Review Article

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

Samira Pourtaghi Anvarian, Mahdi Khodayari, Hamid Tayyebi Khosroshahi, Afshin Gharekhani, Mohsen Amjadi, Hadi Hamishehkar

DOI: 10.34172/PS.026.43061

To appear in: Pharmaceutical Science (https://ps.tbzmed.ac.ir/)

Received date: 19 Aug 2025

Revised date: 10 Oct 2025

Accepted date: 11 Oct 2025

Please cite this article as: Pourtaghi Anvarian S, Khodayari M, Tayyebi Khosroshahi H, Gharekhani A, Amjadi M, Hamishehkar H. Targeting calcium kidney stones with oral sodium thiosulfate: from mechanism to clinical implication- a review. Pharm Sci. 2026. doi: 10.34172/PS.026.43061

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

Running Title:

Oral Sodium Thiosulfate in Nephrolithiasis

Authors & Affiliations:

Samira Pourtaghi anvarian[1,2], Mahdi Khodayari[1,3], Hamid Tayyebi Khosroshahi[4], Afshin Gharekhani[5,2], Mohsen Amjadi[6], Hadi Hamishehkar[2*]

[1] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Department of Clinical Pharmacy, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

[3] Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[4] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[5] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[6] Department of Urology, Tabriz University of Medical Sciences, Tabriz, Iran

***Corresponding Authors:**

Hadi Hamishehkar

E-mail: hamishehkar@gmail.com

Authors' ORCID IDs:

Samira Pourtaghi anvarian: 0000-0003-3601-7181

Mahdi Khodayari: 0009-0006-6729-2804

Hamid Tayyebi Khosroshahi: 0000-0002-1131-0413

Afshin Gharekhani: 0000-0003-1791-9120

Mohsen Amjadi: 0000-0003-3221-5877

Hadi Hamishehkar: 0000-0002-2090-5478

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.

Keywords

Sodium Thiosulfate (STS), Calcium Kidney Stone, Nephrolithiasis

1. 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 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.

2. Methodology

A comprehensive literature search was performed across major electronic databases, including PubMed, Scopus, Google Scholar, the Cochrane Library, 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.

3. 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 (H_2S).[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.

4. 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 acidosis[20]. 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]

5. 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 H_2S donor), STS, and Na_2SO_4 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***.

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-	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	Post-induction and concurrent 21-day treatments	Serum creatinine, urea, ALP; kidney histopatholo gy; in vitro CaOx	STS renders renal protection not only through chelation and antioxidant effect but also by modulating the mitochondrial	[51]

	induced nephrolithiasis	i.p.), each alone or combined with STS			inhibition gel assay	KATP channel for preventing urolithiasis.	
Rakesh K. Bijarnia et al. (2015)	Male Wistar rats with ethylene glycol-induced hyperoxaluria	STS administered; compared to NaCl and Na_2SO_4 controls	NaCl and Na_2SO_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, histopatholo	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

					gy; plus in vitro ROS scavenging in LLC-PK1 cells		
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	NaSH (H_2S donor) showed the strongest inhibition, followed by $Na_2S_2O_3$ and Na_2SO_4; all destabilized CaOx crystallization via pH alteration and Ca-complexing.	[53]

					stone-formers		
Greg M. Landry et al. (2016)	***Drosophila melanogaster Malpighian*** tubules and ***Xenopus laevis*** 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	**STS** 0.4 mg/kg, i.p., 3 times/week and **Candesartan** 70 µg/mL	**Cystone** (750mg/kg, oral) used as reference treatment	28 days	Serum and urine biochemistry, kidney oxidative stress markers, histology,	Both treatments reduced oxalate levels, oxidative stress, and crystal deposition, improved renal function, and	[55]

nephrolithiasis	in drinking water	and crystal count	had effects comparable to or better than Cystone's.

