Hypertension is one of the most common co morbidities of gout. Gout is an acquired auto-inflammatory disorder characterized by severe joint inflammation and deposition of monosodium urate crystals in the joints. Hypertension is independently associated with the risk of incident gout through reduced renal blood flow with increased renal and systemic vascular resistance which leads to decreased renal excretion of urate. Normotensive individuals with baseline hyperuricemia have an 80% excess risk for developing HTN compared with those who do not have hyperuricemia. Hyperuricemia is a classic feature of gout, but it occurs nearly half of the time without hyperuricemia, and most people with raised uric acid levels never develop gout. Hyperuricemia is defined as a plasma urate level greater than 420 µmol/l (7.0 mg/dl) in males and 360 µmol/l (6.0 mg/dl) in females. Certain antihypertensive drugs also increase the levels of serum uric acid and thus may contribute to the risk of gout. Calcium channel blockers and losartan were associated with lower risk of incident gout among individuals with hypertension. By contrast, diuretics, β-blockers, angiotensin-converting enzyme inhibitors and nonlosartan angiotensin II receptor blockers were associated with an increased risk of gout. These may have practical implications for choosing the appropriate anti-hypertensive drugs in patients with hypertension, a common co morbidity of gout. In addition, both duration of treatment and dose influenced the magnitude of the response to both calcium channel blockers and losartan.

**Key words:** Hypertension, gout, hyperuricemia, calcium channel blockers, losartan, diuretics, β-blocker, diuretics.

**INTRODUCTION**

Hypertension is one of the most common co morbidities of gout. According to the latest estimates from the US National Health and Nutrition Examination Survey (2007-8), 74% of patients with gout have hypertension [1] which corresponds to 6.1 million adults in the United States alone. This substantial burden of co morbidity possibly stems from co pathogenesis of the two conditions or renal changes in hypertension leading to decreased urate excretion. Studies have shown that the presence of hypertension is independently associated with the risk of incident gout [2] through reduced renal blood flow with increased renal and systemic vascular resistance and decreased renal excretion of urate.

Certain antihypertensive drugs also increase the levels of serum uric acid and thus may contribute to the risk of gout. For example, in addition to the well known entities of diuretic induced hyperuricaemia and gout, [3] the use of β blockers has been shown to increase levels of serum uric acid in short-term trials [4]. However, calcium channel blockers and losartan have been found to lower serum uric acid levels [5], carrying the potential to lower the risk of gout. To date, however, no study has investigated the relation between various antihypertensive agents and the risk of gout.

Gout can present in a number of ways, although the most usual is a recurrent attack of acute inflammatory arthritis (a red, tender, hot, swollen joint) [6]. The metatarsal-phalangeal joint at the base of the big toe is affected most often, accounting for half of cases. Other joints, such as the heels, knees, wrists and fingers, may also be affected. Joint pain usually begins over 2-4 hours and during the night. The reason for onset at night is due to the lower body temperature then. Other symptoms may rarely occur along with the joint pain, including fatigue and a high fever. Long-standing elevated uric acid levels (hyperuricemia) may result in other symptomatology, including hard, painless deposits of uric acid crystals known as...

**ABSTRACT**

Hypertension is one of the most common co morbidities of gout. Gout is an acquired auto-inflammatory disorder characterized by severe joint inflammation and deposition of monosodium urate crystals in the joints. Hypertension is independently associated with the risk of incident gout through reduced renal blood flow with increased renal and systemic vascular resistance which leads to decreased renal excretion of urate. Normotensive individuals with baseline hyperuricemia have an 80% excess risk for developing HTN compared with those who do not have hyperuricemia. Hyperuricemia is a classic feature of gout, but it occurs nearly half of the time without hyperuricemia, and most people with raised uric acid levels never develop gout. Hyperuricemia is defined as a plasma urate level greater than 420 µmol/l (7.0 mg/dl) in males and 360 µmol/l (6.0 mg/dl) in females. Certain antihypertensive drugs also increase the levels of serum uric acid and thus may contribute to the risk of gout. Calcium channel blockers and losartan were associated with lower risk of incident gout among individuals with hypertension. By contrast, diuretics, β-blockers, angiotensin-converting enzyme inhibitors and nonlosartan angiotensin II receptor blockers were associated with an increased risk of gout. These may have practical implications for choosing the appropriate anti-hypertensive drugs in patients with hypertension, a common co morbidity of gout. In addition, both duration of treatment and dose influenced the magnitude of the response to both calcium channel blockers and losartan.

