Effectivity and safety profile of oxalate decarboxylase in hyperoxaluria patient: A meta-analysis and systematic review

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ABSTRACT

Introduction: The high incidence of urinary stones leads to many related medical issues and substantial financial burdens. In addition to treatment interventions, executing preventive measures is crucial in reducing the likelihood of kidney stone recurrence. Oxalate decarboxylase is now being developed as a preventive measure for treating hyperoxaluria, a risk factor for stone formation. This study aims to evaluate the efficacy and safety of oxalate decarboxylase in treating hyperoxaluria.

Methods: A comprehensive review of the existing literature was performed by conducting a systematic search across various databases, including Cochrane Library, Google Scholar, PubMed, and Embase. The mean difference (MD) of 24-hour urinary oxalate excretion from baseline to treatment was assessed in each study. Cochrane Collaboration's Review Manager 5.4.1 software was used for statistical analysis, and RoB 2 tools were used for bias risk assessment.

Result: Five studies that satisfied the specified criteria were included in the analysis, of which were analyzed for meta-analysis data, while the other for systematic review. Meta-analysis showed that oxalate decarboxylase had a statistically significant efficacy compared to placebo in reducing oxaluria with MD of 9.72 mg/day (95% CI 7.43 to 12.10). Regarding safety, there is not much difference in the number of complications between oxalate decarboxylase and placebo, with only one study reporting a serious adverse event (SAE) of sacral radiculopathy in the intervention group.

Conclusion: Oxalate decarboxylase is a potential and promising alternative treatment for reducing urinary oxalate levels in hyperoxaluria patients. Therefore, it can be regarded as a viable choice in pharmacological treatment for preventing the occurrence of oxalate stones in patients in the future.

Keywords: oxalate decarboxylase, oxaluria, hyperoxaluria, meta-analysis, systematic literature review.


INTRODUCTION

Kidney stones, or nephrolithiasis, are aggregates in the renal system due to the buildup of minerals and waste substances. The incidence of nephrolithiasis in the United States increased from 3.8% in the late 1970s to 8.8% in the late 2000s. Kidney stones are roughly 11% in males and 9% in females. Calcium oxalate stones are the most common among the several varieties.

Calcium oxalate crystals form when calcium joins with oxalate in the urine. Oxalate is an inherent organic compound in a diverse range of dietary sources. Hyperoxaluria is a condition marked by higher levels of oxalate being excreted in the urine. When the oxalate concentration exceeds 40-45 mg per 24 hours, it is classified as clinical hyperoxaluria. Hyperoxaluria can lead to severe outcomes, including an increased susceptibility to the formation of calcium oxalate crystals and the development of end-stage renal disease (ES RD). When urinary oxalate excretion increased from 20 to 40 mg per day, the relative risk of calcium oxalate stone disease increased 2.5–3.5 fold.

Over time, the crystals, as mentioned above, have the potential to undergo growth, resulting in the formation of larger stones that can impede the normal passage of urine, hence inducing discomfort and various associated issues. Due to the distressing characteristics of these stones and the possibility of consequences, innovative treatments have been pursued to treat or prevent the disease both operatively and by non-operative approach.

In addition to therapeutic interventions, implementing preventative measures is essential in mitigating the recurrence of kidney stones, which can contribute to the development of comorbidities. The latest guidelines for preventing and managing nephrolithiasis suggest some pharmaceutical interventions like calcium and magnesium and diet prevention.

However, due to the restrictions on the types of foods that are available, general dietary prevention is not effective for all people. While using calcium is beneficial, there is a consequence of excess calcium...
excretion that can form other forms of stones. It is, therefore, necessary to adopt alternate strategies available to all facets of society. One of the pharmaceutical compounds now undergoing development is oxalate decarboxylase. The enzyme oxalate decarboxylase facilitates oxalate’s decarboxylation process, leading to oxalate’s conversion into formate and carbon dioxide. As mentioned above, the method can decrease the oxalate concentration in urine, hence mitigating the likelihood of stone formation. Oxalate decarboxylase can degrade oxalate, the principal constituent of the prevailing renal calculi form. This intervention can potentially hinder the formation of urinary stones, particularly those composed of calcium oxalate.

