61)]. The growing evidence suggesting the equivalence of HU and T2D has significant implications for managing both conditions. Targeting HU through lifestyle modifications, such as dietary changes and weight management, may help to prevent or delay the onset of T2D. Similarly, interventions to improve insulin sensitivity and reduce inflammation can benefit individuals with HU in preventing T2D.

In recent years, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have emerged as a promising advancement in managing T2D and HU. In addition to its glycemic control, this drug offers several advantages, including uric acid-lowering effects, improved systemic inflammation, weight reduction, and CKM syndrome (cardiovascular-kidney-metabolic syndrome) benefits. This unique effect further extends their potential utility in managing these dual conditions.

Unless urgent measures are taken to address the issues of unhealthy eating, sedentary lifestyles, rapid urbanization, and other factors associated with economic development, the global incidence of

diabetes is projected to keep rising [62]. Adopting a healthy lifestyle and food habits can significantly decrease chronic inflammation.

MEASURES TO PREVENT HU AND T2D

Maintaining an ideal body weight, eating a balanced diet, drinking plenty of water, doing regular exercise, avoiding high-purine foods and high fructose-containing food, limiting alcohol, – and, in short, following a low-inflammatory diet may help in the preventive measures. If UA is shown to be a mediator of incident T2D in humans, then lowering SUA would represent a simple and cost-effective way to prevent the development of T2D and to slow the metabolic epidemic. Many authors have reported that a reduction in SUA is associated with a decreased risk of T2D. In terms of clinical significance, monitoring SUA regularly and maintaining SUA at a safer level may contribute to preventing and delaying T2D [63].

CONCLUSION

Hyperuricemia and T2D are two different metabolic disorders known since ancient times. The prevalence of these conditions has surged substantially in recent years, specifically among young adults. Researchers observed a significant relationship between these two conditions, aggravating each other's severity and overlap. Several factors, such as cause, pathophysiology, complications, and management, are identical. The basic pathophysiological similarities observed are oxidative stress, endothelial dysfunction, systemic inflammation, and insulin resistance. At present, it is not fully understood what is causing the rapid rise in diabetes cases, but hyperuricemia has been attributed as a significant factor because both diseases are associated with a modernized lifestyle and unhealthy eating habits. Furthermore, a reduction in serum uric acid may delay the development of T2D. Screening for hyperuricemia could be an essential initial step in the T2D preventive program in the future. The perception of hyperuricemia as an equivalent of T2D gradually transforms from a myth into reality. Further research is needed to elucidate the underlying mechanisms and develop effective preventive strategies fully. By understanding and addressing the connection between hyperuricemia and T2D, healthcare professionals can work towards better management and improved outcomes for at-risk individuals.

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