

The Management of Diabetes with Hyperuricemia: Can We Hit Two Birds with One Stone?

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Abstract: Serum urate (SU) is an independent predictor for the incidence of diabetes. In current diabetes treatment regimens, there is insufficient appreciation of the importance of hyperuricemia (HU) in disease control and prevention. To summarize the updated knowledge on the effects of SU on β -cell function, insulin resistance and chronic diabetic complications, as well as to evaluate the management of patients with both HU and diabetes, we searched the MEDLINE PubMed database, and included 285 journal articles. An inverted U-shaped relationship between fasting plasma glucose and SU levels was established in this review. Elevated SU levels may enhance the development of chronic diabetic complications, including macrovascular and microvascular dysfunction. Diet and exercise are essential parts of the lifestyle changes necessary for HU and diabetes management. Glucose- and urate-lowering drug selection and combination should be made with the principle of ameliorating, and at least not deteriorating, diabetes and HU. Medical artificial intelligence technology and monitoring systems can help to improve the effectiveness of long-term management of HU and diabetes through digital healthcare. This study comprehensively reviews and provides a scientific and reliable basis for and viewpoints on the clinical management of diabetes and HU.

Keywords: diabetes, hyperuricemia, U-shaped relationship, urate-lowering treatment, management

Introduction

A large body of recent evidence suggests that hyperuricemia (HU) may play a role in the development and pathogenesis of a number of metabolic, hemodynamic and systemic pathological diseases, including diabetes mellitus (DM).^{1,2} Serum urate (SU) is a strong and independent risk factor for type 2 diabetes (T2D), and the incidence of HU increases in diabetic patients compared with their unaffected counterparts.^{3,4} In the past few decades, a great many clinical, epidemiological and experimental studies have revealed that HU mediates all stages of diabetes as well as diabetic chronic complications,^{5,6} from initiation to progression. In addition, uric-acid based metabolic indices are associated with T2D⁷ and its complications, including diabetic kidney disease.⁸ Moreover, conditions that are related to T2D are also associated with uric acid elevations, such as hypertension,⁹ metabolic syndrome¹⁰ and hepatosteatosis.¹¹ However, in current diabetes treatment regimens, there is insufficient appreciation of the importance of HU in disease control and prevention. The management of hyperuricemic patients demands more attention and specific features in diagnosis and the therapeutic approach.

We searched the MEDLINE PubMed database with the terms “((urate) OR (uric acid)) OR (hyperuricemia)) AND ((diabetes [MeSH])) AND ((epidemiology) OR (mechanism) OR (treatment))” and found 285 journal articles that had published experimental results (ie, not reviews) in English between 2012 and October 2023. This article summarizes the most recently published evidence on the relationship between diabetes and HU, and adds some updated knowledge, with an emphasis on how to improve the management of diabetic patients with HU.

Epidemiology

HU is defined as an SU level greater than 420 $\mu\text{mol/L}$ (or 7.0 mg/dL). Increased life expectancy and changes in diet and lifestyle have resulted in rising incidences and prevalences of both HU and diabetes worldwide, and especially in China. A nationally representative epidemiological survey by Li et al indicated that the overall prevalence of diabetes in mainland China in 2017 was 12.8%, using the American Diabetes Association (ADA) diagnostic criteria.¹² Although there is an absence of nationwide epidemiological data for HU, a meta-analysis published in 2020 showed that the pooled prevalence in Chinese adults was 11.7% in rural areas and 16.8% in urban areas.¹³ A cross-sectional survey by our team indicated a dramatic increase in prevalence of 25.4% among Chinese adolescents.¹⁴

Some prospective studies found that SU is an independent predictor for the incidence of T2D in middle-aged and elderly Chinese people.^{15–17} Dose–response analysis showed the risk of T2D increased by 6% per 1 mg/dL increment in SU (multivariate adjusted relative risk: 1.06; 95% confidence interval: 1.04–1.07).¹⁵ Another meta-analysis of 11 combined cohort studies found a significant relationship between elevated SU level and risk of developing T2D, indicating a 17% increment in the risk of diabetes per 1 mg/dL increase in SU level.¹⁸ Uricase (Uox) catalyzes the first reaction of oxidative uricolysis, eliminating purine nitrogen through a water-soluble compound in hominids. It has been postulated that the loss of uricase in humans may have raised hepatic uric acid levels, thereby stimulating hepatic glucose production and serum glucose levels.¹⁹ Thus, the loss of uricase may have functioned as a “thrifty gene”, as proposed by James Neel,²⁰ which would have improved survival during food scarcity but in modern societies may predispose to diabetes.

