

Review Article



Targeting Calcium Kidney Stones with Oral Sodium Thiosulfate: From Mechanism to Clinical Implication- A review

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Abstract

Nephrolithiasis is the most prevalent of kidney diseases and is associated with high recurrent rates, and the preventive pharmacologic options are limited. Historically, sodium thiosulfate (STS) has been used for conditions like cyanide poisoning, vascular calcification, and nephrocalcinosis, thanks to its calcium-chelating, anti-inflammatory, and antioxidant effects. With established applications and some evidence of STS in managing calcium-based kidney stones, interest in this potential role is growing nephrolithiasis. This review aims to evaluate the efficacy of sodium thiosulfate in preventing or treating calcium-based kidney stones based on existing evidence in animal and human investigations. A comprehensive literature review was performed using the central electronic database to identify relevant animal and human studies that had been published. Studies evaluating STS in the context of nephrolithiasis were included and organized according to their design, population, and reported outcomes. Animal studies have shown mixed outcomes, with some suggesting reduced stone formation through crystal solubilization, oxidative stress reduction, and mitochondria-mediated effects. Research on humans has limitations, including being small-scale, methodologically diverse, and lacking clear conclusions. As a result, the clinical benefits of oral STS in calcium nephrolithiasis are uncertain and sometimes conflicting. However, the established effectiveness of STS in treating vascular calcification and nephrocalcinosis provides a solid basis for understanding its mechanisms and potential benefits. The evidence on oral STS for calcium-based nephrolithiasis is limited and inconsistent. However, the previous success in treating other calcification-related disorders advocates further investigation. Well-designed clinical trials are necessary to validate its efficacy, define appropriate dosing regimens, and determine its role in managing recurrent calcium kidney stones.

Introduction

Nephrolithiasis, also known as kidney stone disease, is a prevalent and multifactorial condition affecting individuals of all ages.^{1,2} The increasing incidence of nephrolithiasis in both genders is primarily linked to changes in dietary habits and obesity.^{2,3} Genetic predisposition and environmental risk factors significantly influence the formation of kidney stones.^{4,5} Nephrolithiasis is often associated with a range of comorbidities, including metabolic syndrome, diabetes mellitus, elevated body mass index (BMI), chronic kidney disease, cardiovascular disorders, and vascular calcification.^{6,7} Recent dietary

recommendations for these patients emphasize increased fluid intake, moderate calcium consumption, reduced sodium and animal protein intake, maintenance of a healthy BMI, and higher dietary fiber intake.^{8,9} Calcium stones are the most common type of kidney stones, primarily consisting of calcium oxalate, either alone or combined with calcium phosphate.¹⁰ Elevated urinary calcium and oxalate levels, reduced citrate or magnesium levels, and other metabolic abnormalities contribute to stone formation.^{11,12} Getting kidney stones is considered one of the most painful medical conditions, often causing considerable physical pain, emotional stress, and

