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# Effect of diuretic medication and coffee consumption on serum uric acid levels: A review of literature

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## Abstract

Various factors like diet, medications, beverages, and congenital conditions have been shown to have an effect on uric acid levels. Hyperuricemia (serum uric acid level > 6.8mg/dL) is detrimental to health and is an independent risk factor for all-cause cardiovascular mortality and ischemic stroke mortality. It is one of the best independent predictors of chronic diseases like obesity, hypertension, and diabetes. Hyperuricemia causes inflammatory arthritis also known as gout. In this review, the authors have focussed on the iatrogenic cause of hyperuricemia, particularly diuretic medications. The mechanism of action of these medications and the critical interactions at cellular and receptor levels, which are responsible for hyperuricemia, were reviewed. In various studies, coffee consumption has been shown to facilitate urate excretion and thus lower the risk of gout. This study has reviewed various studies detailing the reduced risk of gout with coffee consumption and the possible mechanisms involved in the inverse association between coffee consumption and the risk of developing gout.

***Keywords***: Uric Acid; Gout; Diuretics; Coffee; Caffeine; Hyperuricemia.

## Introduction

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen and hydrogen with the formula $C_5H_4N_4O_3$. It forms ions and salts known as urates and acid urates, such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purine nucleotides, and it is a normal component of urine.

Hyperuricemia is defined as a serum uric acid level >6.8 mg/dl (404 mmol/l). Gout is an inflammatory arthritis resulting due to hyperuricemia. According to estimates, it is the most common inflammatory arthritis affecting an estimated 2.5% of the population in the UK and 3.9% in North America [1].

Hyperuricemia is detrimental to health as an independent risk factor for all cause cardiovascular and ischaemic stroke mortality [2]. For chronic diseases like obesity, hypertension and diabetes; hyperuricemia is one of the best independent predictors [3]. According to some estimates, the prevalence of hyperuricemia is up to 20% in some populations [2].

Many factors contribute to hyperuricemia, including genetics, insulin resistance, hypertension [4], hypothyroidism, chronic kidney disease, obesity, diet, iron overload, use of diuretics (e.g. thiazides, loop diuretics), and excessive consumption of alcoholic beverages [5]. Of these, alcohol consumption is the most important [6].

One of the increasingly prevalent cause of hyperuricemia in clinical practice is use of diuretic medications. One study have shown that iatrogenic hyperuricemia was responsible in 20% cases of hyperuricemia among patients admitted in hospital [7].

Some factors like caffeine consumption have shown inverse relationship with incidence of gout among the study population [8,9].

Coffee and green tea are one of the most widely consumed beverages across global populations. Caffeine is an active component in both the beverages. Caffeine is widely used in many other foods and medications. There has been great deal of research on the health consequences of caffeine ingestion due to complex pharmacogenetic and physiological effects of caffeine [10]. Caffeine with a known diuretic action may increase uric acid excretion due to increased renal perfusion [11].

In this review we intend to shed light on causes and pathophysiology of hyperuricemia. We would also discuss the mechanism involved in complex interactions between diuretic drugs, caffeine and hyperuricemia. We also intend to review various studies detailing these complex interactions and effect of diuretic medications and caffeine on uric acid levels.

## Hyperuricemia

Body urate amount depends on a delicate balance between amount of purines consumed, synthesised and excreted by a person [12]. Hyperuricemia may be a result of loss of this delicate balance. It may be a result of increased production, decreased excretion or both for uric acid [4].

Hyperuricemia can be classified into 3 functional types as follows:

### 1. Increased production of uric acid

A purine rich diet may cause hyperuricemia. Studies have found higher uric acid levels to be positively associated with higher consumption of meat, seafood and inversely associated with dairy food consumption [13]. Increased purine metabolism may also lead to hyperuricemia. In conditions of metabolic myopathies like glycogenosis type III, V and VII , there is increased exercise induced purine metabolism leading to hyperuricemia which decreases over hours with rest [14].

Hyperuricemia due to increased production of uric acid may occur in certain conditions like solid organ transplant, tumour lysis syndrome, Lesch-Nhyan syndrome [15,16].

### 2. Decreased excretion of uric acid

Causes of decreased excretion include kidney disease, certain drugs, and competition for excretion between uric acid and other molecule [17].

Antiuricosuric is the term used for drugs that impair renal excretion of uric acid. These include diuretics, salicylates, pyrazinamide, ethambutol, nicotinic acid, ciclosporin, 2-ethylamino-1,3,4-thiadiazole, and cytotoxic agents [18].