Regarding the association between fasting blood glucose and SU levels, we analyzed the data from an epidemic survey of 1367 male participants in Shandong Province, China ([Supplementary Methods, sTable 1](#)). An inverted U-shaped relationship between fasting plasma glucose (FPG) and SU levels was found in Chinese populations aged 18–94 years, showing an upward trend of SU with increased FPG and then a downward slope of the relationship ([Figure 1](#)). After adjusting for age, body mass index, triglycerides and fasting plasma insulin, the same trend was found, with the FPG threshold decreasing from 7.01 mmol/L ([Figure 1A](#)) to 6.63 mmol/L ([Figure 1B](#)).

Hyperuricemia, Diabetes and Chronic Diabetic Complications

Effects of Urate on β -Cell Function and Insulin Sensitivity

Insulin resistance and β -cell failure are regarded as two key events in T2D development. The association of HU with insulin resistance and β -cell dysfunction has already been well demonstrated, but whether there is a causal relationship is still inconclusive.

Wan et al²¹ found that urate directly induces hepatic insulin resistance in diet-induced HU mice. Mice fed a high-fat and purine-rich diet showed more impaired glucose metabolism compared with those fed a high-fat diet (HFD) alone. Their study also indicated Nod-like receptor protein 3 (NLRP3) as the modulator between urate and insulin resistance.²¹

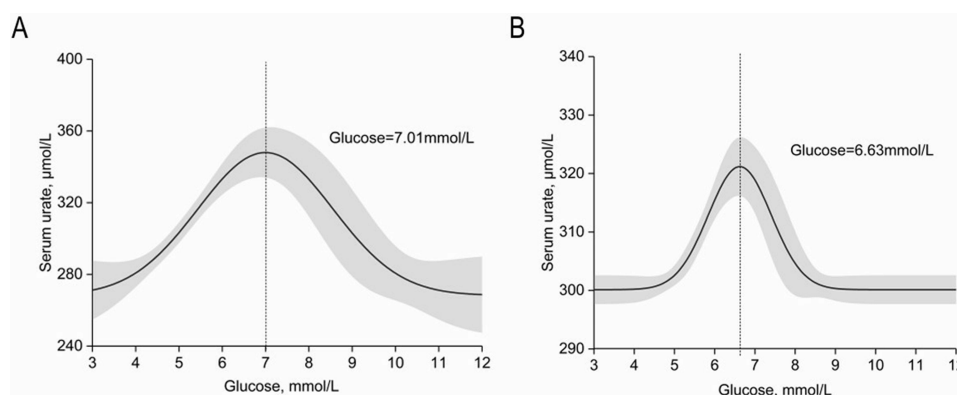


Figure 1 Relationship between fasting plasma glucose and serum urate level. The possible nonlinear relationship between glucose (mmol/L) and SU ($\mu\text{mol/L}$) was calculated by generalized smoothing splines with four knots in generalized additive models. An inverted U-shape is shown, with glucose thresholds of **(A)** 7.01 mmol/L in the unadjusted model and **(B)** 6.63 mmol/L in the model adjusted for age, body weight index, triglyceride and fasting plasma insulin. The 95% confidence intervals are shown as gray shaded areas. Data management and analyses were performed using SPSS v25.0 and Origin v9.0.