6. 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 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 (IRCT20231017059974 8N2) 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	STS; endogenous thiosulfate measured;	Endogenous urinary thiosulfate	Patients had significantly lower thiosulfate	37

		nephrolithiasis vs 25 healthy adult males	suggestion; 5mM STS twice daily	(µM/24h) via HPLC	excretion(6-10µM/24h) compared to controls (11-16µM/24h); one patient excreted none. Low endogenous STS suggests that stone recurrence may occur; 5mM STS twice daily is recommended therapeutically.	
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 ~36-40µM/24h; returned to baseline after delivery. Suggests a protective role of hyperthiosulfaturia against nephrolithiasis	[56]

					during pregnancy	
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^+, $SO4^{2-}$, 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 sroups (n not specified) Model 2: Existing data from healthy &	-	Urinary ionized Ca (iCa) Supersaturation (SS) of CaOx & CaP Upper Limit of Metastability (ULM) Urine pH	Sulfate→↓iCa& ↓SS↑(CaOx, caP) Thiosulfate(STS) → had no direct effect on iCa or SS, but lowered pH, which decreased CaP SS and	58

		hypercalciuric subjects			increased CaOx SS.	
IRCT20231017059974N2	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)	-

7. 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.

8. 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.

Declaration of conflict of interest

The authors declare that there is no conflict of interest.

Declaration of Generative AI and AI-assisted technologia in the writing process

The authors acknowledge the use of Grammarly and ChatGPT to rephrase and improve grammar, language clarity, and avoid unintended plagiarism during the preparation of this work. The final manuscript was thoroughly reviewed and edited by the authors, who take full responsibility for its content of publication.

Authors' Contribution:

Supervision: Hadi Hamishehkar

Conceptualization: Hadi Hamishehkar, Hamid Tayyebi Khosroshahi

Methodology: Hadi Hamishehkar, Samira Pourtaghi anvarian

Investigation: Samira Pourtaghi anvarian, Mahdi Khodayari

Data Curation: Mahdi Khodayari, Samira Pourtaghi anvarian

Writing Original draft: Samira Pourtaghi anvarian, Mahdi Khodayari

Writing- Review & Editing: Hadi Hamishehkar, Hamid Tayyebi Khosroshahi, Afshin Gharekhani, Mohsen Amjadi

Acknowledgments

We would like to appreciate the cooperation of the Clinical Research Development Unit, Imam Reza General Hospital, Tabriz, Iran in conducting of this research.

References

1. Alibrahim H, Swed S, Sawaf B, Alkhanafsa M, AlQatati F, Alzughayyar T, et al. Kidney stone prevalence among us population: Updated estimation from nhanes data set. *JU Open Plus* 2024;2(11):e00115. doi: 10.1097/JU9.0000000000000217

2. Pintus F, Giordano N, Giachino DF, Mandrile G. Genetics of kidney stones and the role of genetic testing in prevention: A guide for urologists. *Front Med (Lausanne)* 2025;12:1631281. doi: 10.3389/fmed.2025.1631281

3. Liu H, Jin M, Hao H, Yuan Y, Jia H, Zhou Y. Association between relative fat mass and kidney stones in american adults. *Sci Rep* 2024;14(1):27045. doi: 10.1038/s41598-024-78061-7

4. Awedew AF, Han H, Berice BN, Dodge M, Schneider RD, Abbasi-Kangevari M, et al. The global, regional, and national burden of urolithiasis in 204 countries and territories, 2000–2021: A systematic analysis for the global burden of disease study 2021. *EClinicalMedicine* 2024;78:102924. doi: 10.1016/j.eclinm.2024.102924

5. Shoag J, Tasian GE, Goldfarb DS, Eisner BH. The new epidemiology of nephrolithiasis. *Adv Chronic Kidney Dis* 2015;22(4):273-8. doi: 10.1053/j.ackd.2015.04.004

6. Ding X, Du Q, Li J, Ji C, Zhang E, Hu W. Prevalence of kidney stones based on metabolic health and weight criteria: Reports from the national health and nutrition examination survey 2007-2018 data analysis. *Front Physiol* 2025;16:1625100. doi: 10.3389/fphys.2025.1625100

7. Zhou L, Gu W, Jiang Y, Zhang H. Age-stratified analysis of the bmi-kidney stone relationship: Findings from a national cross-sectional study. *Front Med (Lausanne)* 2025;12:1513799. doi: 10.3389/fmed.2025.1513799

8. Black AJ, Moussaoui G, Forbes CM. Population-based dietary risks for kidney stones: Implications for dietary counseling and prevention. *Can Urol Assoc J* 2024;19(3):E75-E9. doi: 10.5489/cuaj.8913

9. Tan N, Zhang Y. Associations between dietary fatty acids and kidney stones. *Sci Rep* 2025;15(1):2500. doi: https://doi.org/10.1038/s41598-025-86850-x

10. Alelign T, Petros B. Kidney stone disease: An update on current concepts. *Adv Urol* 2018;2018(1):3068365. doi: 10.1155/2018/3068365