To date, no systematic review studies and meta-analysis discuss and analyze the function of oxalate decarboxylase in preventing and treating calcium oxalate stones. Therefore, we carried out this study to evaluate the efficacy of oxalate decarboxylase in treating hyperoxaluria. This study aimed to conduct a meta-analysis and systematic review to assess and explain the effectiveness of oxalate decarboxylase compared to a placebo.

METHODS

A comprehensive review of the existing literature was performed by systematically searching various databases, including Cochrane Library, Google Scholar, Science Direct, and PubMed. The search encompassed relevant literature up until October 2023. Relevant research is identified using specific keywords tailored to each search engine’s specifications. The keyword employed in this particular search is ((Oxalate Decarboxylase) OR (OxDC) OR (ALLN-177) OR (Reloxilase)) AND ((Hyperoxaluria) OR (Oxalate stone)). The meta-analysis was conducted and described in adherence to the guidelines delineated by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Study Selection and Data Extraction

The study included in this review was (1) Randomized clinical trials (RCTs), cohort studies, case-control studies, and cross-sectional studies aimed to compare the effectiveness and safety of oxalate decarboxylase with either placebo or other interventions. (2) The study population consisted of individuals with hyperoxaluria, regardless of whether it was induced or due to disease progression, with or without comorbidities such as urinary stone former, etc. (3) Studies that provided sufficient data on outcomes, specifically the mean change in 24-hour urinary oxalate excretion from baseline to treatment, along with information on safety and adverse effects. There were no restrictions placed on the country of origin, age, race, or sex of the patients included in the articles.

The criteria for exclusion were as follows: The exclusion criteria for this study included: (i) Case reports or case series studies; (ii) Research involving nonhuman subjects; and (iii) Studies that were inaccessible in their entirety or had unusable data, despite efforts to communicate with the authors via email.

Standard deviations of the mean changes from baseline are common missing outcome data. The same problems have been mentioned in many studies. Based on Cochrane data, to determine the missing standard deviations, a formula was established as follows:

\[ SD \text{ Change} = \sqrt{(SD \text{ baseline})^2 + (SD \text{ final})^2 - (2 \times r \times SD \text{ baseline} \times SD \text{ final})} \]

In this formula, SD change represents the standard deviation of the mean that changes from the baseline value. The term “SD baseline” refers to the standard deviation of the pre-test, whereas “SD final” refers to the standard deviation of the post-test. The symbol “r” represents the correlation value of the pre- and final measurements, computed using the prior study’s findings. Nevertheless, the correlation value is sometimes omitted in research studies. In numerous instances, the provided data is inadequate to compute the correlation value, as exemplified by the study analyzed in this review. The present study followed a systematic review approach to obtain missing outcome data. Initially, the missing standard deviation changes from the baseline were adjusted using RevMan after including additional information such as confidence intervals, p-values, and standard errors. However, the first technique was deemed impractical due to the little information provided in the study. In the subsequent effort, we will contact the writers who acted as corresponding authors for the publications incorporated in the study to acquire their respective datasets. Regrettably, it is not possible to contact any of the authors. Furthermore, when the study’s authors did not supply their data for inclusion in this systematic review, the standard deviation (SD) values at baseline and final measurements were utilized to calculate the SD change value. The formula’s correlation coefficient (r) was assigned a value of 0.7, following the methodology used in previous systematic reviews to provide a conservative estimate. If there was no available outcome data, the study was not included in the meta-analysis and is mentioned separately in the text.

Outcome and Quality Assessment

This study evaluates the mean difference in 24-hour urinary oxalate excretion between each journal’s baseline and post-treatment phases. The RoB 2 tools were utilized to assess and analyze the possible bias in randomized controlled trials, and ROBINS-I Tools were used to analyze bias in non-randomized studies of the effects of interventions (NRSI). The outcome was categorized as “Low”, “High”, or “uncertain risk” by each evaluator of the research. Any conflicting evaluations consulted for the third opinion.

