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Elaboration Of Secondary Prevention Measures For Individuals With Cystine Metabolic Disorder To Reduce The Risk Of Urolithiasis : A Critical Review

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ABSTRACT
Urolithiasis in Asia affects about 1% - 19.1% of the population. Urolithiasis disease in young patients has a significant morbidity rate. Basic metabolic disorder such as cystinuria are often associated with urolithiasis. Cystinuria, a congenital cystine metabolism disorder with an incidence ratio of 1:7,000. Cystinuria is a common condition among urolithiasis patients. The paper aims to summarize recent efforts in secondary prevention to reduce the risk of urolithiasis in cystinuria patients through early detection and prompt treatment. This paper is a narrative review using the literature study method regarding the latest secondary prevention efforts. The library used 24 pieces of literature from research journals and international case reports. Early detection efforts include tracing medical history and urinalysis, followed by an initial diagnosis using PCR, sodium cyanide-nitroprusside test, and attenuated total reflection - fourier transform infrared spectroscopy (ATR-FTIR) can confirm the diagnosis of cystinuria. Thiopronine treatment is currently the main choice, accompanied by a special diet and plenty of water consumption. Another pharmacological therapy (tolvaptan) is still under development and showing promising results. Secondary prevention efforts for cystinuria patients are needed to prevent an adverse urolithiasis event and help reducing morbidity rate.

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INTRODUCTION

Urolithiasis in Asia affects about 1% - 19.1% of the population, it is influenced by socioeconomic status and geographic location, so that the incidence and prevalence in various countries vary (Liu et al., 2018). Numerous studies indicate that interactions between genetic factors and the environment are the general cause of urolithiasis (Yasui et al., 2017). In contrast to adolescents and adults, children are less likely than adults to have urolithiasis. Several predisposing factors that can affect, namely, genetic inheritance, nutrition, metabolic and anatomical disorders, urinary tract infections, and environmental factors can trigger urolithiasis (Issler et al., 2017).

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Urolithiasis disease in young patients is increasing considerably and has a significant morbidity rate. Epidemiological studies of urolithiasis are very important to be investigated so that they can provide diagnosis, management, and develop appropriate prevention strategies. Data regarding urolithiasis in patients of young age or adolescence is more difficult to find than data on adult patients. In recent studies, it was found that 44% of the causes of urolithiasis were metabolic disorders, 30% were due to infective disease and the remainder was categorized as an idiopathic event (Issler et al., 2017).

Basic metabolic disorders such as hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and cystinuria are often associated with urolithiasis (Marta et al., 2019). Cystinuria is an autosomal recessive disorder caused by SLC3A1 and SLC7A95 gene mutations (Krishnamurthy et al., 2018). Cystine metabolic disease is a frequent hereditary aminoaciduria with a 1:7000 live births incidence ratio, with a mean onset of urolithiasis at the age of 12-24 years. Some patients with cystinuria have reported an onset of urolithiasis beyond the age of 40 years (Sayer & Hill, 2017).

Studies have shown that common cystinuria is diagnosed by measuring the concentration of cystine in the urine. Early diagnosis and preventive treatment are important, repeat measurement methods of cystine levels are needed. High-quality colorimetric screening tests are available, but their specificity is low. Ion exchange chromatography (IEC) is the gold standard for diagnosing cystinuria, but IEC takes longer, expensive, and not every medical facility has it. Based on these studies, it can be concluded that new diagnostic tools or methods are needed to diagnose cystinuria with or without urolithiasis and can be more easily applied in the field (Oliver et al., 2016).

Management given to cystinuria patients is with d-Penicillamine, but the administration of this drug has quite dangerous side effects such as fever, rash, hematuria, nephrotic syndrome, and agranulocytosis. Recent management efforts as a safer treatment option are needed to control cystinuria, which in this condition requires a lifelong treatment that aims to reduce the chance of urolithiasis (Pierna et al., 2020).

An increase in urine pH can increase the solubility of cystine in urine (Shee & Pais, 2020). Insoluble cystine can cause recurrent urolithiasis and result in obstructive uropathy, hypertension, infection, and kidney failure. More than 50% of cystinuria patients have cystine urolithiasis and 75% of patients have recurrent bilateral urolithiasis. Recurrent urinary stone formation requires continuous urological intervention (Obaid et al., 2017). Patients with cystinuria had the highest percentage of urinary tract stones (> 10 mm), whereas patients with urinary tract stones (<5 mm) tended to have normal metabolic findings.