11. Peerapen P, Thongboonkerd V. Kidney stone prevention. *Adv Nutr* 2023;14(3):555-69. doi: 10.1016/j.advnut.2023.03.002

12. Shastri S, Patel J, Sambandam KK, Lederer ED. Kidney stone pathophysiology, evaluation and management: Core curriculum 2023. *Am J Kidney Dis* 2023;82(5):617-34. doi: 10.1053/j.ajkd.2023.03.017

13. Hyams ES, Matlaga BR. Economic impact of urinary stones. *Transl Androl Urol* 2014;3(3):278-83. doi: 10.3978/j.issn.2223-4683.2014.07.02

14. Scales Jr CD, Tasian GE, Schwaderer AL, Goldfarb DS, Star RA, Kirkali Z. Urinary stone disease: Advancing knowledge, patient care, and population health. *Clin J Am Soc Nephrol* 2016;11(7):1305-12. doi: 10.2215/CJN.13251215

15. Zeinelabden KM, Abdelhalim E, Galal M, Abdelbaky T, Nabeeh H. Flexible ureteroscopy, extracorporeal shock wave lithotripsy and mini percutaneous nephrolithotomy for management of lower pole renal hard stones≤ 2 cm: A prospective randomized study. *BMC urology* 2024;24(1):288. doi: 10.1186/s12894-024-01644-z

16. D'Addessi A, Vittori M, Racioppi M, Pinto F, Sacco E, Bassi P. Complications of extracorporeal shock wave lithotripsy for urinary stones: To know and to manage them—a review. *ScientificWorldJournal* 2012;2012(1):619820. doi: 10.1100/2012/619820

17. Skolarikos A, Somani B, Neisius A, Jung H, Petřík A, Tailly T, et al. Metabolic evaluation and recurrence prevention for urinary stone patients: An eau guidelines update. *Eur Urol* 2024;86(4):343-63. doi: 10.1016/j.eururo.2024.05.029

18. Khan SR. Oxidative stress, inflammation and kidney stones. *Urolithiasis* 2025;53(1):137. doi: 10.1007/s00240-025-01808-y

19. Sun Y, Sun H, Zhang Z, Tan F, Qu Y, Lei X, et al. New insight into oxidative stress and inflammatory responses to kidney stones: Potential therapeutic strategies with natural active ingredients. *Biomed Pharmacother* 2024;179:117333. doi: 10.1016/j.biopha.2024.117333

20. Asplin JR, Donahue SE, Lindeman C, Michalenka A, Strutz KL, Bushinsky DA. Thiosulfate reduces calcium phosphate nephrolithiasis. *J Am Soc Nephrol* 2009;20(6):1246-53. doi: 10.1681/ASN.2008070754

21. Baskin SI, Horowitz AM, Nealley EW. The antidotal action of sodium nitrite and sodium thiosulfate against cyanide poisoning. *J Clin Pharmacol* 1992;32(4):368-75. doi: 10.1002/j.1552-4604.1992.tb03849.x

22. Meijer AJ, Diepstraten FA, Ansari M, Bouffet E, Bleyer A, Fresneau B, et al. Use of sodium thiosulfate as an otoprotectant in patients with cancer treated with platinum compounds: A review of the literature. *J Clin Oncol* 2024;42(18):2219-32. doi: 10.1200/JCO.23.02353

23. Cohen GF, Vyas NS. Sodium thiosulfate in the treatment of calciphylaxis. *J Clin Aesthet Dermatol* 2013;6(5):41-4.

24. Bian Z, Zhang Q, Shen L, Feng Y, Chen S. The effect of sodium thiosulfate on coronary artery calcification in hemodialysis patients. *ASAIO Journal* 2022;68(3):402-6. doi: 10.1097/MAT.0000000000001531

25. Guerra G, Shah RC, Ross EA. Rapid resolution of calciphylaxis with intravenous sodium thiosulfate and continuous venovenous haemofiltration using low calcium replacement fluid: Case report. *Nephrol Dial Transplant* 2005;20(6):1260-2. doi: 10.1093/ndt/gfh825

26. Couser SK, Claes DJ, Huesman S, Hooper DK. Treatment of a patient with inoperable tumoral calcinosis associated with end stage kidney disease: A case report. *Hemodial Int* 2025;29(1):116-20. doi: 10.1111/hdi.13179

