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Major metabolic and epigenetic predictors of lithiasis and nutrological management: a meta-analysis

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Abstract

Introduction: Urinary tract lithiasis is the third most prevalent condition in men. The composition of the stones is 80% calcium. The main metabolic alterations are hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, low urine volume, urinary tract infection, primary hyperparathyroidism, renal tubular acidosis, and cystinuria. In this scenario, uric acid stones represent about 5 to 10% of all kidney stone formation. The high prevalence of obesity or metabolic syndrome, diabetes, and hypertension is also commonly associated with nephrolithiasis. **Objective:** To elucidate the main metabolic and epigenetic predictors of lithiasis, focusing on the nutritional management of treatment. **Methods:** The systematic review rules (PRISMA) were followed. The search was carried out from June to August 2025 in the Scopus, Embase, PubMed, Science Direct, SciELO, and Google Scholar databases. The quality of the studies was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. Common descriptive statistical analysis was performed using mean, standard deviation, and minimum/maximum values of general numerical clinical data. Binary Logistic Regression analysis was performed, with $p<0.05$, with statistical significance at the 95% confidence interval (CI) in relation to the reference group adopted for each variable. The Odds Ratio (OR) was calculated to determine the probability ratio between the analyzed groups, respecting the 95% CI. **Results and Conclusion:** A total of 138 articles were found. A total of 64 articles were fully evaluated, and 32 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 9 studies at high risk of bias and 24 studies that did not meet the GRADE criteria. Most studies showed homogeneity in their results, with $X^2=91.4\%>50\%$. The symmetrical funnel plot does not suggest a risk of bias between small sample-size studies. It was identified that the predictors male gender, altered BMI, alcoholism, hypertension, diabetes mellitus, dyslipidemia, and altered parathyroid hormone showed a strong probability of contributing to the event of kidney stones. Furthermore, it showed important correlations and odds ratios (OR) of the variables BMI, DM, and staghorn calculi with metabolic alterations, highlighting hypercalciuria and BMI in categories 2 and 3 ($p=0.001$; OR=3.28), hypocitraturia and staghorn calculi ($p=0.003$; OR=2.21), hyperuricosuria and BMI in categories 2 and 3 ($p=0.017$; OR=2.01), hyperoxaluria and BMI in categories 2 and 3 ($p=0.002$; OR=2.81), urinary tract infection and DM ($p=0.005$; OR=1.73), urinary tract infection and staghorn calculi ($p=0.003$; OR=1.77), parathyroid hormone alteration and BMI in categories 2 and 3 ($p=0.008$; OR=2.69), and hyperphosphaturia and BMI in categories 2 and 3. ($p=0.021$; OR=1.99). Therefore, metabolic syndromes, obesity, hypertension, diabetes mellitus, dyslipidemia, and altered parathyroid hormone, as well as epigenetic factors such as alcoholism and high-protein diets, were shown to be important triggers of metabolic alterations in kidney stones and, consequently, lithiasis. Furthermore, this study allowed us to understand how many times each predictor can influence these metabolic alterations, thus representing important targets for the treatment of lithiasis.

Keywords: Lithiasis. Metabolism. Obesity. Metabolic syndrome. Diets. Proteins.

Introduction

Urinary tract lithiasis is the third most prevalent condition in men aged 20 to 40 years, with a lifetime prevalence of 1 to 15%, varying according to age, sex, race, and geographic location. The recurrence rate is 50% (5-10 years) **[1]**. The pathophysiology is a complex and multifactorial process, highlighting metabolic disorders, urinary tract infection, anatomical abnormalities, and idiopathic causes **[2]**.

The composition of the stones is 80% calcium (calcium oxalate, 60%; calcium phosphate, 20%) and 20% non-calcium (uric acid, 7%; struvite, 7%; cystine, 2%; others, 4%). The stones can increase in size, leading to severe kidney damage, obstruction, urinary tract infection, and loss of renal function. In this sense, the main metabolic alterations are hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, low urine volume, urinary tract infection, primary hyperparathyroidism, renal tubular acidosis, and cystinuria **[2]**.

In this scenario, uric acid (UA) stones represent about 5 to 10% of all kidney stone formation, being the third most common cause of kidney stones after calcium oxalate and struvite stones. The prevalence is higher in the Middle East (22-28%), and in the United States, it is only 8-10% **[1]**. The exact cause of the global diversity in the prevalence of UA lithiasis has not yet been fully elucidated **[3]**.