The median size of urinary tract stones varied greatly among the patients. The recurrence rate of urolithiasis in cystinuria patients at follow-up was 30.4%, which was substantially higher than in hypercalciuria patients (16.3%) or those with normal metabolic values (17.2%) (Zu'bi et al., 2017). Urolithiasis is a disease that has a high recurrence rate, especially if it is found in patients with hereditary metabolic disorders such as cystinuria (Aung et al., 2020). Cystinuria patients experience abnormal absorption of cystine, so if there is a change in pH in the urine, it will result in crystallization, which can cause repeated

obstruction. Adequate secondary prevention efforts are needed in cystinuria patients to prevent urolithiasis.

This paper aims to briefly present the latest secondary prevention efforts that have resolved several problems in the management of cystinuria patients, consisting of early detection, more applicable early diagnosis efforts, and various modern management efforts that are available as well as in development, so it is hoped that the results will be obtained safer and more effectively in preventing new cases and recurrence of urolithiasis in patients with cystinuria.

METHODS

This paper is a narrative review study using a literature study method regarding secondary prevention efforts including early detection, early diagnosis, and the latest management of cystinuria patients to prevent urolithiasis. The literature used in this paper is research journal articles and international case reports. Published articles can downloaded in full text and has open access, articles with qualitative, quantitative, mixed method designs and literature reviews regarding secondary prevention efforts for patients for cystine metabolic disorder. The presentation of the writing begins with the following stages,

1. Determining the main purpose of writing that can sharpen and enrich knowledge in the field of medicine, especially for cystinuria patients.
2. Identifying and searching the keywords "cystinuria", "urolithiasis" and "prevention" on the PubMed portal, google scholar, and ScienceDirect from 2013 to 2023 and obtained a total of 231 libraries. Data extraction using Publish or Perish 8 software, data selection based on inclusion and exclusion criteria. The inclusion criteria were articles with three keywords, conducting research using the RCT method, case report, guideline, and systematic review. Exclusion criteria were an article that did not discuss secondary prevention (early detection, early diagnosis, and management) in cystinuria patients with or without urolithiasis, articles using languages other than English, and not published. We review the article using Covidence.
3. After conducting a selection by removing duplicates and irrelevant articles, the results obtained were 25 references.
4. Studying and understanding the literature used to facilitate delivery and writing arrangements. Around 24 articles were used because of their access to full-text and comprehensive explanation.
5. Begin to compile papers using several supporting facilities in writing and conclude the discussion without losing the essence.
6. Final refinement involves proofreading to ensure that the writing results are good and easy to understand.

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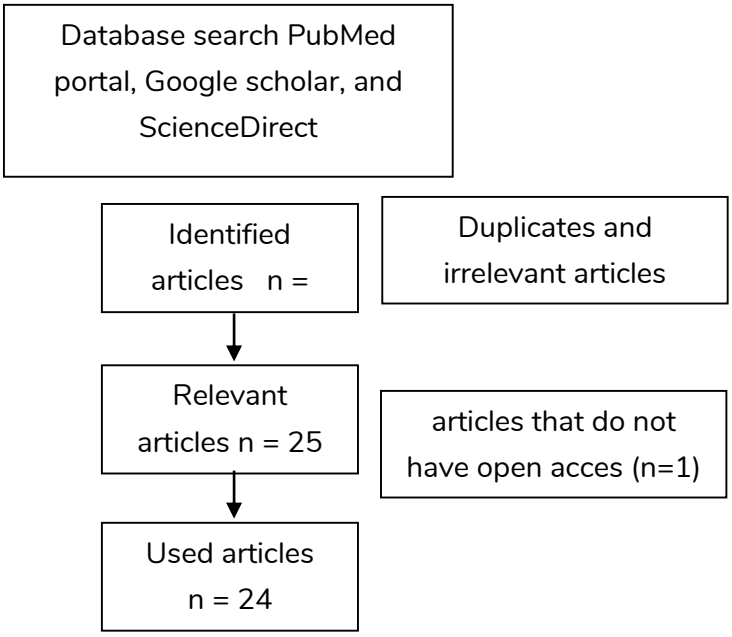

Figure 1. Paper selection algorithm

RESULTS AND DISCUSSION

Early detection of cystinuria should be considered in individuals with recurrent urolithiasis

Bilateral urolithiasis (affecting both kidneys); individuals who develop urolithiasis at an early age (before age 30); and individuals who have a family history of cystinuria or recurrent urolithiasis. Another early detection tool that can be used in high-risk individuals is urinalysis, especially by microscopic examination. Some early diagnosis efforts that can be done after early detection aim to prevent urolithiasis in the future (Pizza et al., 2014).