**Key words:** Hypertension, gout, hyperuricemia, calcium channel blockers, losartan, diuretics, β-blocker, diuretics.
tophi. Extensive tophi may lead to chronic arthritis due to bone erosion. Elevated levels of uric acid may also lead to crystals precipitating in the kidneys, resulting in stone formation and subsequent urate nephropathy [7].

Gout may be diagnosed and treated without further investigations in someone with hyperuricemia and the classic podagra. Synovial fluid analysis should be done, however, if the diagnosis is in doubt. X-rays, while useful for identifying chronic gout, have little utility in acute attacks.

A definitive diagnosis of gout is based upon the identification of monosodium urate crystals in synovial fluid or a tophus. All synovial fluid samples obtained from undiagnosed inflamed joints should be examined for these crystals. Under polarized light microscopy, they have a needle-like morphology and strong negative birefringence. This test is difficult to perform, and often requires a trained observer. The fluid must also be examined relatively quickly after aspiration, as temperature and pH affect their solubility.

Hyperuricemia is a classic feature of gout, but it occurs nearly half of the time without hyperuricemia, and most people with raised uric acid levels never develop gout. Thus, the diagnostic utility of measuring uric acid level is limited. Hyperuricemia is defined as a plasma urate level greater than 420 μmol/l (7.0 mg/dl) in males and 360 μmol/l (6.0 mg/dl) in females.8 Other blood tests commonly performed are white blood cell count, electrolytes, renal function, and erythrocyte sedimentation rate (ESR). However, both the white blood cells and ESR may be elevated due to gout in the absence of infection. A white blood cell count as high as 40.0×10⁹/l (40,000/mm³) has been documented.

**Effect of Antihypertensives on Uric Acid Metabolism**

Effect of antihypertensive on uric acid metabolism differs from class to class. Diuretics and beta blockers raise serum uric acid level whereas calcium channel antagonists increase uric acid clearance by increasing glomerular filtration. Effect of calcium channel blockers and angiotensin converting enzyme (ACE)-inhibitors on serum uric acid level is controversial; some describe the uric acid lowering effect and others do not.

**Calcium Channel Blockers**

Intravenous infusion of diltiazem has uricosuric and hypouricemic effects in rats, possibly due to an increase in glomerular filtration rate [9]. Neither serum uric acid nor clearance and fractional excretion of uric acid changed significantly during 10-day treatment with nifedipine, while nifedipine has been found to reduce serum uric acid levels compared with a placebo in the A Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) trial [10]. Furthermore, it has been suggested that amlopidine and cilnidipine might reduce serum uric acid level.

**Angiotensin Receptor Blockers**

Angiotensin II receptor blocker (ARB), losartan increased excretion of uric acid and decreased the serum uric acid level in both healthy and hypertensive subjects [11]. After 100 mg administration of losartan, plasma concentrations of uric acid decreased by 8% and 16%, at 1.5 and 2.5 hour, respectively. Urinary excretion of uric acid increased by 3.9-fold and 2.6-fold, at 1 to 2 hour and at 2 to 3 hour, respectively, while the fractional clearance of uric acid was increased by 4.3- and 3.2-fold at 1 to 2 hour and at 2 to 3 hour, respectively. Therefore, losartan might be a useful therapeutic tool to control blood pressure and reduce serum uric acid levels in hypertensive patients with hyperuricemia and/or gout. The uricosuric action of losartan is exerted by its inhibition of URAT1 expressed in the brush-border membrane of the renal proximal tubules [12]. Other ARBs have not been considered to affect serum uric acid level. Thus, the effects of various ARBs on the disposition of uric acid might be different.

