WebLog Journal of Nephrology

Review Article
Published: 29 Aug, 2026

# Is Nephrolithiasis a Predictive Factor for Hypertension? A Systematic Review and Meta-Analysis

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## Abstract

Although the mechanisms and timing of the association between nephrolithiasis and hypertension are still controversial, the hypothesis that nephrolithiasis is a predictive factor for the subsequent development of hypertension is postulated. Nephrolithiasis, as a disease with a high incidence and recurrence rate, is always troubling people all over the world.

Epidemiological studies have provided the evidence for association between nephrolithiasis and a number of cardiovascular diseases including hypertension, diabetes, chronic kidney disease, metabolic syndrome. Many of the co-morbidities may not only lead to stone disease but also be triggered by it. Nephrolithiasis is a risk factor for development of hypertension and have higher prevalence of diabetes mellitus and some hypertensive and diabetic patients are at greater risk for stone formation. An analysis of the association between stone disease and other simultaneously appearing disorders, as well as factors involved in their pathogenesis, may provide an insight into stone formation and improved therapies for stone recurrence and prevention. The association between stone formation and development of co-morbidities is a result of certain common pathological features. Review of the recent literature indicates that production of Reactive Oxygen Species (ROS) and development of Oxidative Stress (OS) may be such a common pathway. OS is a common feature of all Cardiovascular Diseases (CVD) including hypertension, diabetes mellitus, atherosclerosis and myocardial infarct. There is increasing evidence that ROS are also produced during idiopathic Calcium Oxalate (CaOx) nephrolithiasis. Both tissue culture and animal model studies demonstrate that ROS are produced during interaction between CaOx/Calcium Phosphate (CaP) crystals and renal epithelial cells. Clinical studies have also provided evidence for the development of oxidative stress in the kidneys of stone forming patients. Renal disorders which lead to OS appear to be a continuum. Stress produced by one disorder may trigger the other under the right circumstances.

**Keywords: Chronic Kidney Disease; Hypertension; Nephrolithiasis; Oxidative Stress; NADPH Oxidase**

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**Received Date**: *10 Jul 2026*
**Accepted Date:** *27 Aug 2026*
**Published Date:** *29 Aug 2026*

***Citation:***
*Marilena Stoian. Is Nephrolithiasis a Predictive Factor for Hypertension? A Systematic Review and Meta-Analysis. WebLog J Nephrol. wjnp.2026.h2910. https://doi.org/10.5281/zenodo.22537586*



## Introduction

Nephrolithiasis is prevalent and burdensome worldwide, with the prevalence varying by age and sex. The disease usually presents in men aged 60 to 69, with a prevalence rate of approximately 1.7 to 8.8% worldwide [1, 2]. In the United States, ~10.6% of men and 7.1% of women suffer deeply from nephrolithiasis, which is comparable to diabetes (9.7%) [2-4]. The worldwide prevalence of urolithiasis in men by age 70 varies from approximately 4% in England to 20% in Saudi Arabia Geographically, kidney stones are more common in places with high humidity and temperatures [5]. It has been predicted that with the expected temperature rise worldwide, there will be an increase of 1.6-2.2 million lifetime cases of kidney stone by 2050 [6]. In addition, urolithiasis is a chronic disease with a 60% chance of recurrence within 10 years of the first episode. Stone disease has also been linked with a number of other chronic diseases such as Obesity (OB) [7], Diabetes Mellitus (DM) [8], Hypertension (HTN) [7], Metabolic Syndrome (MS) [9], and Chronic Kidney Disease (CKD) [10].

The presence of nephrolithiasis can lead to more than short-term pain and infection. Progressive hypertension [11] chronic kidney diseases, and even end-stage kidney failure [12, 13] will be the ultimate outcomes of nephrolithiasis without effective intervention and treatment. Unfortunately, despite surgery or medication, recurrence rates of 50% within 5 years and up to 75% within 20 years

leave many patients suffering [14]. Meanwhile, the medical expenses incurred by patients due to nephrolithiasis crush their economic lives either.

There is growing evidence supporting that nephrolithiasis largely contributes to the occurrence of hypertension. Since the association between arterial hypertension and nephrolithiasis was described in 1965 for the first time by Tibblin [15], much effort has been devoted to this field. Data from several observational studies suggested a risk of hypertension in nephrolithiasis patients of 1.24-1.96 compared to the general population [16-22]. A previous review performed by Cupisti *et al.,* [23] has shown the current understanding of the potential link between nephrolithiasis and the occurrence of hypertension, but no meta-analysis has been used to examine the relationship.

