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# Colchicine and the concepts of nephroprotection; a new feature of an old drug

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**Abstract**
Colchicine as an old drug and is usually the first choice of treatment for acute gout to reduce pain and inflammation. Colchicine seems to prevent various pro-inflammatory mechanisms, whereas it allows increasing concentration of anti-inflammatory molecules, which leads to clinical advantage in patients with gout. Colchicine is using generally as a treatment for acute gout however, it has also newly been revealed to have anti-fibrotic effects in different kinds of nephropathies such as polycystic kidney disease, diabetic nephropathy and amyloidosis. Extended use of colchicine is associated with nephrotoxicity depending on its dose, which results to impairment of renal function. Risk of colchicine therapy is accentuated in chronic kidney disease (CKD) patients; therefore, dose reduction is necessary dependent on CKD stage.

**Keywords:** Colchicine, Chronic kidney disease, Gout, Nephroprotection, Nonsteroidal anti-inflammatory drugs, Rhabdomyolysis
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## Introduction

Colchicine as an old drug and is usually the first choice of treatment for acute gout to reduce pain and inflammation. Colchicine is known to inhibit cell division, migration, polarization and proliferation by binding to tubulin and formation of tubulin-colchicine complex, which induces the depolymerization, and loss of the fibrillar structures of tubulin polymers.

The drugs prescribed to treat gout including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and colchicine all decrease pain and inflammation related to gout flares. Xanthine oxidase inhibitors (such as allopurinol and febuxostat) reduce formation of uric acid in the body. Probenecid increases the kidneys' ability to eliminate uric acid from the blood. Oral colchicine is a candidate in subjects who are not capable to endure NSAIDs or high doses of corticosteroids.

In initial investigation, there are numerous mechanisms by which colchicine inhibits inflammation of gout. Colchicine prevents numerous proinflammatory mechanisms (such as TNF-α receptors, the NF-κB expression and superoxide anion production), whereas allowing release of anti-inflammatory molecules that could be a clinical advantage in patients with gout [such as transforming growth factor (TGF-β1) levels] (1).

## Search strategy

For this review, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase and Google Scholar, using various keywords including; autosomal dominant polycystic kidney disease, Colchicine, chronic kidney disease, gout, nephroprotection, nonsteroidal anti-inflammatory drugs, amyloidosis, nephrotoxicity, rhabdomyolysis.

## Nephroprotective effects of colchicine

Colchicine is using generally as a treatment for acute gout, however it has also newly been revealed to have anti-fibrotic effects. It is showed that colchicine adjusts hypertension-induced kidney fibrosis and lessened glomerular sclerosis and interstitial fibrosis. Its shielding effects are probable intermediated by inhibition of Ras homolog gene family, member A (RhoA) activation, attenuation of glomerular sclerosis and interstitial fibrosis, renal inflammatory infiltration, improvement of glomerular and tubulointerstitial extracellular matrix (ECM) accumulation and inhibition of increased monocyte chemoattractant protein 1 (MCP-1) and intercellular adhesion molecule 1 (ICAM-1) expression in diabetic nephropathy and hypertension-associated kidney disease. Microalbuminuria and podocyte depletion were repealed in diabetic animals by colchicine administration (2,3). In previous studies showed, cyclosporine induced increased TGF-β expression and apoptosis, reduced by colchicine by withholding TGF-β expression and

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**Implication for health policy/practice/research/ medical education**

Colchicine is using generally as a treatment for acute gout; however, it has also newly been revealed to have anti-fibrotic effects in different kinds of nephropathies such as polycystic kidney disease, diabetic nephropathy and amyloidosis.

apoptosis in kidney, and also plasma malondialdehyde (4,5). Accordingly, interstitial fibrosis and thickened tubular basement membranes in cyclosporine plus colchicine treated animals were meaningfully less than in animals treated with cyclosporine alone. This might be interpreted by the effect of colchicine on the release of fibroblast growth factors and collagen accumulation (6).

It is speculated that colchicine could be useful to diminish cyst formation in autosomal dominant polycystic kidney disease (ADPKD) patients due to its anti-mitotic, anti-apoptotic, anti-proliferative and anti-inflammatory effects. Each of these factors has a main role in cyst growth and progression in ADPKD. (7).