However, in our more recent research performed on genetically modified HU mouse models, HFD-fed *Uox* deficiency (*Uox*-KO) male mice only displayed glucose intolerance, without changed insulin sensitivity.²² We presume that the relationship between urate and insulin resistance would be detected in sugar-/fructose-fed *Uox*-KO mice, as urate-dependent insulin resistance occurred in models of sugar/fructose induction.²³ Moreover, several clinical trials have suggested that urate-lowering therapy in hyperuricemic patients does improve insulin resistance or fasting glucose concentrations.^{24,25} Although Han et al²⁶ presented a cross-lagged path analysis in China and found that urate was likely to be causal for insulin resistance, three Mendelian randomization studies found that genes that predict SU levels do not predict the risk of T2D.^{27–29} Another clinical study, on 299 women with recent gestational diabetes, showed that SU does not track with changes over time in insulin sensitivity, β -cell function or glycemia, adding to evidence suggesting that HU does not directly contribute to the development of diabetes.³⁰

The effects of HU on pancreatic islet β -cells are also controversial. In vivo data suggest that an elevated level of urate causes β -cell injury directly via the nuclear factor-kappa B-inducible isoform nitric oxide synthase–nitric oxide (NF- κ B-iNOS-NO) signaling axis.³¹ Lu et al²² reported that urate participates in the transition from impaired glucose tolerance to diabetes via the action of prompting β -cell apoptosis. In this study, the *Uox*-KO mouse models received the HFD accompanied by multiple low-dose streptozotocin injections, and eventually developed diabetes, accompanied by increased β -cell apoptosis and hypoinsulinemia, which are pathophysiological determinants of diabetes.²² However, substantial short-term urate-lowering therapy did not enhance β -cell survival,²² which could be explained by the hypothesis in Figure 2. Tang et al³² report that subjects with higher levels of SU had higher levels of insulin secretion, including the early-phase and total insulin secretion. Although subjects with higher SU secrete more insulin, this does not mean that high SU is beneficial to β -cell function.

Although investigations on the effects of urate on inflammatory cell activation initially focused on the effects of urate crystal, more recent studies have found soluble urate to have many pro-inflammatory and pro-oxidative effects in the intracellular environment. Zhang et al³³ showed that HU induced oxidative stress and increased reactive oxygen species (ROS) levels in cultured rat pancreatic β -cells, which activated adenosine monophosphate-activated protein kinase (AMPK) and the extracellular signal-regulated kinase (ERK) signaling pathway, and ultimately decreased cell growth and insulin secretion. Another study showed that HU impaired mitochondrial function and reduced insulin secretion through the IRS2/Akt signaling pathway in pancreatic β -cells.³⁴ Since T2D is also characterized by an increased burden of inflammation,³⁵ SU elevation may be a reflection of the inflammatory burden. Compelling evidence suggests that

