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Review

Drug-induced hyperuricaemia and gout

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Abstract

Hyperuricaemia is a common clinical condition that can be defined as a serum uric acid level >6.8 mg/dl (404 μmol/l). Gout, a recognized complication of hyperuricaemia, is the most common inflammatory arthritis in adults. Drug-induced hyperuricaemia and gout present an emergent and increasingly prevalent problem in clinical practice. Diuretics are one of the most important causes of secondary hyperuricaemia. Drugs raise serum uric acid level by an increase of uric acid reabsorption and/or decrease in uric acid secretion. Several drugs may also increase uric acid production. In this review, drugs leading to hyperuricaemia are summarized with regard to their mechanism of action and clinical significance. Increased awareness of drugs that can induce hyperuricaemia and gout, and monitoring and prevention are key elements for reducing the morbidity related to drug-induced hyperuricaemia and gout.

Key words: hyperuricaemia, gout, drug-induced, uric acid, diuretics, organic anion transporters, prevention, management

Rheumatology key messages

- Drug-induced-hyperuricaemia and gout present an emergent and increasingly prevalent problem in clinical practice.
- Drugs raise serum uric acid level by increasing uric acid reabsorption and/or decreasing uric acid secretion in gout.
- Adequate hydration and routine uric acid level monitoring should be encouraged for drugs known to induce hyperuricaemia.

Introduction

Hyperuricaemia, the biochemical precursor to gout, is usually defined as a serum uric acid level >6.8 mg/dl (404 μmol/l). Gout is the most common inflammatory arthritis in adults, affecting an estimated 2.5% of the population in the UK and 3.9% in North America [1]. Hyperuricaemia may be present at up to 20% in some populations. It is an independent risk factor for all-cause cardiovascular and ischaemic stroke mortality [2]. Elevated serum uric acid is also one of the best independent predictors of diabetes, obesity and hypertension [3].

In addition to alcohol and purine-rich foods, drugs also play an important role in the pathogenesis of hyperuricaemia. They raise serum uric acid level by an increase of uric acid reabsorption and/or decrease in uric acid secretion (Table 1). Several drugs may also increase uric acid production.

Drug-induced hyperuricaemia and gout present an emergent and increasingly prevalent problem in clinical practice. Although, the exact incidence and prevalence of drug-induced hyperuricaemia are unknown, Paulus *et al.* [4] noted that drugs were a major factor in the development of an elevated serum uric acid concentration in up to 20% of the hyperuricaemic subjects in one hospital study.

In this review, we shed light on the potential drugs causing hyperuricaemia and gout, the mechanisms underlying iatrogenic hyperuricaemia, and pertinent issues for the optimal management of drug-induced hyperuricaemia. Data were identified from MEDLINE and SCOPUS from January 1960 to December 2015, and from Reactions Weekly from 1992 to December 2015, regardless of the language. We used the keywords hyperuricaemia and gout with the subheading drug-induced, drug-interaction. Certain drugs were directly inserted as keywords, such as diuretics, calcineurin inhibitors, pyrazinamide and cytotoxic drugs. Searches also included the terms blood and uric acid. If there were relevant articles in many languages that described the same topic, only English articles were

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Table 1 Common drugs leading to hyperuricaemia

Drug	Suggested mechanism
Anti-tubercular drugs	Increased uric acid reabsorption (pyrazinamide) Decreased uric acid secretion (pyrazinamide) Reduction in the fractional excretion of uric acid (ethambutol)
Aspirin (low dose)	Increased uric acid reabsorption Decreased uric acid secretion
Cytotoxic chemotherapy	Massive disruption of tumour cells
Diuretics	Increased uric acid reabsorption in the proximal tubules Increased uric acid secretion Volume contraction
Immunosuppressant agents	Increased uric acid reabsorption in the proximal tubules (ciclosporin) Decreased glomerular filtration rate secondary to afferent arteriolar vasoconstriction (ciclosporin) Reduced urate excretion (tacrolimus) Inhibition of the synthesis of guanine nucleotide (mizoribine)
Fructose	Increased nucleotide turnover and nucleotide synthesis Increased uric acid tubular reabsorption
Lactate infusion	Increased uric acid reabsorption
Nicotinic acid	Increased uric acid reabsorption Decreased uric acid secretion Increased uric acid synthesis
Testosterone	Increased uric acid reabsorption
Xylitol	Increased purine degradation Increased production of lactate

analysed. In this review, we focus only on drug-induced hyperuricaemia and gout. Alcohol and herbal remedies are excluded from this review.