27. Wu M, Lu J, Wang Y-J, Li Y-Q, Wei Q, Gong Y-X, Tang R-N. Primary hyperoxaluria type i diagnosed after a kidney transplant presenting with subcutaneous calcification: A case report of sodium thiosulfate treatment. *Front Pharmacol* 2025;16:1485024. doi: 10.3389/fphar.2025.1485024

28. Ishikawa M, Motegi Si, Toki S, Endo Y, Yasuda M, Ishikawa O. Calciphylaxis and nephrogenic fibrosing dermopathy with pseudoxanthoma elasticum-like changes: Successful treatment with sodium thiosulfate. *J Dermatol* 2019;46(7):e240-e2. doi: 10.1111/1346-8138.14780

29. Tan SW, Wong J, Kee T, Chai ZT, Ho QY, Chan M, et al. Successful treatment of calciphylaxis in a renal transplant recipient with combination of intralesional sodium thiosulphate, intravenous sodium thiosulphate and fish skin graft. *Australas J Dermatol* 2021;62(2):e358-e9. doi: 10.1111/ajd.13556

30. O'Neill WC, Hardcastle KI. The chemistry of thiosulfate and vascular calcification. *Nephrol Dial Transplant* 2012;27(2):521-6. doi: 10.1093/ndt/gfr375

31. Jiménez-Gallo D, Ossorio-García L, Linares-Barrios M. Calcinosis cutis and calciphylaxis. *Actas Dermosifiliogr* 2015;106(10):785-94. doi: 10.1016/j.ad.2015.09.001

32. Yu Z, Gu L, Pang H, Fang Y, Yan H, Fang W. Sodium thiosulfate: An emerging treatment for calciphylaxis in dialysis patients. *Case Rep Nephrol Dial* 2015;5(1):77-82. doi: 10.1159/000380945

33. Zhang MY, Dugbartey GJ, Juriasingani S, Sener A. Hydrogen sulfide metabolite, sodium thiosulfate: Clinical applications and underlying molecular mechanisms. *Int J Mol Sci* 2021;22(12):6452. doi: 10.3390/ijms22126452

34. Hayden MR, Tyagi N. Sodium thiosulfate: An innovative multi-target repurposed treatment strategy for late-onset alzheimer's disease. *Pharmaceuticals (Basel)* 2024;17(12):1741. doi: 10.3390/ph17121741

35. Nguyen IT, Klooster A, Minnion M, Feelisch M, Verhaar MC, van Goor H, Joles JA. Sodium thiosulfate improves renal function and oxygenation in l-nna–induced hypertension in rats. *Kidney International* 2020;98(2):366-77. doi: 10.1016/j.kint.2020.02.020

36. Grases F, Costa-Bauzá A. Kidney stones and oxidative stress. Types of papillary renal calculi. *Urolithiasis* 2025;53(1):88. doi: 10.1007/s00240-025-01746-9

37. Yatzidis H. Absence or decreased endogenous thiosulfaturia: A cause of recurrent calcium nephrolithiasis. *Int Urol Nephrol* 2004;36(4):587-9. doi: 10.1007/s11255-004-8786-y

38. Agroyannis B, Tzanatos H, Vlahakos D, Mallas E. Does long-term administration of sodium thiosulphate inhibit progression to renal failure in nephrocalcinosis? *Nephrol Dial Transplant* 2001;16(12):2443-4. doi: 10.1093/ndt/16.12.2443

39. LaGrange CA, Lele SM, Pais Jr VM. The effect of sodium thiosulfate administration on nephrocalcinosis in a rat model. *J Endourol* 2009;23(3):529-33. doi: 10.1089/end.2008.0204

40. Braverman B, Ivankovich AD, Shah G. Thiosulfate pharmacokinetics in normal and anuric dogs. *Proc Soc Exp Biol Med* 1982;170(3):273-80. doi: 10.3181/00379727-170-41430

41. Farese S, Stauffer E, Kalicki R, Hildebrandt T, Frey BM, Frey FJ, et al. Sodium thiosulfate pharmacokinetics in hemodialysis patients and healthy volunteers. *Clin J Am Soc Nephrol* 2011;6(6):1447-55. doi: 10.2215/CJN.10241110

42. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* 1984;9(3):239-51. doi: 10.2165/00003088-198409030-00005

43. Mao M, Lee S, Kashani K, Albright R, Qian Q. Severe anion gap acidosis associated with intravenous sodium thiosulfate administration. *J Med Toxicol* 2013;9(3):274-7. doi: 10.1007/s13181-013-0305-z