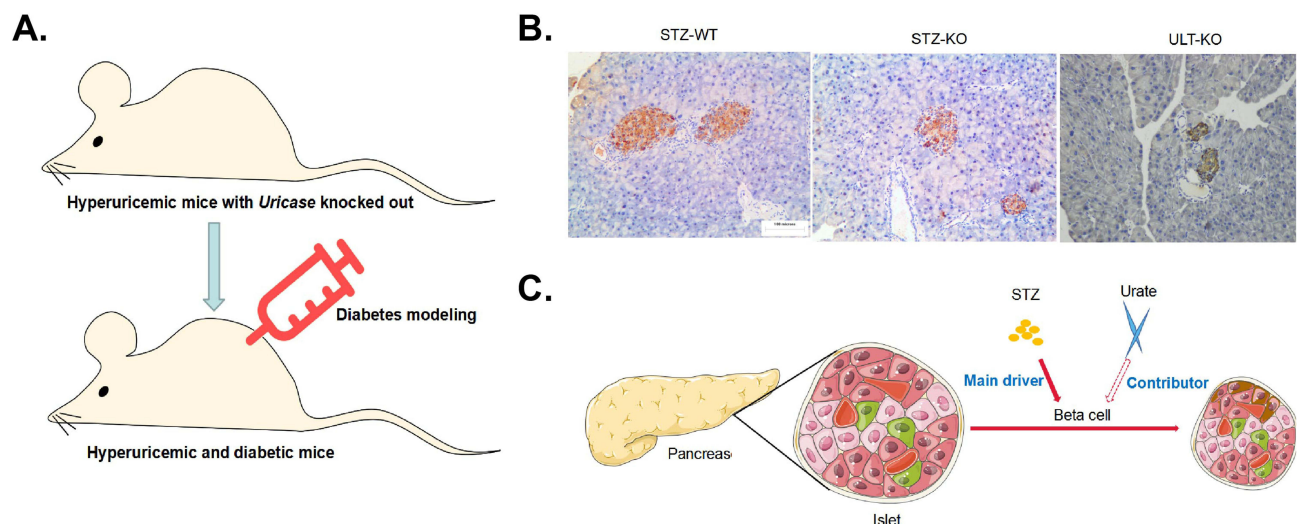


Figure 2 Hypothesis of the effects of urate on the streptozotocin (STZ)-induced diabetic mouse model. **(A)** Establishment of the hyperuricemic and diabetic mouse model based on uricase-knockout mice. **(B)** Urates lowering therapy reversed few pancreatic β -cell deaths stimulated by multiple low-dose STZ. Pancreatic sections were immunohistochemically stained for insulin (data from Lu et al, 2020).²² **(C)** Schematic figure showing that STZ is the main driver in the toxic attack on β -cells, while urate just plays a contributory role in diabetes, explaining why urate-lowering therapy could only partially reverse β -cell apoptosis.

activation of the NLRP3 inflammasome has a central role in both soluble urate³⁶ and T2D.³⁷ Therefore, NLRP3 inflammasome could be a possible therapeutic target for attenuating HU- and T2D-induced inflammation.

Effects of Urate on Chronic Diabetic Complications

Effects of Urate on Macrovascular Dysfunction

Resl et al³⁸ conducted a prospective observational study in which 494 patients with diabetes were followed for 12.8 months, and underscored the importance of SU as a cardiovascular risk marker in patients with diabetes. SU is related to known risk factors such as hypertension and cerebral infarction. Further, Bjornstad et al³⁹ indicated a positive association between SU and systolic blood pressure (SBP) in adults with diabetes over a 6-year follow-up period. More recently, it was demonstrated that HU strongly predicts the onset of hypertension in adolescents with T2D.⁴⁰ A Mendelian randomization study among a Chinese population of females with diabetes supported a causal effect of SU on diabetic macrovascular disease through a genetic risk score, which was calculated using 17 selected single-nucleotide polymorphisms and the strength of their effects on SU levels.⁴¹ The possible mechanism of SU and diabetic macrovascular dysfunction could be the stimulation of the renin–angiotensin–aldosterone system (RAAS), thereby promoting ROS production and resulting in inflammation.⁴²

Effects of Urate on Microvascular Dysfunction

Diabetic nephropathy is one of the most common diabetic microvascular complications. HU was found to be associated with an increased rate of progression of chronic kidney disease (CKD) in a prospective cohort of 422 individuals with an average of 15 years of T2D and a follow-up period of 43-months.^{43,44} Of patients with diabetic nephropathy, a large proportion of patients with SU levels higher than 378 $\mu\text{mol/L}$ will have a poor prognosis.⁴⁵ Other research reported that a doubling in the SU level is an independent risk factor for the loss of the kidney function in patients with T1D, including a decline in the estimated glomerular filtration rate (eGFR) of $\geq 30\%$ and an increase in the urine albumin creatine ratio.⁴⁶ A Japanese cohort study of 1802 patients with T2D found that an elevated SU level and male gender are risk factors for albuminuria, but not a decrease in eGFR.²⁵ However, there was no evidence of a causal relationship between SU and the development of diabetic nephropathy in a Mendelian randomization study.⁴⁷ Moreover, SU levels were higher in patients with peripheral arterial disease (PAD) than in those without PAD (345.0 ± 95.2 vs 309.3 ± 89.2 $\mu\text{mol/L}$).⁴⁸ PAD in hyperuricemic patients may be caused by elevated purine oxidation, which leads to increased ROS, accompanied by reduced NO, and subsequent vascular injuries.