Causative drugs

Diuretics

Diuretics are one of the most important causes of secondary hyperuricaemia. The use of loop diuretics, thiazide diuretics and thiazide-like diuretics was associated with an increased risk of incident gout [5, 6]. The clinical features of diuretic-induced gout do not differ from other causes of gout. The increase in serum uric acid concentration caused by diuretics may be noted within a few days after the initiation of treatment. It seems to be dose dependent and persist during prolonged administration [7, 8]. The elevation in serum uric acid caused by diuretics varies from 6 to 21% from corresponding baseline values [9]. Uric acid level usually returned to the baseline a few months after stopping diuretics.

Diuretics have different effects on the renal handling of uric acid, and therefore the occurrence of gout. Gout seems to be more strongly related to loop diuretics than thiazides [10, 11]. Only a few studies have evaluated differences between diuretic subclasses or differences between individual diuretic agents. A recent study has directly compared gout risk between two thiazides, chlorthalidone and hydrochlorothiazide [12]. In this study, patients taking chlorthalidone for hypertension have a similar risk of developing new-onset gout to patients prescribed similar doses of hydrochlorothiazide.

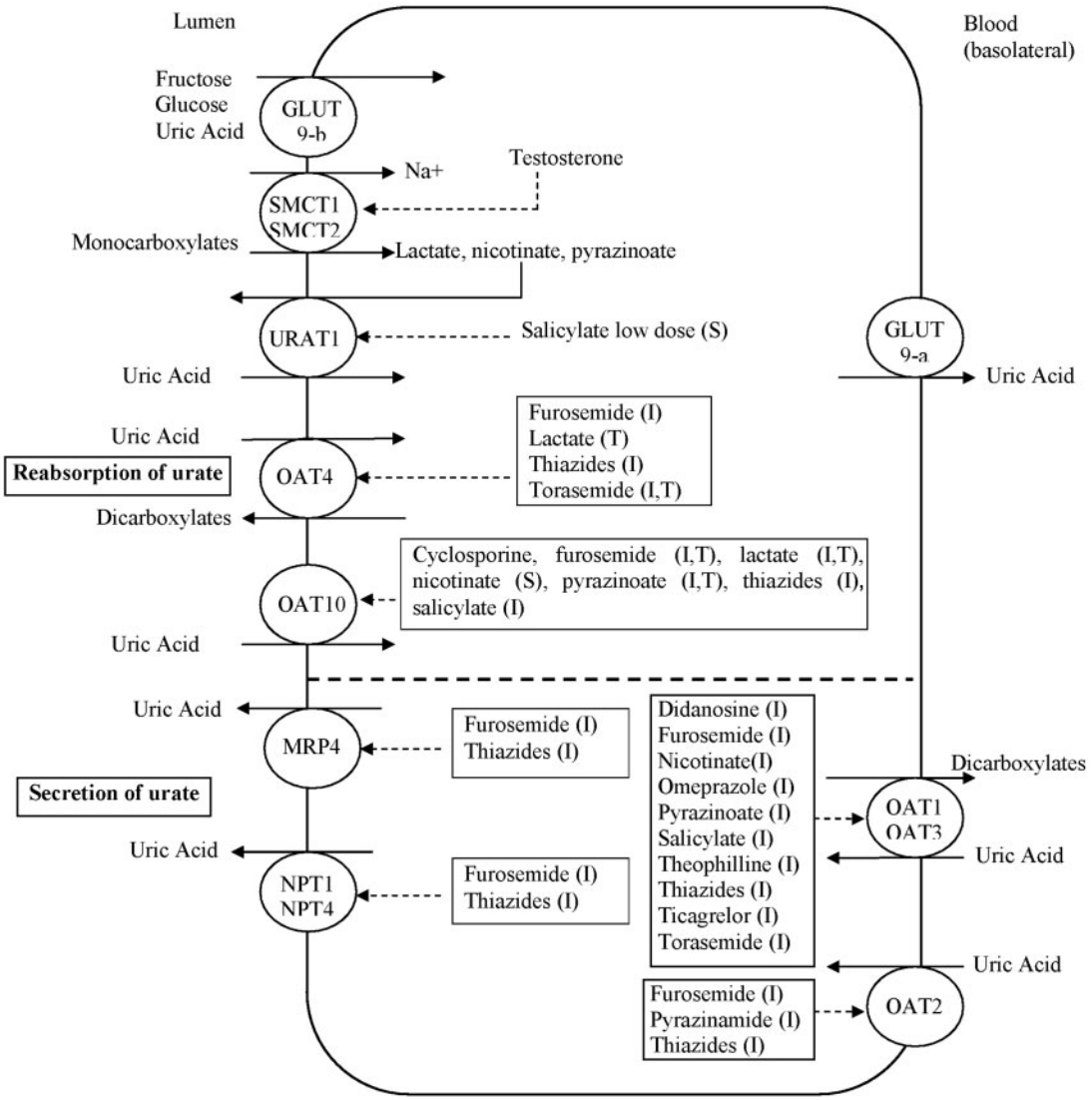
Loop diuretics and thiazide diuretics interact with renal urate transporters. Like diuretics, many other drugs inducing hyperuricaemia and gout may also interfere with these renal urate transporters (Fig. 1). Loop diuretics and thiazide diuretics inhibited basolateral organic anion transporters OAT1 and OAT3, involved in the active uptake of plasma uric acid as a first step in its tubular secretion in renal proximal tubules. Diuretics enter the proximal tubular cell from the blood side via OAT1 and OAT3 transporters and may be considered as competitive substrates of uric acid [13].