A rabbit model of renal glomerular sclerosis induced by anti-glomerular basement membrane antibody (anti-GBM disease) was applied to conclude whether colchicine could protects kidney function and decrease fibrosis. This study showed colchicine mainly protected kidney function by about one fourth through decreased interstitial fibrosis in crescentic glomerulonephritis (8). In addition colchicine, by its immunosuppressive and anti-inflammatory effects, may decrease the progression of kidney transplant allograft nephropathy. A previous experimental study showed colchicine allowed long-graft survival in the absence of conventional antirejection treatment (9). Moreover, the anti-fibrotic and anti-apoptotic characteristics of various dosages of colchicine on renal fibrosis and apoptosis at both cortical and medullary zones in unilateral ureteral obstruction (UUO) model was detected. Findings of this study showed a novel view on the nephroprotective characteristics of colchicine. This study showed a reduced acetylated α-tubulin expression and decreased fibronectin expression following colchicine therapy, along with diminished TGF-β immunoreactivities in the UUO kidneys (10).

Meanwhile, the preserved nephritic rats with colchicine had significantly less proteinuria and less glomerular injury than unpreserved rats in an experimental study. Colchicine prevents leucocytes loss or reduces the proteinuria after use of a nephrotoxic agent in animals. This finding shows the anti-inflammatory effect of drug (11).

Amyloidosis is an uncommon disease, in which insoluble amyloid particles are deposited in various organs, inducing advanced tissue injury. The kidney is one of the most common tissues of amyloid deposition in AL, AA Amyloidosis, and other genetic variants of this disease. Without treatment, amyloidosis-induced renal damage frequently develops to end-stage renal disease (ESRD). Reappearance of AA amyloidosis in the transplant happened in 71% of cases. According to the colchicine efficiency in avoiding AA amyloidosis in familial Mediterranean fever (FMF), amyloidosis recurrence in the transplant should be preventable following colchicine therapy (12,13). In a retrospective study, 21 FMF patients who were renal allograft receiver for final stage of chronic kidney disease (CKD) due to amyloidosis were investigated to assess the protective effect of colchicine on transplant amyloidosis. This study showed that, the progression of amyloidosis in the renal allograft in FMF is unavoidable at a colchicine amount <1 mg/d, random at 1 mg/d and generally avoidable in > 1.5 mg/d (14). Colchicine in addition to its capability to avoid amyloid deposition may avoid the progression of interstitial fibrosis in patients with amyloidosis who had suffered kidney allograft (15).

Previous reports also showed the effect of colchicine on the result of amyloid nephropathy of FMF in childhood. Colchicine when used properly can improve proteinuria and avoid progression of CKD in patients with amyloid nephropathy of FMF. However, the treatment effect of colchicine depends principally on two parameters including the stage of the CKD and its dose. Extended colchicine therapy (1.5–2 mg/d) can diminish proteinuria, even when it is started at the advanced stage of amyloid nephropathy, and can avoid progression of CKD (16).

Likewise, colchicine may decrease proteinuria in passive Heymann nephritis. Colchicine decreases albumin excretion and dyslipidemia in passive Heymann nephritis by renal prostaglandin stimulation (17). In general, colchicine prevents acute inflammatory responses by various effects, comprising preventing neutrophil adhesion, motility, and chemotaxis (14-17).

## Nephrotoxicity effects of colchicine

Several large clinical studies and small follow-ups suggest that gout is accompanied with the progression of hypertension and CKD. There are numerous causes to illuminate why gout may induce CKD, comprising high uric acid level, inflammation, simultaneous hypertension and diabetes, and use of NSAIDs. However, some clinicians are often challenged with treatment of gout by colchicine when there is renal injury and recommended other drugs (18,19).