The data analysis used in this study is Review Manager Software (RevMan v.5.4.1, Cochrane Collaboration, Oxford, UK). The assessment of heterogeneity was conducted utilizing Cochrane’s Q test and I2 statistics. Significant heterogeneity was indicated by I2 values exceeding 50% and a p-value below 0.10. The efficacy parameters were estimated by calculating mean differences with a 95% Confidence Interval (CI). The findings of this investigation will be presented using forest plots.

RESULT

Characteristics and Quality of the Studies

A comprehensive search across all available databases yielded 708 publications and
papers. After eliminating duplicate journal entries, 669 data were obtained for the first screening. Based on the screening outcomes of titles and abstracts, 14 papers were identified as pertinent to the established study requirements. Upon conducting a more thorough examination, 9 reports have been excluded from the analysis. This decision was mainly based on the fact that most of these reports did not possess the necessary data as indicated by the predetermined inclusion criteria.

In summary, this analysis incorporated a total of 5 studies. The comprehensive process of screening the studies is illustrated in Figure 1. All included studies were plotted in a funnel plot, which exhibited a symmetrical distribution. Table 1 presents a comprehensive overview of the summarized data derived from the three research. All the studies included in the analysis were randomized controlled trials (RCTs), with two employing a cross-over design. The quality rating of each journal is depicted in Figure 2.

Of the 5 studies assessed, 3 were RCT studies, and the other 2 were open pilot studies. Two of the included RCT studies from Langman et al. and Quintero et al. study healthy people as the population and induce hyperoxaluria from the diet, while the other study by Lieske et al.—Lingeman et al. and Pfau et al. studies adults with a history of hyperoxaluria without diet intervention. In the study done by Lieske et al., the patient was also attributed to a previously diagnosed enteric disorder associated with fat malabsorption like bariatric surgery, Crohn's disease, etc. At the same time, Pfau et al. study a population with comorbidity of chronic kidney disease.

Four included studies from Langman et al., Lieske et al., Lingeman et al., and Pfau et al. give oxalate decarboxylase as capsules with a dose of 7500 U/meal. In contrast, the Quintero et al. study gave oxalate decarboxylase as a sachet with a dose of 1000 U/meal that was taken during meals.

**Efficacy & Safety Profile**

A total of 143 patients in the intervention group and 123 patients in the placebo group were included in this study. A low heterogeneity was found between studies, so we used a fixed-effects model for analysis. The mean difference (MD) from the fixed model was 9.72 (95% CI 7.34 to 12.10; I² = 0%), indicating oxalate decarboxylase had a statistically significant effect compared to placebo in reducing oxaluria. The same results were shown in a study conducted by Lingeman et al.. The results demonstrated a statistically significant decrease in hyperoxaluria, with a mean reduction of 14 mg/24 h (95% CI −23.71, −4.13). Lastly, a study conducted by Pfau et al. also demonstrated a substantial decrease of up to 42% in urinary oxalate levels following treatment.

Results from a systematic review of the pilot study from 2 studies included also show a statistically significant result. Figure 5 displays the funnel plots of the meta-analyses. Minimal publication bias was detected.