Losartan Intervention For End point Reduction In Hypertension (LIFE) study suggest treatment-induced decrease in serum uric acid may contribute to the treatment benefit of a losartan based versus atenolol-based therapy on the composite endpoint (death, myocardial infarction, or stroke) [13]. Losartan reduces serum uric acid levels by 20-25% by producing a uricosuric effect in healthy volunteers, patients with hypertension, and transplant recipients. The uricosuric effect of losartan has been described to be similar to that observed with classic uricosuric agents such as probenecid. However, this uricosuric mechanism does not seem to be related to angiotensin II antagonism, as other angiotensin II antagonists do not share the property. For example, other angiotensin II antagonists, including valsartan 80 mg once daily, candesartan 8-16 mg daily, telmisartan 16 mg daily, eprosartan 600 mg do not increase uricosuria and thus do not decrease serum uric acid levels.

Similarly, angiotensin converting enzyme inhibitors have not been associated with lower serum uric levels. Several experiments, including a Xenopus oocyte model of urate transport injected with URAT1-encoding RNA, have indicated that losartan can directly inhibit URAT1 from the apical side of tubular cells through cis-inhibition as with other uricosuric compounds such as probenecid and benz bromarone. These suggest that URAT1 could be the key action site of losartan, as with other uricosuric agents.

**Diuretics**

It has been considered that diuretics raise serum uric acid concentration by decreasing circulating plasma volume. Diuretics reduce uric acid excretion by both directly and indirectly increasing uric acid reabsorption and decreasing uric acid secretion [14]. Recent studies on uric acid transporters revealed that multidrug resistance-associated protein 4 (MRP4), sodium-dependent phosphate transport protein 4 (NPT4), and organic anion transporters (OATs) are involved in the diuretics induced hyperuricemia.

Loop diuretics are widely used to treat excessive fluid accumulation and edema of the body caused by cardiac failure, chronic kidney disease (CKD) and liver cirrhosis. Furosemide (20 mg, IV) decreased renal excretion and fractional clearance of uric acid when measured 1 to 2 hours after administration.
Moreover, furosemide increased the plasma concentration of uric acid at 1.5 hours after administration. Whether furosemide has any effect on URAT1 (SLC22A12) remains unknown. Torasemide is the most potent of a newer of loop diuretics. Although, torasemide and its metabolites did not interact with human URAT1, competitive inhibition of the basolateral OAT for uric acid may reduce tubular secretion. Because hOAT4 can reabsorb uric acid from the urinary lumen, increased uric acid reabsorption may occur as exchange for the secretion of torasemide and its metabolites, which suggests that affinity for OAT of torasemide and its metabolites is proposed a mechanism underlying torasemide-induced hyperuricemia. hNPT4, localized at the apical side of the proximal tubule, functions as uric acid transporter, with which loop diuretics, such as furosemide and bumetanide interact. Therefore, hNPT4 may play an important role in these diuretics-induced hyperuricemia [15].

Thiazides are mainly used to treat high blood pressure. Thiazides compete for the same secretory process by which uric acid is secreted into the proximal tubule, thus reducing the clearance of uric acid, and raise the levels of uric acid in the blood. hOAT4, located at the apical membrane of proximal tubule cells, is responsible for facilitation of membrane of proximal tubule cells, is responsible for facilitation of hydrochlorothiazide-associated hyperuricemia. After furosemide and hydrochlorothiazide are taken up by OAT1 and/or OAT3 into the renal tubular cells, they inhibit MRP4-mediated uric acid efflux competitively and cause retention of uric acid, thus MRP4 has an important role in their hyperuricemic mechanisms [16]. Increasing the dose of diuretic led to progressive hyperuricemia, thus diuretics induced hyperuricemia seems to be dose dependent.