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financial expenses.^{13,14} Management strategies generally include pharmacological and surgical interventions, such as extracorporeal shock wave lithotripsy (ESWL) and endoscopic techniques that use high-powered lasers for stone destruction.¹⁵ However, these techniques are not without risks and may lead to complications such as renal injury, bleeding, ureteral damage, or infection.¹⁶ The recurrence rate, affecting nearly 50% of patients, highlights the urgent need for more effective therapeutic and preventive approaches.¹⁷ Although the exact mechanisms involved in stone formation remain not fully understood, oxidative stress will likely play a significant role. This has generated growing interest in using antioxidants to reduce stone formation.^{18,19} Sodium thiosulfate (STS), an FDA-approved agent recognized for its antioxidant properties and ability to neutralize reactive oxygen species, has recently emerged as a promising candidate for managing kidney stones.²⁰ Clinically, STS is used to prevent kidney damage during cisplatin chemotherapy and in treating cyanide poisoning.^{21,22} More recently, it has demonstrated therapeutic potential in vascular calcification and calciphylaxis (a severe and painful condition characterized by calcium accumulation in soft tissues and blood vessels, leading to thrombosis and non-healing ulcers).^{23,24} In such cases, STS exerts its effects by chelating calcium ions and converting them into more soluble compounds that the body can eliminate most easily.²⁵ Recent literature suggests that STS has appeared as an effective treatment option for managing calcification disorders associated with renal disease. In a report of a patient with advanced renal failure and tumoral calcinosis, combined therapy with intravenous STS, increased hemodialysis, and nutritional support resulted in a significant reduction of calcified masses and symptomatic relief, and the patient was able to undergo a successful kidney transplant.²⁶ In another study, a case of primary hyperoxaluria type I, who presented with subcutaneous calcific deposits after kidney transplantation, revealed significant radiological and clinical improvement with six courses of STS treatment, emphasizing the importance of genetic testing and the use of STS in such patients.²⁷ Another report also discussed the co-occurrence of calciphylaxis, nephrogenic fibrosing dermatopathy, and pseudoxanthoma elasticum-like skin changes, and suggested the potential role of STS in improving skin lesions caused by calcium deposition.²⁸ The successful treatment of calciphylaxis in a kidney transplant recipient, achieved through concurrent intravenous and topical STS injections, along with fish skin grafting, demonstrated that this approach can be highly effective in managing refractory conditions.²⁹ Overall, these reports highlight the significant potential of STS in mitigating the clinical burden of calcification and enhancing the quality of life in renal and transplant patients. This review aims to investigate the latest findings on the role of STS in calcium-based nephrolithiasis and evaluate its potential as a new therapeutic strategy for this challenging condition.

Methodology

A comprehensive literature search was performed across major electronic databases, including PubMed, Scopus, Google Scholar, the Cochrane Library, [ClinicalTrials.gov](https://www.clinicaltrials.gov), and the Iranian Registry of Clinical Trials (IRCT), to evaluate existing evidence on the efficacy of sodium thiosulfate in the prevention and treatment of nephrolithiasis. The search encompassed studies published up to May 2025. Only articles published in English with accessible full texts were included. The search strategy incorporated Medical Subject Headings (MeSH) and relevant keywords, including “sodium thiosulfate” AND (“kidney stones” OR “nephrolithiasis” OR “urolithiasis” OR “calcium oxalate” OR “renal calculi”). Results from both preclinical (animal) and clinical (human) studies were extracted and summarized in tabular format.

Mechanism of action of sodium thiosulfate in nephrolithiasis

STS is used for reducing the side effects of cisplatin and providing emergency treatment for cyanide poisoning.^{21,22} It has also shown remarkable effects in treating calciphylaxis, although the exact mechanism of action remains unclear.³⁰ Research demonstrates that STS can effectively treat calciphylaxis by binding to calcium ions in the blood and soft tissues.³¹ This binding effectively inhibits the formation of calcium deposits and decreases tissue calcification.³² Thiosulfate is an endogenous molecule derived from hydrogen sulfide (H₂S).³³ It has been reported to have antioxidant, anti-inflammatory, and chelating properties, which may help reduce tissue damage and improve kidney function.^{34,35} Oxidative stress is known to contribute to the growth of nephrolithiasis.³⁶ STS, which can donate electrons and scavenge free radicals, may act as a potential anti-stone agent. Nevertheless, the exact mechanism by which thiosulfate ameliorates pathological crystallization remains unknown. *Aspelin et al.* and *Yatzidis* have shown that thiosulfate can control calcium phosphate nephrolithiasis.^{20,37} *Yatzidis* suggested that thiosulfate forms a calcium thiosulfate complex and is more soluble than calcium oxalate or phosphate. It is crucial to note that the solubility of a salt does not reflect a molecule's ability to form a complex with another.³⁸ Besides, *LaGrange et al.* reported opposing results regarding the efficacy of thiosulfate in preventing calcium stone disease.³⁹ Generally, in all studies, the specific mechanism by which STS facilitates calcium deposition was not clearly defined.