From the result of the safety profile from the 5 included studies, only one study reports a serious adverse event (SAE) where the patient was diagnosed with sacral radiculopathy with a severe intensity in the oxalate decarboxylase group. Another treatment-emergent
Table 1. Summary of the included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal type</th>
<th>Intervention and Control</th>
<th>Sample Size</th>
<th>Inclusion criteria</th>
<th>Method of intervention</th>
<th>Calculated mean difference</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langman, 2016</td>
<td>RCT, cross-study</td>
<td>ALLN-177 vs Placebo</td>
<td>33</td>
<td>Adult with a BMI of 18 to 29.9 kg/m² with urine calcium excretion &lt; 300 mg and normal 24-hour urinary citrate excretion.</td>
<td>1. Participants do a 24-day screening period, followed by two 10-day periods separated by a 1-week outpatient washout phase. Participants stayed in the hospital and followed the HOLC diet. (3-day induction period and a 7-day treatment period). 2. Follow up 7 days after the second treatment cycle</td>
<td>ALLN-177: 13.6 ± 17.32  Placebo: 0.3 ± 20.18</td>
<td>1) 1 participant experienced TEAE (diarrhea) in the control group. The highest TEAEs occur in the gastrointestinal system (6 cases, evenly split between 2 groups). The conclusion of the research addressed all TEAEs. 2) No significant adverse events occurred during the research.</td>
</tr>
<tr>
<td>Quintero, 2020</td>
<td>RCT, Crossover study</td>
<td>Reloxilase vs Placebo</td>
<td>115</td>
<td>1. Adults (18-55 years old), with BMI (18.5-29.9 kg/m²), eGFR &gt; 60 ml/min /1.73 m², urine oxalate levels &lt; 40.5 mg/24 h, and urinary uric acid levels &lt; 750 mg/24 h. 2. Male and non-pregnant female participants who had not smoked for 3 months at the time of the study.</td>
<td>1. All participants were assigned to a 4-day controlled high oxalate diet after the screening. 2. Participants were given either OxDC or a placebo for 2 days. The 4-day controlled diet meal plan recommenced on day 3, coinciding with the beginning of the 2-day washout phase. 3. Participants were administered approximately 1000 U (micromoles /min /mg) of OxDC or a placebo with meals three times daily in four treatment days.</td>
<td>Reloxilase: 16.1 ± 21.3  Placebo: 6.5 ± 30.34</td>
<td>1) No SAEs were reported during the research. 2) In the OxDC group, 5 mild adverse events occurred, with one moderate adverse event (vomiting). Meanwhile, in the placebo group, 3 participants experienced 4 TEAEs (back stiffness, neck stiffness, menstrual cramps, and heartburn). All TEAEs were resolved by the end of the research. 3) No significant aberrant clinical test results were found during the study.</td>
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<tr>
<td>Lieske, 2022</td>
<td>RCT</td>
<td>OxDC vs Placebo</td>
<td>33</td>
<td>Adults (&gt;18 years old) with a history of hyperoxaluria that was caused by a previously diagnosed gastrointestinal disorder associated with poor absorption of fat (such as bariatric surgery, Crohn’s disease, short bowel syndrome, or another malabsorptive disorder).</td>
<td>Participants maintained their regular food habits during the study, and a concise dietary background was collected throughout the screening process and at week 4 3. Subjects ingested two capsules of reloxilase (3750 units each, or 7500 units in total) or a placebo orally, three to five times/day, during every meal or snack.</td>
<td>OxDC: 14.56 ± 5.11  Placebo: 5.11 ± 5.45</td>
<td>1) Both groups have similar TEAE events - Adverse events in the gastrointestinal system were higher in the reloxilase group (36.2% vs 24.6%). - kidney stone-related adverse events were higher in the placebo group (14.0% vs 12.1%) 2) One participant in the reloxilase group experienced a major adverse event characterized by severe sacral radiculopathy.</td>
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<td>Study</td>
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<td>Lingeman, 2019</td>
<td>Open Label Pilot Study</td>
<td>ALLN-177</td>
<td>16</td>
<td>Adults (&gt;18 years old), male and female, with a documented history of at least one kidney stone within the past 2 years. Additionally, (Uox) &gt;36 mg/24 h, and eGFR must be &gt;60 mL/min/1.73 m2 at the initial screening.</td>
<td>1. Following a 35-day screening phase, participants entered a 3-day baseline and collected two 24-hour urine samples. During the 4-day treatment phase that followed the baseline period, participants orally consumed ALLN-177 capsules with meals and collected 24-hour urine samples on the last 3 days. On the fourth day post-treatment, a conclusive 24-hour urine sample was obtained.</td>
<td>ALLN-177: 13.9 ± 18.4</td>
<td>1) 56.3% experienced (AEs), all of which were of mild or moderate severity. 2 patients (12.5%) experienced adverse events that were potentially linked to the study medicine. These events were resolved within a day. 2) Adverse effects seen include stomach distension, dyspepsia, and nausea in one individual and abdominal distension and flatulence in another subject.</td>
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<tr>
<td>Pfau, 2021</td>
<td>Open Label Pilot Study</td>
<td>Reloxilase</td>
<td>3</td>
<td>Participants (12 years or older) with EH and advanced CKD and an elevated plasma oxalate (hyperoxalemia), defined by an eGFR &lt;45 mL/min/1.73m2, Uox oxalate ≥ 40 mg/24 h and plasma oxalate &gt;5 mmol/L.</td>
<td>1. Assessments obtained at the beginning and throughout Weeks 4, 8, and 12. Before starting the medicine, a baseline measurement of POx was obtained. In addition, two 24-hour urine samples were taken from patients having an eGFR &gt;15 mL/min/1.73m2. During 12 weeks, the participants were given reloxilase orally, five times daily, with meals and snacks. During the therapy phase, a solitary blood sample was obtained after fasting to quantify POx levels. In addition, two 24-hour urine samples were gathered after weeks 4, 8, and 12.</td>
<td>Reloxilase: 35.4 ± 8.8</td>
<td>1) There were no major adverse events reported that were related to drug use. 2) Adverse events related to treatment were predominantly documented in the GI system.</td>
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RCT = Randomized Controlled Trial, BMI = Body Mass Index, TEAE = treatment emergent adverse events, SAE = Serious Adverse Events, eGFR = estimated Glomerular Filtration Rate, Uox = urinary oxalate, Pox = plasma oxalate, HOLC = high oxalate low calcium
adverse effect (TEAE) mainly was not significant from both the intervention and control group, with the most common adverse effect being gastrointestinal system problems (a combination of diarrhea, vomiting, abdominal distention, flatulence, dyspepsia, and abdominal pain). Other TEAE reported from the study include back stiffness, neck stiffness, menstrual cramps, and heartburn. Most of the TEAEs reported were resolved by the end of the study.