The gene SLC2A9 encodes a protein that helps to transport uric acid in the kidney. Several single nucleotide polymorphisms of this gene are known to have a significant correlation with blood uric acid [19].

Hyperuricemia coexisting with osteogenesis imperfecta has been shown to be associated with a mutation in GPATCH8 using exome sequencing [20].

A ketogenic diet impairs the ability of the kidney to excrete uric acid, due to competition for transport between uric acid and ketones [21].

Elevated blood lead is significantly correlated with both impaired kidney function and hyperuricemia [22,23].

### 3. Mixed type

Causes of hyperuricemia that are of mixed type have a dual action, both increasing production and decreasing excretion of uric acid. Alcohol consumption is a significant cause of hyperuricemia. The hyperuricemia due to alcohol consumption is of mixed type with multiple mechanisms at play. Ethanol increases production of uric acid by increasing production of lactic acid, hence lactic acidosis. Ethanol also increases the plasma concentrations of hypoxanthine and xanthine via the acceleration of adenine nucleotide degradation, and is a possible weak inhibitor of xanthine dehydrogenase. As a by-product of its fermentation process, beer additionally contributes purines. Ethanol decreases excretion of uric acid by promoting dehydration and (rarely) clinical ketoacidosis [6].

Fructose consumption in high amounts leads to hyperuricemia [24-26].

Higher consumption of sugar sweetened soft drinks have higher odds ratio for hyperuricemia [27]. Increased production of uric acid is the result of interference, by a product of fructose metabolism, in purine metabolism. This interference has a dual action, both increasing the conversion of ATP to inosine and hence uric acid and increasing the synthesis of purine [25]. Fructose also inhibits the excretion of uric acid, apparently by competing with uric acid for access to the transport protein SLC2A9 [28].

The effect of fructose in reducing excretion of uric acid is increased in people with a hereditary (genetic) predisposition toward hyperuricemia and/or gout [25].

Starvation causes the body to metabolize its own (purine-rich) tissues for energy. Thus, like a high purine diet, starvation increases the amount of purine converted to uric acid. A very low calorie diet lacking in carbohydrates can induce extreme hyperuricemia; including some carbohydrate (and reducing the protein) reduces the level of hyperuricemia [29]. Starvation also impairs the ability of the kidney to excrete uric acid, due to competition for transport between uric acid and ketones [30].

## Diuretic medications and hyperuricemia

Diuresis means increased production of urine. A diuretic is any substance promoting diuresis. Diuretics are used to treat heart failure, liver cirrhosis, hypertension, influenza, water poisoning, and certain kidney diseases. The diuretics are classified into various categories depending on the mechanism of action. All diuretics increase the excretion of water from the body, through the kidneys. Among all the types of diuretics, loop diuretics, thiazide diuretics and thiazide like diuretics are associated with an increased risk of hyperuricemia. In fact, hyperuri-

cemia is one of the well documented side effect of these class of diuretics [31,32].

The hyperuricemia resulting from diuretic medication use may lead to gout. The clinical features of iatrogenic gout are similar to the gout resulting from other causes. Serum uric acid elevation occurs within a few days after treatment initiation and seems to be dose dependent. The elevated uric acid levels persist throughout treatment duration [33,34].

Studies have shown the uric acid levels to be elevated from 6% to 21% from baseline values after start of diuretics [35].

After stopping the diuretics, the levels have shown to return to baseline values after few months. The renal excretion of uric acid varies for different diuretics. Hence, the clinical presentation of gout varies among different patients on various class of diuretics. It is observed that compared to patients on thiazides diuretics, those on loop diuretics have more preponderance to develop gout [36,37].

Among the few studies comparing different diuretic subclasses and different diuretic agents, in one of the study, the risk of developing new onset gout was found to be similar for patients taking chlorthalidone and hydrochlorthiazide [38]. The aforementioned study compared hydrochlorthiazide, chlorthalidone and two loop diuretics for risk of gout.