Hydrochlorothiazide also increases significantly the uric acid uptake via organic anion transporter OAT4 [14]. The exchange of diuretics for uric acid may lead to increased serum uric acid concentrations. Certain genetic variants in *SLC22A11*, which encodes OAT4, may lead to an increased transport capacity of OAT4, and the intake of diuretics may lead to an additional activation of the transporter, resulting in the highest incidence of gout in individuals [15]. However, this finding was not confirmed in a recent study [16].

Loop diuretics and thiazide diuretics may also increase serum uric acid levels by inhibiting the human voltage-driven drug efflux transporter NPT4 [13]. The latter is located at the apical side of renal proximal tubules and induces uric acid secretion.

Furosemide and hydrochlorothiazide were also identified as substrates of human multidrug resistance-associated protein 4 (MRP4). They inhibited MRP4-mediated uric acid transport, which might lead to hyperuricaemia [17].

FIG. 1 Interference of drug leading to hyperuricaemia with renal urate transporters



The dotted arrows indicate drug interference. GLUT9: glucose transporter 9; I: inhibition; MRP4: multi-drug resistance-associated protein 4; NPT: human sodium-dependent phosphate transporter; OAT: organic anion transporter; S: stimulation; SMCT: Na^+-dependent anion cotransporter; T: trans-stimulation; URAT1: urate/anion exchanger; Adenosine triphosphate (ATP)-dependent unidirectional efflux transporter.

Moreover, diuretics produce sufficient salt and water loss to lead to volume contraction, which stimulates uric acid reabsorption. Indeed, intravenous saline in a dose sufficient to prevent volume depletion prevents the hyperuricaemia induced by acute administration of intravenous furosemide and ethacrynic acid [18]. Volume contraction induced by thiazides leads to increased H^+ secretion in the proximal tubule via the apically located NHE3. Consequently, cell pH increases, which in turn drives urate uptake via OAT4 as a result of increased urate/OH^- exchange [7].

Other factors may also contribute to the hyperuricaemic effect of diuretics. Furosemide induces hyperlactacidaemia sufficient to suppress tubular excretion of uric acid [19].

For the sodium channel blockers amiloride and triamterene, data are contradictory. Chronic use of triamterene was shown to induce hyperuricaemia without clinical evidence of gout in several studies, whereas no effect was noted in other studies [20]. Amiloride has been shown not to alter the uric acid level.

Like triamterene, studies of spironolactone have shown conflicting results on serum uric acid levels. Previous data reported that spironolactone does not alter or tends to reduce the serum uric acid levels [21]. However, a recent study showed that low dose spironolactone

increases serum uric acid levels in patients with chronic kidney disease [22]. Roos *et al.* [23] investigated the effect of spironolactone on uric acid handling by the kidney in a small study. They found that spironolactone causes a decrease in uric acid renal clearance, probably mediated by the induced volume depletion and plasma renin activity elevation, as with other diuretics, and, probably, inhibits endogenous uric acid production to approximately the same degree as the clearance is decreased, so that serum uric acid concentration does not change.