The relation between nephrolithiasis and hypertension is rather unclear, but from literature data, there are several potential reasons which may explain the observed associations. First, alterations in calcium metabolism maybe have an important role in the pathogenesis of both nephrolithiasis and hypertension [24, 25]. Second, the traits of metabolic syndrome are factors highly prevalent in hypertensives as well as in kidney stone formers, so insulin resistance may be a common pathophysiological mechanism [26, 27]. Third, Chronic Kidney Disease (CKD) is a condition which may occur more frequently in nephrolithiasis patients and in hypertensive patients. Therefore, CKD may be another factor involved in the linkage between nephrolithiasis and hypertension. Finally, inflammation and oxidative stress have been recently hypothesized as possible links between stone disease and hypertension [28]. Obviously, all of these potential reasons are comorbidities in nephrolithiasis and hypertension. However, more medical research is needed to explore and test the relevant presumption.

## The Relationship Between Hypertension and Nephrolithiasis from the Beginnings to the Present

One of the earliest epidemiological studies to demonstrate an association between hypertension and nephrolithiasis was performed in Sweden. Tibblin performed a cross-sectional retrospective study of 850, 50-year-old males [15] living in Goteberg. Based on radiological or historical data 6.5% of the patients were stone formers. When stratified by blood pressure into four groups, the prevalence of urolithiasis increased from 1.1% in the lowest blood pressure group (<145/90 mmHg untreated) to 13.3% in the subjects with the highest blood pressure (>175/115 mmHg or treated hypertension). Cirillo et al. confirmed these observations through a cross-sectional retrospective study of 3,431 European patients. There was an increased prevalence of stones in hypertensive patients (5.22%) compared to the normotensive ones (3.36%) [29].

To test the hypothesis that kidney stones are more common in hypertensive men, a cross-sectional study of 688 male workers aged 21-68 years, of The Olivetti factory in Naples, Italy, was performed [30] 118 had untreated hypertension while 61 were under treatment for hypertension. The overall prevalence of urolithiasis was 16.3% of which 13.4% were normotensive subjects, 24.3% were untreated hypertensive patients and 32.8% were treated hypertensives ($p$<0.001). The relative risk of hypertensive patients having a history of urolithiasis was twice that of the normotensive subjects [Odds Ratio (OR) of 2.11; 95% Confidence Interval (CI) 1.17-3.81]. The age-adjusted relative risk of kidney stones in hypertensive patients remained twice that of normotensive subjects (OR 1.79; 95% CI 1.53-2.09). It was concluded that an independent clinical association existed between urolithiasis and hypertension. The results of a recent South Korean study showed hypertension as an independent predictor of stone recurrence [31].

The Olivetti Prospective Heart Study participants were then followed up after 8 years. 503 male workers aged 21-68 years, who previously did not report a history of urolithiasis were evaluated for stone disease [32]. After 8 years, 10.3% of the participants reported stone episode. The incidence of urolithiasis was higher in hypertensive patients (16.7%) than normotensives (8.5%, $p$=0.011). The risk was unaffected by treatment (relative risk 2.01; 95% CI 1.13-3.59), age (RR 1.89; 95% CI 1.12-3.18), body weight (RR 1.78; CI 1.05-3.00) or height (RR 2.00; CI 1.19-3.38). It was concluded that hypertension was a significant predictor of kidney stone disease. In a separate study, 381 male normotensive participants of the Olivetti Study, 15.2% with history of stone disease, were also evaluated after 8 years [33]. Patients with history of stones were more prone to develop hypertension (age-adjusted RR 1.96; 95% CI 1.25-3.07).