One of the early diagnosis efforts after early detection that can be done is to carry out a thorough genetic examination of children with a family history of cystinuria or recurrent urolithiasis, so that parents of children with cystinuria can have appropriate prompt prenatal and antenatal counseling (Krishnamurthy et al., 2018). Type A cystinuria has been linked to mutations in the SLC3A1 gene, and type B cystinuria has been linked to mutations in the SLC7A9 gene in half of the cases, according to previous research (Reis et al., 2019).

PCR analysis studies of the SLC7A9 gene and SLC3A1 gene employ DNA samples (peripheral whole blood cells) of five people from one family who have cystinuria to demonstrate early diagnosis after early identification through genetic testing. Six distinct mutations in the SLC7A9 gene were discovered in the study's findings. Six heterozygous mutations were found in the mother's mild case of cystinuria. Cystinuria was not evident in the father or any of their daughters. All six homozygous mutations caused severe cystinuria in another son and daughter. Additionally, the two afflicted siblings displayed homozygous mutations in the SLC3A114 gene (Reis et al., 2019).

Mutations in the SLC3A1 and SEC7A9 genes are believed to be responsible for the clinical symptoms of cystinuria, as per the studies mentioned above. The mutation occurs homozygously and causes severe urolithiasis. To take appropriate and timely preventive

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measures in patients with cystinuria or family history of recurrent urinary stones and prevent urinary stones in these patients, early diagnosis with post-screening genetic testing (PCR) is recommended (Reis et al., 2019).

An easier initial diagnosis after early detection is to perform the sodium cyanide – nitroprusside test.

This test can be used as a diagnostic test for early detection of cystinuria, especially in individuals with a family history of cystinuria and recurrent urolithiasis, to quickly assess urine concentrations of cystine. The sodium cyanide nitroprusside test is used for qualitative diagnosis. The test demonstrates that cysteine is released with a sodium hydroxide (SH) group when cyanide breaks its disulfide bonds, and then nitroprusside bonds the SH group in an alkaline medium. A positive result is a bright red color change that occurs within 2 to 10 minutes. Cystine levels exceeding 75 mg/g can be detected by this test (Krishnamurthy et al., 2018).

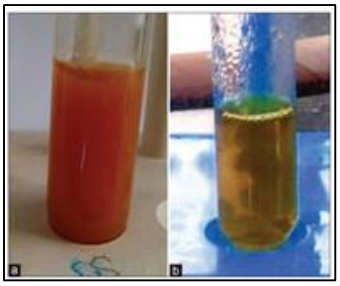

Figure 2. sodium cyanide – nitroprusside test (a) positive (b) control
Source: Krishnamurthy et al., 2018

This test can detect and diagnose cystinuria quickly by using concentrated urine samples, unless there is a history of ampicillin, other sulfa drugs, or Fanconi syndrome. All mentioned earlier can lead to false positive results. Based on several research articles that have been reviewed, it can be concluded that early detection efforts accompanied by an early diagnosis have their place in the prevention of urolithiasis in cystinuria patients. Individuals who have a high risk of cystinuria can use early detection efforts along with early diagnosis to avoid risk factors for urolithiasis (Krishnamurthy et al., 2018).

Infrared Vibrational Spectroscopy: a new diagnostic and monitoring tool that can be used on cystinuria patients.

The gold standard for the diagnosis of cystinuria using Ion-Exchange Chromatography (IEC) is slow, tedious, and expensive. Much faster monitoring of urinary cystine concentrations would allow for the diagnosis and clinical management of cystinuria (Oliver et al., 2016).

A new method for detecting insoluble cystine in cystinuric patients Attenuated Total Reflection - Fourier Transform Infrared Spectroscopy (ATR-FTIR), which is both cost-effective and fast. The insoluble cystine content can be estimated using FTIR, which is consistent with data obtained with IEC. Although the IEC method provides quantitative information on total cystine along with other amino acids, it must be emphasized that the cost required for FTIR is much lower than IEC. When factoring in processing time and labor costs,

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specifically. For initial diagnosis and clinical management, FTIR may be more effective than other urine tests to detect cystine in urine. FTIR can also be used to screen cystinuric patients, assess disease severity, and respond to treatment (Oliver et al., 2016).

Guidelines for diagnosing urolithiasis patients to direct the diagnosis towards cystinuria

A summary of the guidelines for diagnosis based on the AUA (American Urological Association) (Pearle et al., 2014).