**DISCUSSION**

Hyperoxaluria is a metabolic disorder characterized by elevated oxalate levels, which can occur either due to increased production of oxalate in the liver or excessive absorption of oxalate in the gastrointestinal tract.20 It may also stem from the development of bowel diseases or other yet unidentified causes, which can also be referred to as secondary hyperoxaluria. Although the quantity of oxalate in urine is merely one-tenth of that of calcium, the saturation limit of calcium oxalate is reached. Consequently, even a minor elevation in oxalate concentration can augment the likelihood of crystal precipitation. Epidemiological data indicates that there is a continual risk associated with increasing levels of hyperoxaluria, which can enhance the possibility of developing kidney stones.21–24

The primary treatment for secondary hyperoxaluria involves adhering to a diet low in oxalate, salt, and protein while maintaining a high fluid intake. However, the level of adherence to this therapy and its overall efficiency are widely regarded as suboptimal.25–27 Nevertheless, maintaining a low-oxalate, low-sodium, and normal-calcium diet presents difficulties due to the wide range of oxalate levels found in various foods, which vary significantly in each food.28 Numerous pharmaceutical interventions have been investigated with promising results in the context of kidney stone prevention and management. One compound currently under development for non-surgical prevention and management is oxalate decarboxylase. Oxalate decarboxylase is a chemical that is presently being developed for non-surgical prevention and management. The enzyme known as oxalate decarboxylase

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**Figure 3.** Risk of bias graph. A) ROB for RCT. B) ROBINS-I for NRSI

**Figure 4.** Forest plot of Mean difference in oxaluria between oxalate decarboxylase and placebo

**Figure 5.** Funnel’s plot of the study
has been shown to effectively mitigate hyperoxaluria by catalyzing the conversion of oxalate into formate and carbon dioxide. The efficacy of oxalate decarboxylase as a therapeutic intervention for decreasing hyperoxaluria has been demonstrated in multiple investigations. The advancement of this novel therapeutic approach holds promise for enhancing future possibilities in the context of hyperoxaluria and stone prevention and management.\(^5\),\(^10\)