Clinical consideration and drug interactions of sodium thiosulfate

STS in oral form is regarded as a safe drug that does not have any direct or life-threatening drug interactions. According to limited studies on pharmacokinetics, pharmacodynamics, and drug interactions, this substance is poorly absorbed when taken orally and primarily excreted by the kidneys. This feature allows for its use without any special problems in most patients.

However, several critical clinical considerations should be considered when administering STS orally.⁴⁰⁻⁴² Because this drug is mainly excreted through the kidneys, it may accumulate in people with renal failure or reduced kidney function. This can cause electrolyte imbalance (especially sodium and potassium) and even metabolic complications. Long-term use or high doses may cause increased sodium levels and decreased potassium levels in the blood. For this reason, regular laboratory monitoring should be performed in patients taking diuretics (such as furosemide or hydrochlorothiazide) or with cardiac or renal diseases. Since STS is alkaline, it may affect the absorption and effect of some drugs whose absorption relies on the pH of the environment (such as some antibiotics or antifungal drugs).^{41,43,44} Additionally, if the human body experiences a significant increase in acid production with STS treatment, there is a risk of bone demineralization during long-term therapy. Particularly concerning for individuals with hypercalciuric stone formation, as it heightens the risk of fractures and reduces bone mineral density. Patients with calcium phosphate stones and distal renal tubular acidosis may not be eligible for STS treatment due to their inability to excrete acid, which can lead to metabolic acidosis²⁰. Only minimal side effects have been reported in all human studies of STS. When used orally in the kidney stone population, *Yatzidis et al.* reported that the only adverse effect observed was the presence of foul-smelling stools; however, they noted that no patients discontinued the drug due to side effects. In patients with restricted sodium intake (such as those with high blood pressure or heart failure), the amount of sodium in the drug formulation (e.g., in solution or tablet form) should be considered.^{45,46} According to available evidence, data on the safety of STS use during pregnancy and lactation are limited. Animal studies have shown potential teratogenic consequences. Since human data are limited, the drug is classified as category C. It's only recommended for use during pregnancy in emergency situations when the potential benefits outweigh the risks, and under close supervision. Also, due to the lack of information about excretion properties into breast milk and the possible adverse effects in infants, breastfeeding should be avoided or temporarily discontinued during treatment. Hence, the administration of STS in these situations should be cautiously approached and reserved for specific clinical conditions.⁴⁷⁻⁵⁰

Sodium thiosulfate in nephrolithiasis: Evidence from in vitro and Animal studies

STS has emerged as a therapeutic agent in managing nephrolithiasis, especially calcium-based kidney stones. Experimental and preclinical data suggest that STS may act through different mechanisms. *Asplin et al.* (2009) investigated a long-term (18-week) model and found that STS significantly decreased calcium phosphate stone formation, even in hypercalciuria. This supports a mechanism related to urinary pH reduction rather than calcium complexation alone.²⁰ *Baldev et al.* (2015) studied