About two-thirds of human uric acid excretion happens via the kidneys, thus reduced kidney function is linked with hyperuricemia. Colchicine-associated toxicity has been detected when the drug was administrated for acute therapy of gout. With extended usage of colchicine, rhabdomyolysis, low neutrophil count, acute pancreatitis and myopathy may develop in patients with CKD (20). As colchicine may be myotoxic even in spite of normal kidney function, colchicine treated patients must be cautiously checked for signs of myopathy and rhabdomyolysis, by

assessment of creatine kinase. In addition, it should be reminded that colchicine has a constricted benefit to risk limit, while an overdose may cause acute multiple organ dysfunction syndrome (21).

Previous authors showed subjects with normal kidney function and mild kidney injury or ESRD getting hemodialysis do not display colchicine accumulation, while those with moderate or severe kidney injury showed up to two-fold risk for colchicine accumulation (22).

In another study, hemodialysis patients which treated with colchicine tested for probable risks of colchicine therapy with a superior emphasis on neuromuscular side effects. Creatine kinase and myoglobin were applied to identify any clinical muscle damage or rhabdomyolysis, respectively. This study showed hemodialysis patients on colchicine had no signs of toxicity against control subjects (23). Besides colchicine toxicity could lead to acute kidney injury (AKI) accompanied by glycosuria, due to renal proximal tubular injury. Electrolyte imbalance including disturbed absorption or strengthened excretion of magnesium, phosphate, and calcium was reported although it can be recovered under care (24).

Nephrotoxicity was demonstrated by significant rise of serum urea, creatinine along with histology changes in kidney. Extended use of colchicine resulted to nephrotoxicity depending on its dose (25).

Colchicine can lead to serious myoneuropathy since its toxicity is intensified in patients with simultaneous use of cyclosporine and cholesterol-lowering drugs. It has also been reported that colchicine withholding is associated to quick clinical improvement. Thus, clinical doubt and quick withdrawal of colchicine is vital. In addition, invasive and expensive diagnostic tests can be prevented by a proper identification of problem. Therefore, all clinicians who are concerned on the treatment of kidney allograft receivers should be aware with colchicine-associated myoneuropathy (26).

Colchicine and NSAIDs are suggested first-line therapies for acute gout. However, in CKD patients, NSAIDs are not suggested because their administration can worsen or lead to AKI. In addition, the colchicine risk is strengthened in CKD patients, thereby dose reduction is necessary dependent on CKD stage. Up to one fifth of an orally used dosage of colchicine is eliminated unaltered from the kidneys, therefore in subjects with advanced kidney injury, the elimination time of colchicine is two to three-folding slower against subjects without kidney injury. Colchicine cannot be eliminated by dialysis; hence, the risk of colchicine accumulation is particularly great in patients with renal failure (27).

## Guideline for consumption of colchicine

There is not available high confidence data on dosing schedule of colchicine, however authors suppose dose decreases in subjects with glomerular filtration rate (GFR) <50 mL/min/1.73 $m^2$. Some clinicians suppose its whole withhold in patients with GFR <10 mL/min/1.73 $m^2$ and in hemodialysis patients (28). It is postulated a dose of 0.6 mg/d in GFR of 35- 49 mL/min and 0.6 mg every 2-3 days if GFR is 10-34 mL/min are reasonable. The overall suggested dose for patients with ESRD experiencing dialysis is 0.3 mg used twofold every week, or 0.6mg dose every two weeks for acute gout therapy. It should be checked patients with CKD on colchicine for leukopenia or elevated creatine kinase and aspartate aminotransferase levels (29).

## Conclusion

Colchicine as an old drug is the first choice of treatment for acute gout to decrease pain and inflammation. The anti-fibrotic and anti-inflammatory effects and low toxicity make colchicine, a good choice for the treatment of fibrotic syndromes in different kinds of nephropathies such as ADPKD. There are several causes to illuminate why gout may induce CKD, comprising high uric acid level, inflammation, simultaneous hypertension and diabetes, and the use of NSAIDs. However, the treatment effect of colchicine depends principally on two parameters including the stage of the CKD and its dose. Extended use of colchicine is associated to nephrotoxicity depending on its dose, which results to impairment of renal function. Risk of colchicine therapy is accentuated in CKD patients; hence, dose reduction is necessary dependent on CKD stage.

### Author's contribution

HN is the single author of the manuscript.

### Conflicts of interest

The author declares that he has no competing interests.

### Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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