Anti-tubercular drugs

Pyrazinamide, an anti-mycobacterial drug, not only induces hyperuricaemia, but may also lead to acute gouty attacks. It is a strong urate retention agent, causing a >80% reduction in renal clearance of uric acid at a 300 mg therapeutic daily dose [24].

Pyrazinecarboxylic acid or pyrazinoate (PZA), an active metabolite of pyrazinamide, increases serum uric acid based on its trans-stimulatory effect on URAT1, which is a member of the organic anion transporter (OAT) family, causing the reabsorption of urate from the luminal side into tubular cells [25]. Patients with renal hypouricaemia and loss-of-function mutations in the gene for URAT1 lack a full response to pyrazinamide, providing genetic confirmation of the linkage between PZA and urate reabsorption [26].

In addition, pyrazinamide inhibits OAT2 a protein expressed at the basolateral membrane of human proximal tubule cells and implicated in the secretory urate transport [27]. OAT2 is a potential target of the anti-uricosuric effect of pyrazinamide, as well as URAT1.

PZA interferes also with OAT10, an organic anion/dicarboxylate exchanger transporter. OAT10-mediated urate uptake was elevated by an exchange with PZA [28].

The incidence of hyperuricaemia in studies of patients undergoing combination therapy (isoniazide, rifampicin and pyrazinamide) or therapy with pyrazinamide alone varies widely from 43.4 to 86.3% [29, 30].

Ethambutol, another antitubercular drug, induces also a significant increase in serum uric acid levels. This effect was observed mainly in the second, third and fourth week of ethambutol therapy [31]. However, an increase in the serum urate concentration was noted as early as 24 h after the administration of a single dose of ethambutol. Ethambutol therapy can not only lead to raised serum uric acid but also precipitate gouty arthritis [32]. The withdrawal of ethambutol led to a fall of serum uric acid levels to normal. Re-introduction of the drug was followed by the reappearance of hyperuricaemia [33, 34]. The exact mechanism of ethambutol-induced hyperuricaemia has not been elucidated; however, a substantial reduction in the fractional excretion of uric acid was noted in patients treated with this drug [35].

Immunosuppressant agents

Hyperuricaemia and gout are common complications of organ transplantation, with a prevalence ranging from 5 to 84% for hyperuricaemia and 1.7 to 28% for gout [36]. Ciclosporin, a calcineurin inhibitor, is considered the most important risk factor for the development of gout in transplant recipients [36]. In the pre-ciclosporin era, hyperuricaemia was found in ~25% of renal transplant patients, but the prevalence increased to over 80% after the use of ciclosporin became widespread [37].

Ciclosporin therapy may lead to an accelerated form of gout, even with tophi occurring over a relatively short time period and in unusual locations including soft tissues, intraspinal sites and sacroiliac joints [38, 39]. Gouty arthritis develops in 4–10% of all ciclosporin-treated patients [40]. The mean time from transplantation to the first episode of gout was a few months. Compared with patients who had hyperuricaemia without gout, those with episodes of gout induced by ciclosporin were mostly men, were taking diuretics, and had more advanced renal dysfunction [41]. Ciclosporin may induce an increase of proximal uric acid reabsorption, especially in the presence of volume depletion associated with diuretic use, and a decrease in glomerular filtration rate secondary to afferent arteriolar vasoconstriction [42, 43]. Experimental studies demonstrated that ciclosporin enhanced urate uptake via the human organic anion transporter OAT10, which may be responsible for ciclosporin-induced hyperuricaemia [28].

Tacrolimus, another calcineurin inhibitor, may also cause hyperuricaemia in patients with renal transplantation [44]. Hyperuricaemia rate of patients taking tacrolimus was significantly lower than it was for those patients taking ciclosporin [45]. However, there are also studies that show no difference between the two drugs with regard to the occurrence of hyperuricaemia [46].

Hyperuricaemia was also a common adverse event with mizoribine, a potent immunosuppressant widely used in Asia [47]. It mostly occurred within a few weeks and was usually transient. It may be due to the action of this drug, which inhibits the synthesis of guanine nucleotides [48].