the interaction of STS with agents that affect mitochondrial K-ATP channels. Their results suggest that STS exerts mitochondria-mediated protective effects, lowering oxidative damage and crystal precipitate, revealing a novel mechanism of nephroprotection.⁵¹ In a 4-week rat model of hyperoxaluria, *Bijarnia et al.* (2015) reported that STS remarkably maintained creatinine clearance and renal SOD activity while decreasing urinary 8-isoprostane levels. These findings emphasize STS's antioxidant and nephroprotective properties, developing beyond its effects on crystallization inhibition.⁵² *Vaitheeswari et al.* (2015) showed that NaSH (an H₂S donor), STS, and Na₂SO₄ significantly inhibited calcium oxalate (CaOx) crystal growth in both buffered media and human urine. Among these, NaSH had the most potent inhibitory effect, but STS also demonstrated considerable activity, mainly through modulation of urinary pH and calcium binding.⁵³ *Landry et al.* (2016) revealed that sulfate and thiosulfate inhibit oxalate transport via the Slc26a6 transporter (dPrestin) in *Drosophila* and *Xenopus* oocyte models. This cellular-level effect can be described as a decrease in urinary oxalate concentration, suggesting a new therapeutic target.⁵⁴ *El-Ashmawy et al.* (2021) reported that STS's synergistic or additive protective effect was observed when administered concurrently with RAS blockade.⁵⁵ Generally, these studies illustrate converging evidence that STS ameliorates kidney stone formation through numerous mechanisms, including the suppression of oxalate transport, inhibition of crystal precipitation, antioxidant effects, and changes in urinary chemistry. Long-term genetic models demonstrate that STS can reduce stone formation, even in hypercalciuria. Currently, cellular studies provide further insights into interventions targeting transporters. These findings collectively support a vigorous preclinical basis for well-designed clinical trials to assess the efficacy and safety of STS in human nephrolithiasis. The details of these studies are presented in Table 1.

Sodium thiosulfate in nephrolithiasis: Evidence from Human studies

Several human studies have investigated the possible role of STS in preventing and treating nephrolithiasis. One of the earliest clinical studies was published by *Yatzidis* in 1985, in which patients with recurrent calcium oxalate stones received 20 mmol of oral STS daily for 4 years. The results showed a notable decrease in stone formation rates—from 0.98 to 0.11 stones per year—without critical adverse effects. This initial clinical evidence emphasized the therapeutic potential of STS in preventing stone formation.⁴⁶ Subsequently, in 2004, *Yatzidis* published two more studies investigating the endogenous role of thiosulfate. Based on research, stone formers had remarkably lower urine thiosulfate levels than healthy individuals, and some patients had no thiosulfate excretion at all. These results proposed that a deficiency of endogenous thiosulfate may contribute to stone pathogenesis.³⁷ In another observational study

Table 1. Evidence from in vitro and Animal studies

Study, Year	Model	Intervention	Other treatments	Follow-up time	Outcome measures	Key findings	Ref.
John R. Asplin et al. (2009)	Genetic hypercalciuric rats are prone to calcium phosphate stone formation	STS was added to the diet for 18 weeks	None- no pharmacologic control beyond STS vs untreated.	6, 12, and 18 weeks after treatment	Urine Chemistry(calcium, phosphorus, citrate, pH), stone incidence via X-ray and histology	STS drastically reduced stone formation(3/12 vs 11/12 rats, $P<0.002$); despite higher Ca/Phos, urine pH drops likely suppressed stones; this suggests action beyond calcium chelation.	20
N. Baldev et al.(2015)	Wistar rats with ethylene glycol+ ammonium chloride-induced nephrolithiasis	STS (400mg/Kg i.p. daily for 21 days)	Diazoxide(mito-K ₊ ATP opener, 5mg/kg i.p.) and Glibenclamide(mito-k ₊ ATP blocker, 10mg/kg i.p.), each alone or combined with STS	Post-induction and concurrent 21-day treatments	Serum creatinine, urea, ALP; kidney histopathology; in vitro CaOx inhibition gel assay	STS renders renal protection not only through chelation and antioxidant effect but also by modulating the mitochondrial KATP channel for preventing urolithiasis.	51
Rakesh K. Bijarnia et al. (2015)	Male Wistar rats with ethylene glycol-induced hyperoxaluria	STS administered; compared to NaCl and Na ₂ SO ₄ controls	NaCl and Na ₂ SO ₄ served as non-interventional controls	4weeks concurrent with EG exposure	Renal function(creatinine clearance), oxidative stress markers(tissue SOD activity, urinary 8-isoprostanes), crystal deposition, histopathology; plus in vitro ROS scavenging in LLC-PK1 cells	STS uniquely preserved renal function and antioxidant defense despite a similar reduction in crystal load by all treatments. In vitro, STS dose-dependently quenched oxalate-induced ROS and directly inactivated hydrogen peroxide.	52
S. Vaitheeswari et al. (2015)	In vitro buffer and human urine assays using calcium oxalate crystallization setups	Sodium hydrogen sulfide, STS, and sodium sulfate were tested for inhibitory effects.	Trisodium citrate was used as a positive control.	Acute kinetics were evaluated over hours, with measurements carried out in triplicate.	Crystal growth inhibition percent, morphology(optical microscopy, FTIR), kinetics in buffer and urine from healthy and stone-formers	NaSH (H ₂ S donor) showed the strongest inhibition, followed by Na ₂ S ₂ O ₃ and Na ₂ SO ₄ ; all destabilized CaOx crystallization via pH alteration and Ca-complexing.	53
Greg M. Landry et al. (2016)	<i>Drosophila melanogaster</i> Malpighian tubules and <i>Xenopus laevis</i> oocytes expressing dPrestin	Sulfate and thiosulfate to assess their inhibitory effects on oxalate transport	None	Acute assessment(no long-term follow-up)	Oxalate transport activity via dPrestin in both models	Both anions inhibited oxalate transport in a dPrestin-dependent manner, suggesting potential for stone prevention	54
El-Ashmawy et al. (2021)	Wistar rats with ethylene glycol-induced nephrolithiasis	STS 0.4 mg/kg, i.p., 3 times/ week and Candesartan 70 µg/mL in drinking water	Cystone (750mg/kg, oral) used as reference treatment	28 days	Serum and urine biochemistry, kidney oxidative stress markers, histology, and crystal count	Both treatments reduced oxalate levels, oxidative stress, and crystal deposition, improved renal function, and had effects comparable to or better than Cystone's.	55