Health Professional Follow-up Study (HPFS), a longitudinal study of cardiovascular diseases, cancer and other diseases among 51,529 male health professionals aged 40–75 years followed for 8 years [17] indicated that nephrolithiasis can increase the risk of the development of hypertension. At baseline, 8% reported a history of nephrolithiasis and 22.6% reported hypertension. A positive association (age-adjusted OR 1.31; 95% CI: 1.30-1.32) was present between nephrolithiasis and hypertension. The OR for incident hypertension in men with a history of nephrolithiasis was 1.29 (95% CI 1.12-1.41) compared with those without nephrolithiasis. However, hypertensive patients did not have higher incidence of stone formation (OR 0.99; 95% CI 0.82-1.12) compared with the normotensive men. A similar association between stone disease and hypertension was found in middle aged women. A prospective study of the relationship in 89,376 women aged 34-59 years, part of Nurses' Health Study (NHS) over 12 years, showed an increased risk of developing hypertension by women with a history of nephrolithiasis [34]. The age-adjusted relative risk for developing hypertension by women with history of nephrolithiasis compared to those with no nephrolithiasis history was 1.36 (95% CI 1.20-1.43). Women with hypertension were not at greater risk for stone formation compared with those without incident hypertension (OR 1.01; 95% CI 0.85-1.20).

The results of these two studies [17, 34] of large cohorts of US men and women did not agree with the previous Olivetti Study with respect to hypertension being a risk for incident nephrolithiasis. However, results of another study from Parma, Italy [35], confirmed earlier observations and showed that hypertensive males were at a significant risk of forming kidney stones. A prospective 8-year follow-up study of 132 hypertensive and 135 normotensive age-matched males showed that patients with hypertension had significantly higher stones episodes than the normotensive subjects (14.3 *vs.* 2.9%, $p$=0.001, univariate OR 5.5; 95% CI 1.82-16.66).

Another population-based case–control study performed in US also suggested a link between hypertension and nephrolithiasis. There was a significantly higher prevalence of hypertension in people with nephrolithiasis compared with the age- and sex-matched controls (OR 1.19; 95% CI 1.04-1.35) in Olmsted County, MN [1]. Recent histological studies of human kidneys have also provided support for the association between hypertension and stone disease. The presence

of Randall's plaques in cadaveric kidneys correlated only with hypertension [36]. Animal model studies have also indicated a link between stone formation and hypertension. Strains of spontaneously hypertensive rats were found to be more susceptible to developing nephrolithiasis than the normal normotensive ones [37, 38].

Results of the Portuguese National Health Survey (PNHS) in a cross-sectional study also suggested an association between nephrolithiasis and hypertension [39]. Responses of 23,349 subjects to a questionnaire approved by WHO and EUROSTAT were analyzed and showed that after adjusting for age and body mass index kidney stone formers had a higher prevalence of hypertension (OR 1.841; 95% CI 1.651-2.053) than non-stone formers.

Hypertension was also associated with incident stone disease in white and African-American participants of the Atherosclerosis Risk in Communities (ARIC) study [40]. Information on incident kidney stone diseases and co-morbidities was obtained between 1993 and 1995 from 9,541 white and 2,620 African-American middle-aged men. Hypertension (multivariate adjusted hazard ratio 1.69; 95% CI 1.69) was significantly associated with hospitalization for incident kidney stone.

Analysis of the data from the 3rd National Health and Nutrition Examination Survey (NHANES) in United States also provided support for a relationship between kidney stone disease and hypertension. Data collected from 919 stone formers and 19,120 control subjects indicated that female stone formers had 69% increase in the odds of developing hypertension (95% CI 1.33-2.17, $p<0.001$) [19]. The difference in male stone formers was not significant.

In an Italian study of 132 patients with arterial hypertension and 135 normotensive controls, hypertensive males excreted significantly more calcium, magnesium, uric acid and oxalate and had significantly higher CaOx and CaP supersaturation [35]. Hypertensive females, on the other hand, excreted significantly more calcium, phosphorus, and oxalate and had significantly higher CaOx supersaturation. No significant differences were found in urinary *pH* or excretion of citrate. These patients and controls were followed up for an average of 7 years. Nineteen out of 132 hypertensive patients and 4 of the 135 normotensive subjects became stone formers, 12 producing CaOx stones and 4 UA stones. 16 out of 23 stone formers were overweight. Urinary supersaturation with respect to CaOx and UA correlated with the type of stone produced. Increased urinary excretion of oxalate was seen in people with higher BMI [42], obese hypertensive patients [31] as well people with diabetes [41]. Increased urinary oxalate, however, did not change urinary supersaturation for CaOx [42].