Nicotinic acid

Nicotinic acid decreases urinary excretion of uric acid, which may result in elevation of serum uric acid by ~14% and exacerbation of pre-existing gout [49]. It has been reported to occasionally induce gout. Hyperuricaemia occurred in 41–78% of subjects receiving 3–6 g of nicotinic acid [49, 50]. Uric acid-raising effects of nicotinic acid may also occur when the drug is given in therapeutic doses [51]. Nicotinic acid can increase urate reabsorption in the kidney, where nicotinate functions as a counter-ion for uric acid on URAT1 [25].

Nicotinate interferes also with the OAT10 transporter; OAT10-mediated urate uptake was elevated by an exchange with nicotinate [28]. OAT10 is a low affinity urate transporter possibly involved in renal urate reabsorption, like hOAT4. Its interactions with nicotinate may participate in the pathogenesis of nicotinic acid-induced hyperuricaemia. However, nicotinate may serve as a counter-ion for urate reabsorption in the proximal tubule only under therapeutic concentrations. Nicotinic acid may also inhibit

OAT2, which plays a role in renal uric acid uptake from blood as a first step in tubular secretion [27].

Changes in uric acid synthesis during nicotinic acid administration have also been proposed as the explanation of nicotinic acid-induced hyperuricaemia. Nicotinic acid and its amide derivative, nicotinamide, may increase the rate of purine biosynthesis *de novo* [20].

Aspirin

In low dosages (60–300 mg once daily), aspirin reduces uric acid excretion, and may induce hyperuricaemia, whereas higher doses are uricosuric [52]. This paradoxical effect of salicylate can be explained by two modes of salicylate interaction with the urate monocarboxylate exchanger (URAT1): acting as an exchange substrate to facilitate urate reabsorption at low dose, and acting as an inhibitor for urate reabsorption at high dose [53]. Salicylate even at very low doses was able to inhibit MRP4-mediated urate transport [17]. In addition, salicylate may exert its hyperuricaemic effect through interacting with OAT1 and OAT3 (Fig. 1). In a recent large prospective case-crossover study, Zhang *et al.* [54] found that the use of low-dose aspirin ($\leqslant$325 mg/day) was associated with a higher risk of recurrent gout attacks. This association increased as the dose decreased. In this study the effect of low-dose aspirin on recurrent gout attack was neutralized by concomitant use of allopurinol.

Hypoalbuminaemia and concomitant treatment with diuretics enhanced the effects of aspirin on renal uric acid retention [52].

Cytotoxic chemotherapy

Cytotoxic drugs may induce tumour lysis syndrome (TLS). TLS, an oncological emergency, is characterized by massive disruption of tumour cells and dumping of intracellular material into the blood causing hyperuricaemia and electrolyte abnormalities such as hyperkalaemia, hyperphosphataemia, hypocalcaemia and metabolic acidosis. The release of cellular nucleic acids and purine nucleotides by these drugs induces uric acid production and may lead to markedly increase serum uric acid levels with acute uric acid nephropathy in some cases. Hyperuricaemia induced by cytotoxic drugs is the most serious type of drug-induced hyperuricaemia. It usually develops 48–72 h after cytotoxic therapy. TLS induces a higher mortality rate, probably because of delayed presentation and delayed recognition. In fact, if undiagnosed or diagnosed too late, TLS can lead to death in 20–50% of cases [55]. TLS is often associated with cytotoxic chemotherapy. However, it may also occur after treatment with dexamethasone, zoledronic acid, thalidomide and newer chemotherapeutic agents including bortezomib, rituximab and ibrutinib [56].

Non-glucose carbohydrates

The glucose substitutes used in total parenteral nutrition are fructose, glycerol, sorbitol and xylitol. The parenteral infusion of these substrates has several advantages such as a rapid metabolism and a smaller effect on blood glucose concentration as compared with glucose infusions.

Fructose

Intravenous fructose administration or high fructose oral intake over several days is associated with increased uric acid concentration. Fructose is strongly associated with hyperuricaemia and an increased risk of gout in both genders [57, 58].