1. In cases of urolithiasis, doctors should conduct an extensive physical examination that includes a nutritional history and serum chemical analysis, as well as urinalysis. A comprehensive medical history should be provided to the patient, which includes their medical conditions, diet, daily fluid intake, and past use of over-the-counter supplements and medications.The inclusion of electrolytes, calcium, creatinine, and uric acid in serum chemistry is necessary for diagnosis. Urinalysis includes a dip test to assess urine pH and microscopic examination to identify infection and pathognomonic crystals. Patients who have persistent urinary tract infections may undergo a urinary culture procedure.
2. Serum parathyroid hormone testing is required as a screening tool for primary hyperparathyroidism.
3. If urinary tract stones are found, a stone test should be performed. Uric acid, cystine, or struvite stones can impact the structure of metabolic or genetic disorders. Therefore, knowing the composition of urinary stones is very useful for taking preventive measures, especially in patients with cystinuria.
4. Undertake any available imaging studies, because if multiple or bilateral nephrolithiasis is found at the initial presentation, then the patient has a greater risk of relapse.
5. Metabolic testing is required in patients with first-time or recurrent urolithiasis and in high-risk patients. Individuals with persistent urolithiasis can be informed and monitored for treatment using only one 24-hour urine sample.
6. One or two 24-hour urine samples are required. The initial evaluation and monitoring of urolithiasis patients may involve the use of other urinary tract markers. The evaluation of urine cystine levels is recommended for individuals with urolithiasis, cystines in families, or suspected cases.

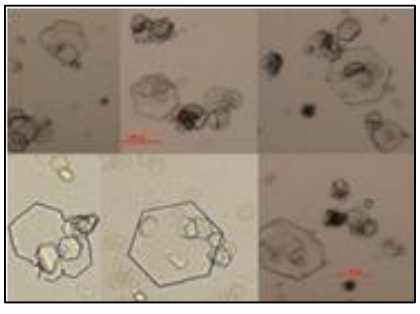

Figure 3. urine microscopic examination "Flat Hexagonal Crystal"
Source: Pierna et al., 2020

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Non-pharmacological management of cystinuria patients to prevent urolithiasis

Is done by adjusting the diet. To prevent the formation of cystine stones, it is important to drink plenty of fluids. Patients with cystinuria need to reduce their urinary cystine concentration to less than 250 mg, the target urine volume should be higher than in patients with urolithiasis for other reasons. To achieve this goal, the patient needs at least 4 liters of drinking water per day. Intake of foods high in sodium should be limited, as low sodium intake has been shown to reduce cystine excretion. The permissible sodium intake for cystinuria patients is less than 100 mEq (2,300 mg) per day. Because all animal foods are rich in cystine and methionine, which are converted to cystine, it is highly recommended to limit animal protein intake to reduce cystine substrates (Malhi et al., 2023).

Pharmacological management of choice for cystinuria patients as prevention of urolithiasis

The solubility of cystine in urine, which is affected by pH, has been known for more than half a century. Alkaline treatment has been widely used in the management of cystinuria. Alkali therapy alone has limited effectiveness, as large doses are required to achieve a high cystine pK (8.5). Also calcium phosphate stones may develop in highly alkaline urine, so a urine pH of 6.5-7.0 is recommended to prevent cystine stone formation in severe cystinuria patients (Wang et al., 2022).

Cystine-binding thiol drugs can be a viable option for patients who do not respond well to conventional therapies. The Thiol derivative can break one cystine molecule into two cysteines and make a disulfide compound from the drug and the highly soluble cysteine molecule. Commonly used drugs are thiopronine and d-Penicillamine. Previous studies have shown urolithiasis formation and recurrence are reduced when d-Penicillamine is administered, but the use of this drug is not recommended for long-term use because it has several adverse effects (allergy, rash, fever, nausea/vomiting, arthralgia, and leukopenia). The most common side effect is drug hypersensitivity, dystonia, joint swelling, and pyrexia (Wang et al., 2022).

Thiopronine is currently the agent most often given to cystinuria patients. Previous studies have compared the effects of conservative treatment on hydration and alkalization with treatment with d-Penicillamine or thiopronine. The results showed a reduction in the incidence of urolithiasis from 1.6 to 0.452 per year. The study demonstrated thiopronine induced urolithiasis remission in 63% of patients who had previously received d-Penicillamine treatment and in 71% of patients who were not given specific treatment. Stone formation rates were reduced by 81% and 94%, due to thiopronine administration (Wang et al., 2022).