44. Nigwekar SU, Pai AB, Mueller B, Dean MC, Costello G, Sherman CR. Impact of hemodialysis on the concentrations of sodium and potassium during infusion of sodium thiosulfate using an in vitro hemodialysis model. *PLoS One* 2019;14(11):e0224767. doi: 10.1371/journal.pone.0224767

45. Kenny J, Ostuni M, Musso CG. Is sodium thiosulfate an effective treatment for recurrent calcium nephrolithiasis? Pro and con arguments. *Int Urol Nephrol* 2018;50(10):1921-2. doi: 10.1007/s11255-018-1910-1

46. Yatzidis H. Successful sodium thiosulphate treatment for recurrent calcium urolithiasis. *Clin Nephrol* 1985;23(2):63-7.

47. Chen C-J, Cheng M-C, Hsu C-N, Tain Y-L. Sulfur-containing amino acids, hydrogen sulfide, and sulfur compounds on kidney health and disease. *Metabolites* 2023;13(6):688. doi: 10.3390/metabo13060688

48. Curry SC, Carlton MW, Raschke RA. Prevention of fetal and maternal cyanide toxicity from nitroprusside with coinfusion of sodium thiosulfate in gravid ewes. *Anesth Analg* 1997;84(5):1121-6. doi: 10.1097/00000539-199705000-00031

49. Geller RJ. Amyl nitrite, sodium nitrite, and sodium thiosulfate: Wiley-Blackwell; 2015. 296-303 p.

50. Graeme KA, Curry SC, Bikin DS, LoVecchio FA, Brandon TA. The lack of transplacental movement of the cyanide antidote thiosulfate in gravid ewes. *Anesth Analg* 1999;89(6):1448-52. doi: 10.1097/00000539-199912000-00023

51. Baldev N, Sriram R, Prabu P, Gino AK. Effect of mitochondrial potassium channel on the renal protection mediated by sodium thiosulfate against ethylene glycol induced nephrolithiasis in rat model. *Int Braz J Urol* 2015;41(6):1116-25. doi: 10.1590/S1677-5538.IBJU.2014.0585

52. Bijarnia RK, Bachtler M, Chandak PG, van Goor H, Pasch A. Sodium thiosulfate ameliorates oxidative stress and preserves renal function in hyperoxaluric rats. *PLoS One* 2015;10(4):e0124881. doi: 10.1371/journal.pone.0124881

53. Vaitheeswari S, Sriram R, Brindha P, Kurian GA. Studying inhibition of calcium oxalate stone formation: An in vitro approach for screening hydrogen sulfide and its metabolites. *Int Braz J Urol* 2015;41(3):503-10. doi: 10.1590/S1677-5538.IBJU.2014.0193

54. Landry GM, Hirata T, Anderson JB, Cabrero P, Gallo CJ, Dow JA, Romero MF. Sulfate and thiosulfate inhibit oxalate transport via a dprestin (slc26a6)-dependent mechanism in an insect model of calcium oxalate nephrolithiasis. *Am J Physiol Renal Physiol* 2016;310(2):F152-F9. doi: 10.1152/ajprenal.00406.2015

55. El-Ashmawy NE, El-Bahrawy HA, Ashmawy HH, Khedr EG. Amelioration of lithiatic injury to renal tissue by candesartan and sodium thiosulfate in a rat model of nephrolithiasis. *PLoS One* 2021;16(5):e0251408. doi: 10.1371/journal.pone.0251408

56. Yatzidis H. Gestational urinary hyperthiosulfaturia protects hypercalciuric normal pregnant women from nephrolithiasis. *Int Urol Nephrol* 2004;36(3):445-9. doi: 10.1007/s11255-004-8784-0

57. Okonkwo OW, Batwara R, Granja I, Asplin JR, Goldfarb DS. A pilot study of the effect of sodium thiosulfate on urinary lithogenicity and associated metabolic acid load in non-stone formers and stone formers with hypercalciuria. *PLoS One* 2013;8(4):e60380. doi: 10.1371/journal.pone.0060380

58. Rodgers A, Gauvin D, Edeh S, Allie-Hamdulay S, Jackson G, Lieske JC. Sulfate but not thiosulfate reduces calculated and measured urinary ionized calcium and supersaturation: Implications for the treatment of calcium renal stones. *PLoS One* 2014;9(7):e103602. doi: 10.1371/journal.pone.0103602