The hyperuricaemic effect of fructose seems to be dose-related [59]. However, doses of fructose as low as 160 mg/kg body weight/h may also cause hyperuricaemia in critically ill patients [60]. Renal transplant recipients treated with both calcineurin inhibitors (ciclosporin or tacrolimus) are at similar risk of hyperuricaemia induced by fructose consumption [61].

Fructose increases intracellular and circulating uric acid levels due to increased nucleotide turnover and nucleotide synthesis (Fig. 2) [62]. Fructose may induce an increase of blood lactate concentration, which blocks urate excretion and results in hyperuricaemia [63]. It may also increase the risk of insulin resistance and subsequent hyperinsulinaemia, decreasing uric acid excretion and further promoting hyperuricaemia [58]. It may, too, decrease urinary uric acid excretion, contributing to fructose-induced hyperuricaemia [59]. It facilitates the tubular reabsorption of urate, through glucose transporter 9 (GLUT9), a member of the GLUT family of hexose transporters.

Different alleles influence serum urate responses to fructose. The *SLC2A9* gene variant, which encodes GLUT9, may influence the development of gout on exposure to fructose particularly in European Caucasian populations [64]. Furthermore, genetic variation in *SLC17A1*, which encodes the human inorganic phosphate transporter NPT1, an anion exchanger that secretes uric acid into the urine, has also been associated with hyperuricaemia and gout. In European people, variation in *SLC17A1* influences serum urate and fractional excretion of uric acid throughout a fructose load [65].