According to the results of our study, compared with a placebo, oxalate decarboxylase significantly reduces urine oxalate (\(P<0.01\)). This result was supported by all three studies included in this review.\(^7\)\(-\)\(^9\) Similar results were described by Pfau et al.’s studies in 2021, demonstrating that oxalate decarboxylase can effectively lower plasma and urinary oxalate levels. Despite the limited sample size, this study demonstrated the efficacy of oxalate decarboxylase in patients with chronic kidney disease who had a decreased glomerular filtration rate. This study also mentioned the potential of oxalate decarboxylase that significantly benefits patients with this life-threatening disorder and serves as an additional treatment for improving kidney transplantation outcomes, particularly in enteric hyperoxaluria patients prone to developing oxalate nephropathy.\(^7\)

Another study by Lingemen et al. 2019 also studies oxalate decarboxylase’s efficacy in reducing urine oxaluria. Out of 16 people, it was demonstrated that oxalate decarboxylase is well-tolerated and capable of lowering urine oxalate levels by an average of 14 mg/24 hours. This reduction did not impact other measured parameters related to the risk of developing urinary stones during 24 hours. These findings suggest that the effect of ALLN-177 is immediate and specifically targets oxalate.\(^11\)

From the safety profile perspective, the most common adverse effect was gastrointestinal-related side effects (for example, diarrhea, vomiting, abdominal distention, flatulence, dyspepsia, and abdominal pain). Most of the study showed that the event and control in each group were almost equal, and most of the TEAEs were resolved by the end of the study. As for this side effect, it is still uncertain whether it is a coincidence of different diseases occurring simultaneously or whether there is a specific causal relationship between using oxalate decarboxylase and the incidence of sacral radiculopathy. To date, there is no specific etiology that suggests a direct link to medication-induced sacral radiculopathy, but this should be investigated further in the future.\(^29\),\(^30\)

Hyperoxaluria has long been recognized as a risk factor for producing oxalate stones. Firstly, the excessive concentration of calcium oxalate in urine can directly contribute to the development of calcium oxalate stones. Secondly, an excessive amount of oxalate in the urine can cause damage to the cells lining the renal tubules due to oxidative stress, which in turn promotes the adherence of crystals. Lastly, the immune inflammatory response after injury further encourages the formation of Randall plaques, which play a role in stone formation.\(^21\),\(^24\),\(^31\)

Epidemiological evidence shows hyperoxaluria is associated with a 2.5 to 3.5 times higher risk of stone formation than normal oxalate levels.\(^3\) Studies have indicated that the prevalence of hyperoxaluria in individuals with kidney stones has increased from 24.8% to 45.1% in the past two decades. This increase may also contribute to the growing worldwide prevalence of urolithiasis. Therefore, it is crucial to implement preventative interventions for hyperoxaluria to break the continuous cycle of stone recurrence.\(^33\)

By employing oxalate decarboxylase to decrease the presence of oxalate in the urine, it is hypothesized that the likelihood of oxalate stone recurrence can be reduced. However, the hypothesis must be validated through a more extensive research study. The results prove that using oxalate decarboxylase can significantly reduce oxalate levels in urine, which is expected to help indirectly prevent the formation of stones in urine. Nevertheless, it is important to acknowledge the limitations of this study. Firstly, the small number of conducted studies resulted in a limited research sample, which may affect the applicability of the findings. Secondly, variations in preparations and doses used in one of the studies could potentially introduce discrepancies in the results, particularly at higher doses. However, it is worth noting that the study did yield significant results despite these variations. Lastly, the included studies differed in follow-up duration, with one of the studies only conducting a one-week follow-up. Future research should include randomized controlled trials with larger sample sizes and longer follow-up periods to validate our findings.

CONCLUSION

Based on the results of this study, oxalate decarboxylase is one of the potential and promising alternative treatments for reducing urinary oxalate levels in hyperoxaluria patients. Therefore, it can be regarded as a viable choice in pharmacological treatment for preventing the occurrence of oxalate stones in patients in the future.

CONFLICT OF INTEREST

All authors disclosed no conflict of interest.

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AUTHOR CONTRIBUTION

All authors contributed equally to the study.

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