Treatment with d-Penicillamine or thiopronine decreased the incidence of urolithiasis by 32-65% when compared with conservative management with hydration and alkaline treatment. Both drugs are effective in reducing the incidence of urolithiasis. Thiopronine is more frequently used because it has higher efficacy and fewer side effects compared to D-penicillamine (Wang et al., 2022).

Table 1. Clinical consideration D-Penicilamine versus Thiopronine

Drug	Side Effect (% population)	Discontinue (%)	Research
D-Penicilamine	29,5 %	85 %	Prot-Bertoye et al., 2015
Thiopronine	24,6 %	68 %	Prot-Bertoye et al., 2019

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Development of new pharmacological therapies for cystinuria patients.

Pharmacological therapy for cystinuria patients is still developing. In the last study, an evaluation or trial of the effects of tolvaptan (vasopressin receptor 2 antagonist) was carried out in experimental animals with cystinuria (Bai et al., 2020). Tolvaptan and placebo were administered daily by gavage at 0.4 mg per mouse for 30 days. Urine amino acids and cystine stones were then analyzed to assess the drug's effectiveness in preventing cystine stone formation. Tolvaptan treatment resulted in a significant increase in both water intake and urine output in mice compared to the control group. The tolvaptan group had urinary cystine levels that were lower than the baseline before the study. Test animals treated with tolvaptan had significantly slower stone formation in the urinary tract and fewer stones accumulated compared to the control group.

The increase in stone volume in the tolvaptan group was smaller than the control group (8.00 ± 4.93 mm3 vs 27.90 ± 4.48 mm3). Compared to the tolvaptan group, serum creatinine was found to be higher in the control group (11.75 ± 1.634 µmol / L) and the tolvaptan group (7.625 ± 1.401 µmol / L) (Bai et al., 2020).

Conclusions can be drawn based on the research conducted that tolvaptan can significantly inhibit the incidence of urolithiasis in experimental animals. Tolvaptan was found to have the ability to decrease the permeability of aquaporin channels in the outer membrane of collecting duct cells, leading to decreased water uptake from the tubular lumen to the interstitium in a clinical trial (Zhang et al., 2016). An increase in urine output was discovered as a consequence of this with changes in electrolyte excretion are minimal. The most common side effects are thirst and dry mouth, which causes patients to drink (Nelson et al., 2020).

Recent research shows that administering tolvaptan for eight days can increase urine volume, so that cystine concentrations will decrease (Sadiq & Cil, 2022). The effectiveness of vasopressin receptor 2 (V2) antagonists as a long-term pharmacotherapy option for cystinuric patients is still uncertain, and further research is required. Other drugs in the same class may also be considered for the treatment of cystinuria patients (Amro & Perrone, 2015).

Table 2. Recent investigation of tolvaptan clinical effect

Subject	Baseline cystine capacity	Cystine capacity post-treatment (tolvaptan)	Cystine supersaturation post-treatment	Urinary volume pre-treatment (L)	Urinary volume post-treatment (L)
Male, 24y	-312	97	Decrease	1,96	11,74
Female, 17y	-82	111	Decrease	3,0	6,5
Female, 24y	-353	75	Decrease	0,91	2,8
Male, 13y	-628	-3	Decrease	2,1	9,9

*) Nelson et al., 2020

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In this research, parameters measured included urine volume, cystine capacity, and cystine supersaturation test. Urinary volume post-treatment increased; some patients even produced extraordinary volumes of urine during treatment. Cystine capacity also increased from baseline. Cystine capacity aims to measure the ability of urine to dissolve a solid cystine sample, normal target therapy is >0 mg/ml. Cystine supersaturation in this study also decreased dramatically with tolvaptan. All four subjects have cystine concentration below 250 mg/dl and increased urinary volume. In this study, tolvaptan had a positive impact (Nelson et al., 2020).

CONCLUSION

Secondary prevention efforts, such as early detection and diagnosis, along with appropriate management, are crucial in preventing adverse urolithiasis events in cystinuria patients. The use of diagnostic methods like attenuated total reflection-fourier transform infrared spectroscopy (ATR-FTIR) and adherence to AUA guidelines for diagnosis are important, and thiopronine is currently the main choice for management, along with diet management and high water (4L) consumption, while other pharmacological therapies (tolvaptan) are being developed with promising results because it is thought to have fewer side effects than existing pharmacological therapies. This study is limited because it does not conduct direct research in the field, especially in Indonesia. Recommendations for conducting observational research to discuss the current diagnosis and treatment of cystinuria are highly recommended, because this disease often causes detrimental complications.

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