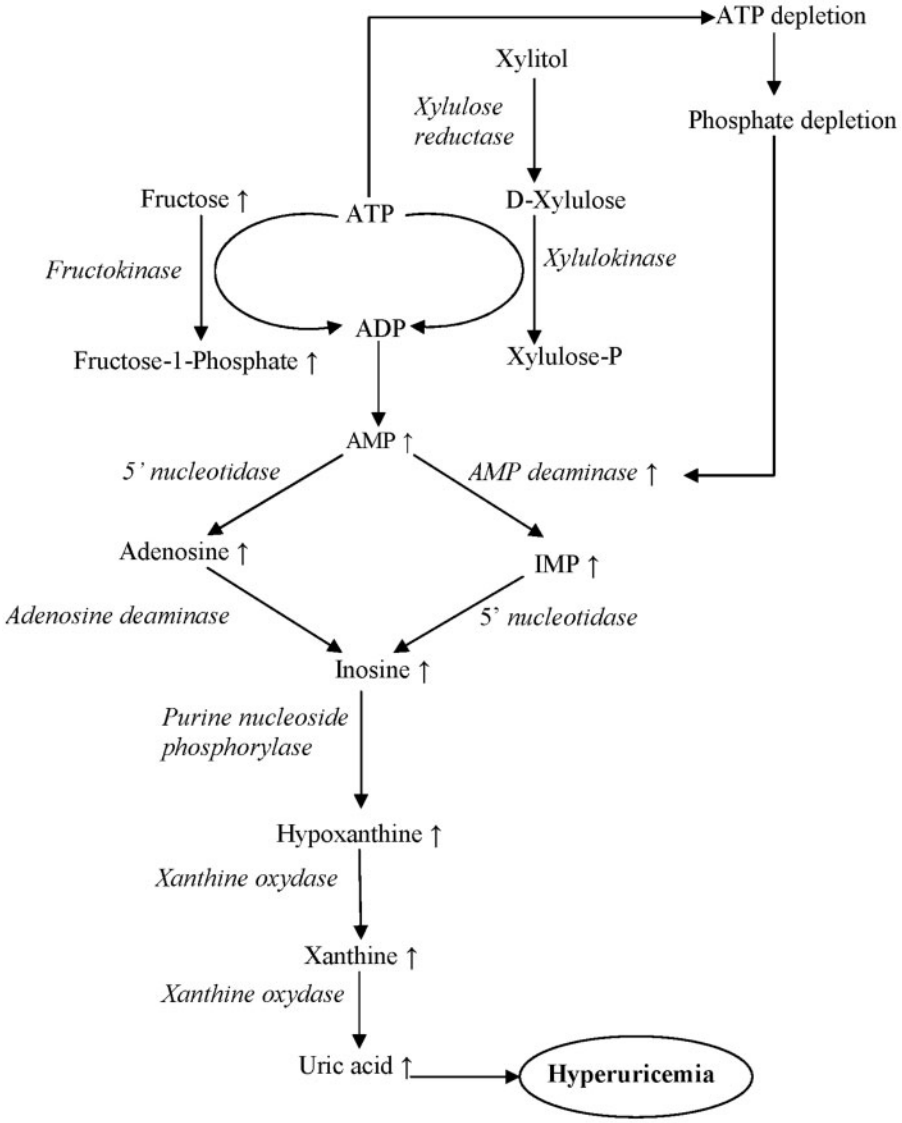
Other non-glucose carbohydrates

Glycerol consumption is also linked to an increase in serum urate concentration [66]. Glycerol stimulates uric acid production, lowers cell ATP and increases glycerol 3-phosphate [67]. Uric acid production correlates inversely with ATP.

Xylitol is a five-carbon sugar alcohol. It is used as a glucose substitute in total parenteral nutrition for diabetic patients. Infusion of xylitol leads to reduced gluconeogenesis, increased protein and muscle RNA content and improved nitrogen balance [68]. It may increase the plasma concentrations of uric acid, hypoxanthine and xanthine by enhancing purine degradation. The increase in purine degradation by xylitol may be due to the impairment of glycolysis in erythrocytes [69]. In addition, administration of large amounts of xylitol can produce lactic acidosis [68].

Sorbitol is converted to fructose when metabolized in the liver and produces biochemical effects similar to those of fructose on hepatic adenosine phosphate levels in

Fig. 2 Non-glucose carbohydrate-induced hyperuricaemia



↑: Increase; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; IMP: inosine monophosphate.

humans, and can therefore increase uric acid production [70]. Hyperuricaemia has been reported in a case of sorbitol overdose [71].

Lactate infusion

Sodium lactate solution has many advantages and appears promising for resuscitation of critically ill patients [72]. However, high dose lactate infusion may induce hyperuricaemia by decreasing urinary excretion and the fractional clearance of uric acid [73]. The infusion of lactate in healthy volunteers reduced the renal clearance of urate by 70–80%, resulting in an increase of 8–18% in serum urate [74].

Lactate interacts with URAT1 [25]. This latter is an important transporter of urate reabsorption in exchange for lactate at the apical membrane of the proximal tubules. Therefore, lactate stimulates urate uptake, leading to hyperuricaemia. In addition, lactate may also interfere with organ anion transporters OAT4 and OAT10 (Fig. 1).

Testosterone

Testosterone replacement therapy (TRT), used for patients with female to male gender identity disorder, increases uric acid level in a dose-dependent manner. In a recent study, the rates of serum uric acid increase after 3 months of TRT (intramuscular injection of testosterone enanthate) were 29 and 43.4% for a dosage of 125

TABLE 2 Miscellaneous drugs inducing hyperuricaemia and their suggested mechanism

Drug	Suggested mechanism	Reference
Acitretin	Increased uric acid production	[79]
Didanosine + ritonavir	Unknown	[80]
Filgrastim	Increased myeloid turnover	[81]
L-dopa	Decreased uric acid excretion	[82]
Omeprazole	Unknown	[83]
Peg-interferon + ribavirin	Unknown	[84]
Sildenafil	Unknown	[85]
Teriparatride	Increased serum parathyroid hormone levels	[86]
Ticagrelor	Increased uric acid synthesis Decreased uric acid secretion	[87]
Topiramate	Inhibition of carbonic anhydrase isoenzymes	[88]

and 250 mg every 2 weeks, respectively [75]. In addition, the percentages of patients with onset of hyperuricaemia (serum uric acid level $\geqslant$7.0 mg/dl) at 3 months after the initiation of TRT in these two dosage groups were, respectively, 5 and 14.8%. Testosterone-induced gout has also been reported [76].

Testosterone treatment leads to increased serum uric acid levels and reduced renal excretion of uric acid [77]. The induction of Smct1 (*SLC5A8*), an Na^+-dependent anion cotransporter that collaborates with urate transporter-1 in proximal tubular reabsorption of urate, by testosterone seems to be the mechanism of the underlying testosterone-induced hyperuricaemia in males [78]. The serum uric acid elevation may be also, at least partially, attributed to an increase in muscle mass during the early phase of TRT [75].

Miscellaneous agents

In addition to the drugs listed above, many miscellaneous agents may induce hyperuricaemia and gout (Table 2) [79–88].