Management of Diabetes with Hyperuricemia

Diet

Carbohydrates

For individuals with HU and diabetes, carbohydrate intake is encouraged, with a focus on fresh vegetables, legumes, fruit and dairy products, and especially foods with a high insoluble fiber content and low glycemic load. Given the contrary effects between whole grains and refined grains, owing to differences in their purine content and glycemic index (GI), patients should carefully balance their daily grain intake. Although fructose has a low GI, there is evidence to suggest that visceral adiposity and increased cardiometabolic risk are linked to the metabolism of fructose, which produces urate as a byproduct.⁴⁹ Although the intake of fruit is limited in patients with HU and diabetes,⁵⁰ we also note that the fiber, vitamin C and flavonoids in fruit can block urate production.^{51–53}

Protein

Avoidance of purine-rich animal protein (eg, red meat, seafood, poultry and visceral organs) is helpful for hyperuricemic patients. In addition to animal products, some vegetable protein sources (eg, legumes, soy products and sea vegetables) contain a high purine load as well, although their protective elements could prevent the elevation of SU levels and reduce the risk of gout attacks.^{51,54} Choosing diets containing high-quality protein is the common principle for both hyperuricemic and diabetic patients.

Fats

Diets high in unsaturated fatty acids increase the level of high-density lipoprotein (HDL) cholesterol, which increases the risk of HU.⁵⁵ A Mediterranean-style eating pattern, which emphasizes less animal protein and less saturated fatty acid, is recommended for both hyperuricemic and diabetic patients.^{56,57} Multiple randomized controlled trials including patients with T2D have reported that a Mediterranean-style dietary pattern, rich in polyunsaturated and monounsaturated fats, can benefit both glucose and lipid control.⁵⁸

Micronutrients

Higher plasma vitamin C is associated with a lower risk of HU, by promoting uricosuria in the renal proximal tubules and resisting the pro-oxidative effects of urate.⁵⁹ Folic acid therapy was shown to have a urate-lowering effect in hypertensive patients in the China Stroke Primary Prevention Trial.⁶⁰ A randomized, double-blind, placebo-controlled study observed that treatments combined with glycine and tryptophan increase the solubility of urate and alkalinize the urine, thus helping to reduce the SU concentrations.⁶¹ Dietary minerals such as zinc and magnesium have been found to be inversely associated with HU among US adults in a cross-sectional study.^{62,63} The dietary suggestions are listed in Table 1.

Physical Activity

Exercise is a double-edged sword for gout patients, with moderate exercise helping to lower SU and excessive exercise leading to gout flare. Avoiding extended sedentary periods, and undertaking regular resistance exercise or moderate-to-vigorous intensity aerobic activity are recommended for diabetic patients.⁶⁴ Randomized controlled trials show that intensity training improves β -cell function and decreases pancreatic fat.⁶⁵ However, slow-motion and non-weight-bearing activities, such as swimming, walking or taiji, are recommended for HU patients. With regard to exercise time, 20–60 minutes daily or 150–300 minutes weekly may be recommended. It is critical to pay attention to exercise-induced hypoglycemia and dehydration.

Pharmacotherapy

Glycemic Control

Accumulating data have proved that diabetes and hypoglycemic agents have an impact on renal urate excretion. Hypoglycemic agents with identified urate-lowering effects include α -glucosidase inhibitors, insulin-sensitizing agents, thiazolidinediones (TZDs), sodium–glucose co-transporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors (DPP-4i) and biguanides, which would be the first choice for patients with diabetes and HU. Insulin initiators are not recommended as they increase the levels of SU via the regulation of urate transporter-1 (URAT1) and ATP-binding

Table 1 Dietary Recommendations for Diabetic and Hyperuricemic Patients

		Diabetes	Hyperuricemia
Carbohydrates	Vegetables	✓	✓
	Fruits	✓	✓
	Whole grains	✓	X
	Refined grains	X	✓
	Sugar-sweetened beverages	X	X
	Nuts	✓	✓
Protein	Plant-based	✓	✓
	Animal-based	X	X
Fats	Saturated fats		
	Unsaturated fats	X	✓
Micronutrients	Vitamin C	✓	✓
	Dietary zinc	✓	✓

cassette subfamily G member-2 (ABCG2).⁶⁶ If insulin initiators are required, one strategy is to combine them with insulin-sensitizing drugs or α -glucosidase inhibitors to neutralize the increase in SU.