The results of the Olivetti Prospective Heart Study, which showed subjects with stone disease had significantly higher risk for developing hypertension, also demonstrated stone formers with significantly higher blood pressure and excretion of calcium [33]. A retrospective study of 462 stone patients to determine the relationship between hypertension and urinary composition found that in stone formers hypertension was significantly associated with urinary calcium which was 12% higher than in the normotensive stone formers [43]. There was a significant relationship between relative risk of hypertension with quintile of calcium excretion and not with citrate excretion. However, an analysis of HPFS and NHS I and II database did not show significantly increased urinary excretion of calcium by hypertensive patients. There was, however, an inverse relationship between hypertension and citraturia [44]. Crystallization is also dependent upon the macromolecular modulators present in the milieu; however, no large-scale study has been performed to determine the potential of urine from hypertensive or diabetic patients to crystallize.

## Inflamation and Oxidative Stress as Possible Links Between Stone Disease and Hypertension

There are two major pathways to the formation of kidney stones, both involving inner medulla. Stone formation in the idiopathic pathway begins with Calcium Phosphate (CaP) deposition in the renal interstitium while in the other, it begins with crystallization of a variety of stone salts in the collecting ducts. There are overt signs of injury and inflammation in the second pathway where renal epithelial cells are directly exposed to crystals indicating that they are proinflammatory. Both *in vitro* cell culture experiments as well as animal model studies indicate that exposure to crystals, particularly Calcium Oxalate (CaOx) and Calcium Phosphate (CaP), leads to the development of oxidative stress, upregulation of MAPK and production of inflammatory molecules including TGF-$\beta$, NF$\kappa$B, prostaglandins, MCP-1, OPN, inter-α-inhibitor. NADPH oxidase appears to play a central role since inhibitors of the enzyme reduce the production of ROS as well as renal injury and crystal deposition. RAS pathway also appears to be critical because inhibition of angiotensin or blockage of angiotensin receptors reduced renal epithelial injury and crystal deposition in rat models of CaOx nephrolithiasis. That oxidative stress, renal epithelial injury and inflammation are also engaged in idiopathic stone formation is indicated by the urinary excretion of reactive oxygen species, products of lipid peroxidation, enzymes indicative of renal epithelial injury as well as many markers of chronic kidney disease. Interestingly, patients who consumed DASH (Dietary Approaches to Stop Hypertension) diet were up to 45% less likely to develop kidney stones.

Hypertension is generally identified by the elevation in blood pressure [45], but its association with arteriosclerosis and microscopic renal glomerular and tubular changes has long been known [46, 47]. Recent clinical as well as animal model studies have provided more evidence of renal involvement and participation of inflammatory processes in the pathogenesis of hypertension with Rennin–Angiotensin System (RAS) and Reactive Oxygen Species (ROS) playing significant roles. It is currently hypothesized that factors such as hyperactive Sympathetic Nervous System (SNS), nephron loss, hyperuricemia can induce renal vasoconstriction, ischemia, oxidative stress and injury prompting an immune response and infiltration of inflammatory cells. A number of excellent reviews are available on this subject [48-54].

Cross-sectional as well as prospective studies have shown that levels of circulating C-reactive protein, the most commonly used marker of inflammation, are increased in hypertensive patients and can even predict the onset of hypertension [49, 55-58]. Circulating levels of osteopontin are also increased in essential hypertension [59]. An increase in the level of monocyte chemo-attractant protein-1 MCP-1, an important modulator of inflammatory cells, has been shown in younger patients with arterial hypertension [60].

An increase in the production of ROS/RNS (reactive nitrogen species), and/or decrease in the extra and intra-cellular antioxidants has been demonstrated in both clinical and experimental hypertensions [61] and leads to oxidative stress. It may not only initiate hypertension but also be developed by the hypertensive state. Major cellular ROS

include superoxide anion (O·−2), nitric oxide radical (NO·), hydroxyl radical (OH·), and hydrogen peroxide ($H_2O_2$), which are generated by several pathways. O·−2 anions are produced by NADPH oxidases, xanthine oxidase, lipoxygenase, cyclooxygenase, hemeoxygenase and as a byproduct of mitochondrial respiratory chain. ROS/ RNS play significant roles in activating pro-inflammatory transcription factors and signaling pathways. In addition, NO and superoxide are important modulators of pressure-natriuresis [62]. Low NO levels are important in vasodilation while at higher levels NO interacts with superoxide and produces peroxynitrite which leads downstream to vasoconstriction. Hypertension is associated with reduced levels of nitrite/nitrate (Nox), in part due to enhanced Nitric Oxide (NO) inactivation [63]. Serum and urinary levels of Nox are significantly higher in normotensive subjects than in patients with essential hypertension, while, serum levels of Malondialdehyde (MDA), an end product of lipid peroxidation, being higher in the hypertensive subjects [64]. Administration of antioxidants, or blocking of angiotensin receptors, results in improving or preventing the hypertension in a number of animal models [52, 54, 65].