### Mechanism associated with hyperuricemia development for different diuretics

Interaction of thiazide and loop diuretics with renal urate transporters is one of the key mechanism for development of hyperuricemia. The renal proximal tubule is the site for organic anion transporters OAT1 and OAT3. These are located basolateral on the proximal tubular cells. The function of these transporters is active uptake of plasma uric acid and its secretion in proximal renal tubule for renal excretion. Loop diuretics and thiazide diuretics have shown to inhibit OAT1 and OAT3 transporters by entering the proximal tubular cells from the blood side. They act as competitive substrates of uric acid [39]. OAT 4 is involved in active reabsorption of uric acid from proximal tubular cells into plasma. Its function is enhanced by use of hydrochlorthiazide [40]. OAT4 is encoded by SLC22A11. There are known genetic variants of SLC22A11 which translate to increased transport capacity of OAT4. Additional activation of variant OAT4 may occur with intake of diuretics compounding the development of gout in such individuals [41]. Another mechanism involved in reduced uric acid excretion with diuretic intake is related to inhibition of human voltage driven drug efflux transporter NPT4. The NPT4 functions by secretion of uric acid in proximal renal tubule. It is located on the apical side of renal proximal tubular cells [39]. Some more mechanisms of diuretic induced hyperuricemia have come forth. Studies have shown that loop diuretic furosemide and hydrochlorthiazide inhibited human Multidrug Resistance Associated Protein 4 (MRP 4) mediated uric acid transport, thus leading to hyperuricemia [42]. The salt and water loss produced by diuretics leads to volume contraction which in turn stimulates uric acid reabsorption leading to hyperuricemia. As a remedial measure, normal saline infused intravenously to prevent volume depletion induced by acute administration of ethacrynic acid and furosemide also prevents development of hyperuricemia [43]. H+ ion secretion in proximal renal tubules is increased as a result of volume contraction driven by diuretic administration especially thiazides. Subsequent increase in proximal tubular cell pH drives urate uptake via OAT4 [33]. Diuretic like spironolactone increase uric acid levels due to reduced uric acid renal clearance mediated by volume contraction and elevated plasma renin activity [44]. Hyperlactacidemia caused by furosemide suppresses renal tubular uric acid secretion [45]. Data on triamterene and amiloride is unequivocal with some studies demonstrating hyperuricemia and some showing no effect of uric acid levels of these medications [46].

### Coffee consumption and gout

Coffee is most widely consumed beverage globally [47]. Researchers through prospective cohort studies have tried to establish relationship between intake of coffee and incidence of gout across men and women [9]. These studies summarize that men drinking 4-5 cups of coffee per day have 40% lower risk of developing gout. If the coffee consumption is ≥6 cups/day, the risk is 59% lower as compared to the men not consuming coffee. For women consuming 1-3 cups of coffee per day, the risk of developing gout was 22% lower. If the coffee consumption was ≥4 cups/day, the risk is 57% lower as compared to the women not consuming coffee [8]. Women had a significantly inverse association between coffee consumption and risk of gout as compared to men. Thus, we can conclude that long-term coffee consumption is associated with a lower risk of developing gout [47]. In one of the studies, the relationship between coffee, tea and caffeine intake was evaluated for serum uric acid levels. The findings of study suggested that coffee consumption is associated with lower serum uric acid levels and the inverse association of gout with coffee appears due to factors other than caffeine [48]. Based on the review of various studies on coffee consumption and gout, we are able to ascertain that coffee consumption reduces the risk of gout and has urate lowering properties in both men and women [47].

### Mechanism of interaction of coffee with uric acid

Caffeine, an active component in coffee, is shown to raise eGFR. This might be one of the possible mechanisms through which caffeine increases excretion of uric acid in urine. The caffeine levels however, are found to be unrelated to serum concentrations of uric acid. The above findings also lend support to the hypothesis that compounds of coffee other than caffeine contribute to an inverse association between coffee and serum concentrations of uric acid [48,49]. It has been observed that there is a strong positive association between hyperinsulinemia and hyperuricemia [50,51]. Excess insulin decreases eGFR levels [52,53]. Coffee consumption has shown to increase insulin sensitivity, thus also helping to alleviate hyperuricemia by increasing eGFR [48]. Plasma C-peptide concentrations were inversely related to the intake of caffeinated and decaffeinated coffee (54). Chlorogenic acid is a major phenolic compound present in coffee. Following an oral glucose challenge test, the ingestion of chlorogenic acid have shown to decrease glucose and insulin concentrations [55]. Xanthine oxidase is an enzyme converting xanthine to uric acid. It is a matter of speculation that coffee contains substances that inhibit xanthine oxidase resulting in reduced serum uric acid levels in population that consume coffee [11]. The above mechanisms also hold true for decaffeinated coffee [49].

### Conclusion

To conclude, this review presents an insight into the various studies that link diuretics with hyperuricemia and beneficial effects of coffee intake on uric acid levels. Iatrogenic hyperurice-

mia due to antihypertensive medications like diuretics is proving to be an emergent medical issue. There needs to be further research into possible prevention of hyperuricemia in this patient population. Coffee consumption to reduce hyperuricemia may be one of the possible ways. However, the cardiovascular risks of caffeine ingestion shall be taken into account before embarking on any such medical decisions.

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