A significant urate-lowering effect of pioglitazone (30 mg/day for 24 weeks) has been observed in patients with urate kidney stones.⁶⁷ Pioglitazone users present a dose-dependent decrease in gout incidence as well.⁶⁸ These two reports indicate that pioglitazone assists the management of HU/gout in diabetes, without changes in renal urate excretion.⁶⁷ A meta-analysis of 62 clinical trials showed that SGLT2i reduce circulating urate by inducing uricosuria, and contribute to cardiorenal benefits.⁶⁹

DPP-4 inhibitors decrease SU; an in vivo experiment proved that DPP-4 inhibitors mediate multiple beneficial effects by inhibiting the adenosine deaminase–xanthine oxidase–urate pathway, improving insulin resistance, and inhibiting oxidative stress and hepatic triglyceride accumulation.⁷⁰ Considering the weight-loss effect of glucagon-like peptide-1 (GLP-1) receptor agonists, there should be a parallel urate-lowering effect. However, the available clinical evidence indicates that liraglutide and exenatide have no effects on SU levels.⁷¹

Urate-Lowering Therapy (ULT)

Allopurinol is the first xanthine oxidase inhibitor (XOI) to be prescribed in patients with HU and gout. Despite its remarkable efficacy and lower price, the risk of allopurinol hypersensitivity syndrome (AHS) is the main concern, especially in patients of Asian and African origin.⁷² Thus, it is a priority to test for the HLA-B*5801 allele before starting allopurinol treatment. For patients with accompanying diabetes, allopurinol was shown to increase the risk of hypersensitive reactions compared with those without diabetes.⁷³ Febuxostat is a specific XOI that is especially suitable for patients with chronic renal insufficiency. However, considering the cost and the potential adverse cardiovascular effects, the European and American guidelines generally recommend febuxostat as an option for patients who are intolerant to allopurinol or present signs of poor efficacy.⁷⁴

Benzbromarone decreases urate reabsorption by inhibiting URAT-1 in the proximal renal tubules, and is suitable for patients with reduced excretion of renal urate. Increased water intake and urine alkalization will protect against the deposition of sodium urate crystals in the kidney. In a retrospective cohort study on a population with gout, the incidence of newly developed diabetes was lower in benzbromarone users than in non-users.⁷⁵ An in vivo study showed that benzbromarone dependently reduced blood glucose levels and rectified insulin resistance in *db/db* mice, and the authors also reported that the glucose-lowering effect is due to the inhibition of fatty acid-binding protein-4 (FABP4), which plays an important role in maintaining glucose homeostasis, making benzbromarone a potential drug candidate for the treatment of diabetes.²⁶ In patients taking benzbromarone, one should pay attention to the liver function, as benzbromarone causes serious hepatotoxicity in Caucasians, although this is rare in Asian populations.

Although accumulating data suggest that higher SU levels have a detrimental effect on renal function, the potential benefits of ULT in individuals with asymptomatic HU are still under debate. Evidence from diabetic rat models indicates the advantages of XOI, including rectification of glucose intolerance and the insulin resistance state,⁴⁸ amelioration of albuminuria and renal oxidative stress,⁷⁶ and different degrees of improvement in glomerular sclerosis and tubulointerstitial fibrosis.⁷⁷ Clinical trials also suggest that allopurinol can decrease albumin excretion and slow the decline in eGFR in adults with diabetes.⁷⁸ However, a multicenter, randomized, double-blind, placebo-controlled study showed that patients receiving febuxostat had no significant benefit or deterioration in renal function after 12 months of follow-up.⁷⁹ Consistently, no detectable effects of febuxostat on the eGFR were observed in patients with T2D and diabetic nephropathy in another double-blinded randomized controlled trial.⁸⁰ The Preventing Early Renal function Loss (PERL) trial found no evidence of clinically meaningful benefits of allopurinol on kidney outcomes among patients with T1D and early-to-moderate diabetic kidney disease.⁸¹

Given the discrepancies between studies and the potential adverse cardiovascular and cutaneous events induced by allopurinol or febuxostat, the risk/benefit ratio of ULT in this indication is unclear. Every effort should be made to avoid prescribing ULT for inappropriate indications.