Prevention and management

Although, there are no published guidelines on how to prevent drug-induced hyperuricaemia, patients receiving drugs known to induce hyperuricaemia should be encouraged to maintain adequate hydration and have their uric acid levels routinely monitored. These patients should also be monitored for symptoms that might precede the onset of gout.

Approximately two out of three patients with drug-induced hyperuricaemia will remain asymptomatic [24]. In drug-induced asymptomatic hyperuricaemia, especially with diuretics, treatment to control serum uric acid levels is rarely required. However, gouty episodes in patients with a personal or family history of established gout may be aggravated by diuretic therapy in hypertensive patients. When gout develops the decision to continue therapy needs to be individualized, and so too does a decision to initiate allopurinol or a uricosuric drug [7].

In drug-induced symptomatic hyperuricaemia and gout, management includes the identification of offending drugs and the institution of appropriate anti-hyperuricaemic agents. Withdrawal of the offending drug should be based on an assessment of the benefit–risk ratio. When alternative therapy is available, the offending drug may be replaced by a drug that does not cause hyperuricaemia. However, in certain cases, the offending drug is necessary. For example, the use of low-dose aspirin for prevention of cardiovascular disease should not be suspended for patients with gout. Close monitoring of serum uric acid when an individual is taking low-dose aspirin may help to avoid the risk of gout attacks. However, allopurinol or uricosuric agents may be necessary in some cases of aspirin-induced gout [54].

In hypertensive patients (controlled on one or two medications) with acute thiazide-induced gout, the reduction of the dose of thiazide rather than its discontinuation is an appropriate option because drug-induced hyperuricaemia is dose-related [8]. In hypertensive patients (controlled on three or more medications) thiazide continuation with dose reduction or pharmacological anti-hyperuricaemic therapy, that is, allopurinol, should be considered. However, the withdrawal of thiazide is a reasonable option if serum uric acid is $>$ 6 mg/dl independently of the status of hypertension control [8].

Treatment of ciclosporin-induced acute attacks may be difficult since interactions with NSAIDs may lead to enhanced renal toxicity. Colchicine, if prescribed in these acute attacks, should also be used cautiously and the dose reduced. Corticosteroids are an effective alternative to colchicine. In patients who develop ciclosporin-induced hyperuricaemia and gouty arthritis with tophi, benzbromarone, a uricosuric agent, may be useful. It should be initiated at a low dose and gradually increased, and liver function should be monitored closely. Allopurinol is also a useful alternative in these patients. Interestingly, the normalization of uric acid levels by allopurinol or benzbromarone reduced the tubulointerstitial disease and arteriolar hyalinosis induced by ciclosporin [89].

Ciclosporin and tacrolimus withdrawal may be considered for transplant patients with recurrent, severe gout that cannot be managed safely or effectively [90]. The cornerstone management of TLS is prevention. Prevention strategies may also include hydration plus

allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients [91]. For nicotinic acid-induced hyperuricaemia, allopurinol is usually used when therapy is indicated. Nicotinic acid inhibits the effect of uricosuric drugs such as sulfinpyrazone and the latter should be avoided.

Pyrazinamide-induced hyperuricaemia can be managed by observation and does not require withdrawal of treatment. It can be also controlled with allopurinol. However, paradoxical increase in uric acid level with allopurinol use in pyrazinamide-induced hyperuricaemia has been reported [92]. Allopurinol was shown to increase plasma concentrations of pyrazinoic acid, which is directly responsible for the inhibition of renal urate secretion [92, 93]. Aspirin may prevent hyperuricaemia and the arthralgia associated with pyrazinamide therapy. Hyperuricaemia due to ethambutol was reversed with probenicid, sulfinpyrazone or allopurinol. The latter, increases the serum level of theophylline and therefore the serum level of theophylline should be carefully monitored when allopurinol is added to a hyperuricaemic patient who is under this treatment [94]. However, benzbromarone and probenecid do not seem to interfere with the theophylline serum level.

In conclusion, drug-induced hyperuricaemia and gout present an emergent and increasingly prevalent problem in clinical practice. Drugs raise serum uric acid level by various mechanisms. Patients receiving these drugs should be encouraged to maintain adequate hydration and have their uric acid levels monitored.

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