NADPH oxidase is a major source of ROS in the kidneys, particularly in the presence of Angiotensin II, which stimulates membrane-bound NAD(P)H oxidase leading to increased generation of superoxide [66-69]. NADPH oxidases are also the major source of ROS in the cardiovascular system [54] and animal models studies have provided experimental evidence of NADPH oxidase involvement in the development of hypertension. The kidneys of Spontaneously Hypertensive Rats (SHR) showed increased production of O·−2 and upregulation of $p47^{phox}$ subunit [70]. Administration of SOD mimetic tempol produced a reduction of blood pressure and renal vascular resistance [71]. Significantly higher $p22^{phox}$ mRNA levels and NADPH oxidase driven O·−2 production was found in the aorta of SHR which were ameliorated by treatment with irbesartan, an angiotensin II receptor antagonist [72]. The importance of $p47^{phox}$ is also shown by moderate hypertensive response to angiotensin II in mice lacking the $p47^{phox}$ [73, 74]. Inhibition by membrane permeable gp91ds-tat of $p47^{phox}$ assembly with $gp91^{phox}$ in Dahl Salt sensitive (DS) rats fed a 4% salt diet, normalized ROS production and endothelium-dependent relaxation as well as expression of LOX-1 and MCP-1 [75]. Administration of apocynin, an antioxidant and an inhibitor of the $p47^{phox}$ assembly with $gp91^{phox}$, to DS rats on high salt diet produced significant reductions in the mRNA expression of $gp91^{phox}$, $p47^{phox}$, $p22^{phox}$, and $p67^{phox}$ subunits. Apocynin also reduced NADPH oxidase activity, renal cortical O·−2, monocyte/macrophage infiltration and glomerular and interstitial damage [76]. Direct administration of apocynin to the renal medulla of DS rats on 4% salt diet significantly reduced interstitial superoxide and mean arterial pressure [77, 78]. Experimental studies involving other animal models of hypertension have similarly shown the involvement of NADPH oxidase in the development of hypertension [52, 54, 69].

## Conclusions

Patients with nephrolithiasis need to be exhaustively investigated, not only regarding the stone disease, urinary tract complications, and prevention of recurrences, but also regarding the systemic conditions for which the stone patients are at risk: renal failure, bone metabolic disease, and CV disease. This concept has been adopted by the recent guidelines for urolithiasis of the European Association of Urology [78]. The evaluation of cardiometabolic risk factors and MS components (blood pressure, cholesterol, glucose, BMI, smoking) should be routine in the assessment of renal stone formers.

Oxidative stress plays a key role in the pathogenesis of endothelial dysfunction and endothelial dysfunction has been demonstrated in stone formers .This may contribute to the explanation of why idiopathic calcium stone formers have increased arterial stiffness ,a known independent predictor of CV morbidity .Interestingly, in secondary forms of calcium nephrolithiasis, arterial stiffness is not impaired ,suggesting that this alteration is specific to the most common idiopathic calcium nephrolithiasis and that the epidemiological association with CV disease might be driven by these common features.

A definite epidemiological association exists between kidney stone disease and arterial hypertension, but the pathophysiological mechanisms are still not fully understood. Hypercalciuria or inflammation and oxidative stress have been proposed as possible links. However, there is more convincing evidence that the association between nephrolithiasis and hypertension may be considered as a part of the association between kidney stone disease, metabolic syndrome and atherosclerosis. From a clinical point of view, this association represents a crucial aspect of the clinical management of patients affected by kidney stone disease. In order to implement early prevention and treatment of cardiovascular and/or renal damage physicians should be encouraged to assess individual cardiovascular risk factors in any adult with kidney stones. Consequently, patients with kidney stones need a comprehensive approach rather than an intervention limited to the urinary tract and focused on stone resolution and recurrence prevention. It is time to view kidney stone disease as a systemic disorder, associated to or predictive of hypertension, chronic kidney disease, bone and cardiovascular damage.

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