in pregnancy, *Yatzidis* found that despite physiologic hypercalciuria, urinary thiosulfate excretion increased markedly through gestation and returned to baseline after delivery. This physiological upregulation may describe a natural protective mechanism against the development of nephrolithiasis in pregnant women.⁵⁶ Conversely, a 2013 pilot study by *Okonkwo et al.* prepared a more cautious view. In this trial, 10 individuals (five with hypercalciuric nephrolithiasis and five healthy controls) obtained oral STS for 7 days. Whereas STS increased urinary sulfate and reduced urinary pH, it did not significantly change urinary calcium levels or supersaturation of calcium stones. Additionally, the observed acid load and potential decrease in urinary citrate could increase the risk of recurrent kidney stones.⁵⁷ In vitro and modeling studies by *Rodgers et al.* in 2014 raised questions about the direct efficacy of STS. They revealed that thiosulfate—unlike sulfate—did not decline free ionized calcium or lower supersaturation of calcium oxalate or phosphate. The STS-induced urinary acidification could potentially increase calcium oxalate saturation in certain circumstances.

These findings show that any beneficial effects of STS are unlikely due to direct chemical inhibition of crystal formation.⁵⁸ Providing context is an ongoing randomized clinical trial (IRCT202310170599748N2) in Iran, which aims to assess the effects of STS in patients with nephrolithiasis. Although the findings have not yet been published, this study retains the potential to explain the therapeutic role of STS through more rigorous clinical information. In summary, *Yatzidis's* research showed that STS could decrease stone formation in the long term. However, the studies by *Okonkwo* and *Rodgers* increased concerns about its direct efficacy and issues related to acid-base imbalance. Only *Yatzidis's* studies included long-term clinical follow-up; others were short-term or preclinical investigations.^{46,57,58} The evidence remains limited and inconsistent, underscoring the need for well-designed, comprehensive, and long-term randomized trials to assess STS's efficacy and safety in nephrolithiasis definitively. The details of these studies are accessible in [Table 2](#).