Potassium-sparing diuretics, spironolactone is generally considered not to affect serum uric acid level [17]. However it has been reported that spironolactone increased serum uric acid levels in the CKD patients, although the mechanism responsible for the increase in uric acid is unclear.

**Beta Blockers**

Although not as impressive as the hyperuricaemic property of diuretics, β blockers, including propranolol, atenolol, metoprolol, timolol, and alpenolol, also have been shown to increase serum uric acid levels. For example, atenolol 50-100 mg daily for 12 weeks increased uric acid levels by 0.5 mg/dL and the addition of propranolol was associated with a 0.3 mg/dL increase of serum uric acid levels. The mechanism of these urate raising effects of β blockers remains unknown as the data on the effects of β blockers on renal urate excretion have been unclear. For example, whereas single doses of atenolol, propranolol, and tertatololol did not modify the renal clearance of uric acid or the 24 hour urinary excretion of uric acid in healthy people, propranolol was found to reduce the mean renal clearance of uric acid in patients with hypertension.

**ACE Inhibitors**

Captopril and enalapril increases uric acid excretion, and captopril significantly reduces serum uric acid in hypertensive patients with hyperuricemia while it has been reported that ACE inhibitors have not been associated with lower serum uric acid levels.

In large general practice cohort representative of the UK population, we found that use of calcium channel blockers and losartan was associated with a moderately lower risk of incident gout among patients with hypertension. These associations were independent of use of other evaluated antihypertensive drugs and other risk factors for gout such as age, body mass index, smoking, alcohol use, and presence of ischaemic heart disease, hyperlipidaemia, hypertension, and renal failure. These inverse associations were stronger with both a longer duration and a higher dose of use. In contrast, we found that use of diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers was associated with an increased risk of incident gout among patients with hypertension. The magnitude of relative risk was strong with diuretic use and more moderate with the other antihypertensive drugs. These associations were also independent of use of other antihypertensives and other risk factors for gout and tended to become stronger with a longer duration of use and a higher dose. The absolute risk difference was the largest with diuretic use (about six cases per 1000 person years) and more moderate with the other agents (one or two cases per 1000 person years). The inverse association between use of calcium channel blockers and risk of incident gout possibly stems from its action on renal function. An increase in uric acid excretion has been observed with calcium channel blockers. Calcium channel blockers could increase the glomerular filtration rate and consequently the clearance rates of uric acid and creatinine. For example, amlodipine has been found to increase the output of fluid from the proximal tubules, as shown by the significant decrease observed in the fractional proximal reabsorption of sodium and the corresponding increase in the reabsorption of sodium in the distal tubule. Furthermore, nifedipine, which possesses renal vasodilatory effects, has been found to reduce serum uric acid levels compared with a placebo in the A Coronary Disease Trial Investigating.
effect may be contingent on vasodilatation and on increases in glomerular filtration rate. Decreased proximal tubular absorption of uric acid may also play a role. Another large trial has demonstrated that nifedipine reduces serum uric acid levels in patients with coronary disease. The urate-lowering effects of losartan, especially compared with other ARBs, are a result of a uricosuric effect not shared by other drugs in this class.

When possible, prescribe losartan and/or calcium channel blockers as antihypertensive therapy in people with gout or in whom gout develops during antihypertensive drug treatment. With the rising number of resistant hypertensive patients (i.e., individuals who require 3 or more medications to control blood pressure), this approach will not always be possible. Despite this specific treatment for recurrent gout will still be required.

CONCLUSIONS

Our findings suggest that calcium channel blockers and losartan may be protective against the risk of gout among people with hypertension. These are compatible with previous findings that suggested these drugs have urate lowering properties. In contrast, diuretics, β blockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers are associated with an increased risk of gout. These may have practical implications for choosing the appropriate antihypertensive drugs in patients with hypertension, a common comorbidity of gout.

REFERENCES