Table 2 Principles of Medical Management of Diabetes with Hyperuricemia

Methods of Treatment	Principle
Glycemic control	a. Insulin-sensitizing agents and biguanides are the drugs of choice for lowering glucose. b. The second option is an α -glucosidase inhibitor. c. Avoidance of or limiting insulin secretagogues or insulin.
Urate-lowering therapy	a. 580I genotyping is necessary when initiating allopurinol treatment. b. Increased water intake and urine alkalization protects against deposition of sodium urate crystals in the kidneys when taking benzbromarone.
Blood pressure control	a. Losartan and amlodipine are the first choices for patients with hypertension complicated with HU. b. Thiazide diuretics should be avoided in patients with HU.
Antilipemic agents	Fenofibrate and atorvastatin calcium are preferred for patients with hyperlipidemia complicated with HU.
Anticoagulant agents	Although aspirin has the potential to significantly elevate serum urate levels, it should not be discontinued in patients with a history of diabetic macrovascular and microvascular dysfunction.

Blood Pressure Control

A prospective study on Japanese men without hypertension showed that HU may have a longitudinal association with the development of hypertension after 9 years' follow-up.⁸² About 40–60% of hyperuricemic patients were complicated with clinical hypertension. Losartan and calcium channel blockers have been found to have a urate-lowering effect and to reduce the risk of gout attacks.⁸³ Potassium diuretics, beta-blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (except for losartan) should be avoided as they have an elevating effect on SU.

Antilipemic and Anticoagulant Agents

HU was found to be associated with dyslipidemia and atherosclerosis. Our previous research demonstrated that allopurinol can alleviate atherosclerosis inflammatory cytokines and neointimal lesions which were possibly induced by HU in mice.⁸⁴ A large randomized controlled trial demonstrated that fenofibrate reduced SU by 20% after 6 weeks' follow-up and halved the incidence of a first gout attack over 5 years.⁸⁵ Therefore, fenofibrate is recommended as the first choice of antilipemic drug in HU patients complicated with hypertriglyceridemia. Besides, atorvastatin calcium was recommended as the first-line drug for HU patients with high levels of cholesterol owing to its role in promoting renal urate excretion.⁸⁶ Aspirin is a widely used antiplatelet agent used to prevent thromboembolic events, but the effect on SU levels is still controversial.⁸⁷ The medical management principles are listed in Table 2.

Monitoring Technology

Lifestyle monitoring technology for the detection of health deterioration in long-term conditions has been applied in diseases such as heart failure⁸⁸ and dementia,⁸⁹ as well as in diabetes. A 3-month follow-up study, including 1354 participants, showed that the higher the levels of patient activation and engagement with remote patient monitoring technology, the better the outcomes of glycemic control.⁹⁰ Wearable sensor technologies help to realize personalized medicine through continuous monitoring, and have been applied to the detection of glucose⁹¹ and uric acid levels.⁹² The development of artificial intelligence technology could be important in improving the effectiveness of the management of HU and diabetes.

Conclusion

An inverted U-shaped relationship between FPG and SU levels was established in this review. SU has been recognized as a predictor of DM development, with effects on chronic diabetic complications, both macrovascular dysfunction (hypertension and cerebral infarction) and microvascular dysfunction (chronic kidney disease and peripheral arterial disease). Furthermore, the association of HU with insulin resistance and β -cell dysfunction has already been well demonstrated, but whether there is a causal relationship remains inconclusive. We have outlined the recent ideas on HU and diabetes management, including diet, physical exercise and medicine. Choosing medicines balancing the SU and blood glucose levels is critical in therapeutic management. Medical artificial intelligence technology and monitoring

systems can help to improve the effectiveness of long-term management of HU and diabetes through digital healthcare. To summarize, in light of the preceding discussion on the relationship between HU and diabetes and their effects on complications, we can reconsider the optimal approach to the management of hyperuricemic and diabetic patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors have read and approved the final submitted manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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