Table 2. Evidence from human studies

Study, Year	Study Type	Participants/Sample Size	STS Dose & Duration	Main Outcome Measures	Key Findings	Ref.
Yatzidis H, 1985	Prospective case series	34 patients with recurrent calcium stones (24 men, 10 women), mean age~40	20mmol/day STS, oral, 4 years (after 3 years observation)	Stone recurrence rate, renal function, side effects	Stone formation reduced from 0.98 to 0.11 stones/ patient/year ($P<0.001$); only side effect: stool odor	46
Yatzidis H, 2004	Case-control study	25 patients with recurrent calcium nephrolithiasis vs 25 healthy adult males	STS; endogenous thiosulfate measured; suggestion; 5mM STS twice daily	Endogenous urinary thiosulfate ($\mu\text{M}/24\text{h}$) via HPLC	Patients had significantly lower thiosulfate excretion (6-10 $\mu\text{M}/24\text{h}$) compared to controls (11-16 $\mu\text{M}/24\text{h}$); one patient excreted none. Low endogenous STS suggests that stone recurrence may occur; 5mM STS twice daily is recommended therapeutically.	37
Yatzidis H, 2004	Prospective cohort (pregnancy)	25 pregnant women + 25 non-pregnant controls	Endogenous urinary thiosulfate during pregnancy	24h-urinary thiosulfate, calcium, sulfate, citrate, pH	Urinary thiosulfate increased to ~36-40 $\mu\text{M}/24\text{h}$; returned to baseline after delivery. Suggests a protective role of hyperthiosulfaturia against nephrolithiasis during pregnancy	56
Okonkwo et al., 2013	Pilot clinical study	5 hypercalciuric stone-formers (mean age~66), 5 healthy controls (mean age~33)	20mmol oral STS (10mmol BID) for 7 days	24h urine: Ca, citrate, NH_4^+ , SO_4^{2-} , pH, CaOx/CaP/UA supersaturations; serum bicarbonate in subset (n=3)	STS increased urinary sulfate & ammonium, decreased pH in both groups; stone-formers had decreased citrate; no change in urinary calcium or CaOx/CaP supersaturation; no significant change in serum bicarbonate (n=3)	57
Rodgers et al., 2014	In silico (modeling) + in vitro	Model 1: Urine from 4 stone-former groups (n not specified) Model 2: Existing data from healthy & hypercalciuric subjects	-	Urinary ionized Ca (iCa) Supersaturation (SS) of CaOx & CaP Upper Limit of Metastability (ULM) Urine pH	Sulfate $\rightarrow$ $\downarrow$ iCa & $\downarrow$ SS $\uparrow$ (CaOx, CaP) Thiosulfate(STS) $\rightarrow$ had no direct effect on iCa or SS, but lowered pH, which decreased CaP SS and increased CaOx SS.	58
IRCT202310170599748N2	Ongoing Randomized Clinical Trial	70 patients with calcium stone formers	Oral STS 500mg TDS for 12 weeks	Changes in urinary, serum, and radiologic characteristics	- (ongoing)	-

Limitations

This narrative review has several limitations. First, due to access restrictions, not all full texts of relevant studies could be recovered, which may confine the universality of data extraction and crucial assessment. Second, since this is a non-systematic review, the choice of studies was not guided by predetermined eligibility criteria, which may raise the risk of selection bias. Additionally, the included studies showed significant differences in design and outcome measures, which made direct comparisons difficult. Human studies were small-scale, observational, or preliminary, with short follow-up periods and little statistical power. These limitations emphasize the need for large-scale, well-designed randomized clinical trials to determine the actual efficacy and safety of STS in nephrolithiasis.

Conclusion

STS shows promising potential as a therapeutic agent for calcium-based kidney stones, as evidenced by preclinical studies demonstrating reduced crystal deposition and favorable biochemical effects. However, inconsistent results in human studies and the possibility of adverse effects limit its current clinical applicability. Future well-designed randomized controlled trials with larger sample sizes, longer follow-up periods, and standardized outcomes are crucial for validating the efficacy and

safety of STS. Elucidating the underlying mechanisms and incorporating patient-centered endpoints will be necessary for determining the actual clinical value of STS in nephrolithiasis management.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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