Another reason may be a high prevalence of obesity or metabolic syndrome, diabetes, and hypertension that are commonly associated with nephrolithiasis. It has been established that stone formers with metabolic syndrome or type 2 diabetes have UA with a higher prevalence than other populations **[4]**. Pak et al. **[5]** reported that 33.9% of 59 patients with stone formation with type 2 diabetes had AU stones compared to only 6.2% among non-diabetic stone formers. In this context, the Western diet, rich in protein-rich foods and poor in vegetables, is likely responsible for the development of an excess of acidic compounds, leading to metabolic dysregulation and the onset or worsening of chronic disorders. Available results seem to suggest that diets with a high proportion of protein may induce the development of calcium lithiasis. In addition, recent epidemiological findings highlight a specific role of dietary acid load in glucose metabolism dysregulation and insulin resistance **[6]**.

Microtomography can detect stones, anticipating lithiasis. There are different factors that influence stone formation depending on its composition. In calcium lithiasis, it is essential to review the modification of hypercalciuria categories. In fasting hypercalciuria, it is important to emphasize the relationship between this factor and bone mineral density loss in patients with recurrent renal calcium lithiasis, so that in this type of patient, the study of bone metabolism by bone remodeling markers and bone densitometry is mandatory. Regarding the other factors that participate in the formation of calcium lithiasis, we should especially highlight hypercalciuria and its increasing prevalence due to its relationship with obesity and metabolic syndrome, as well as hypocitraturia, present in a significant percentage of patients and related in some cases to metabolic acidosis and osteopenia-osteoporosis **[2]**.

Regarding uric acid lithiasis, it should be noted that urinary pH is the most determining factor and, therefore, its control and modifications would be fundamental for the prevention of this type of lithiasis. In infectious lithiasis, the presence of germs that separate urea is mandatory. They generate ammonia ions with the ability to damage the urothelium and, mainly, to form ammonium or magnesium phosphate lithiasis. Regarding cystine, it has been classified into type A and B depending on the gene silenced, with direct measurement of 24-hour urine being more useful than screening tests that have low sensitivity **[7]**.

Drug-induced stone account for 1 to 2% of all kidney stones. Poorly soluble drugs with high urinary excretion favor crystallization in the urine, such as atazanavir and other protease inhibitors, and sulfadiazine. In addition to these drugs, about 20 other molecules can induce nephrolithiasis, such as ceftriaxone or preparations containing ephedrine. There are also drugs that cause the formation of urinary stone as a result of their metabolic effects on urinary pH and/or excretion of calcium, phosphate, oxalate, citrate, uric acid, or other purines. Examples of metabolically induced stone are those formed in patients who administer uncontrolled calcium/vitamin D supplements or who are being treated with carbonic anhydrase inhibitors, such as acetazolamide or topiramate, requiring careful clinical investigation to differentiate between common stone and metabolically induced stone **[8]**.

Studies have shown that the prevalence of symptomatic nephrolithiasis is higher in patients with inflammatory bowel disease (IBD) compared to the general population. In IBD, kidney stones can arise from chronic inflammation, alterations in intestinal absorption due to inflammation, surgery, or intestinal

malabsorption. Kidney stones are more associated with Crohn's disease (CD) than with ulcerative colitis (UC) in adult patients due to malabsorption. Secondary enteric hyperoxaluria is the main risk factor in IBD. In the long course of CD, recurrent urolithiasis and calcium oxalate deposition can cause severe chronic interstitial nephritis and, consequently, chronic kidney disease **[9]**.

There are concepts of uric acid metabolism that affect the renal parenchyma and current therapies to reduce hyperuricemia (HU) and prevent the progression of kidney disease. Elevated uric acid plays an important role in several chronic diseases, including kidney diseases such as lithiasis, gouty nephropathy, and pre-eclampsia. Over the past 30 years, it has been shown that reducing uric acid levels with low-protein, low-purine diets, in addition to allopurinol, creates pathophysiological conditions that produce a slight increase in glomerular filtration rate (GFR). In recent years, in a new era of research in the clinical, genetic, pharmacological, and epidemiological fields, they have advanced to support the idea that reducing uric acid levels could benefit patients with chronic kidney disease (CKD) (stage III-IV), thus preventing the drop in GFR due to undefined mechanisms **[10]**.

In this sense, risk factors should be assessed in all patients with urinary lithiasis. The type of assessment, simplified or expanded, depends on the composition of the stone and, in patients with calcium lithiasis, on the clinical presentation. Patients with uric acid, infectious stone, and cystine require only a more abbreviated selective assessment. In calcium lithiasis, extensive metabolic assessment is performed in recurrent patients and also in patients with a single episode, when they present a high risk of recurrence. Extended assessment has proven to be economical in patients with recurrent lithiasis. There is still insufficient clinical evidence on what would be the most convenient study methodology for an adequate metabolic assessment, and clinical guidelines are mainly based on opinions from expert committees **[11]**.

Therefore, the present study aimed to elucidate which were the main metabolic and epigenetic predictors of lithiasis, focusing on the nutrological management of treatment.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: August 18, 2025. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: August 18, 2025.

Data Sources and Search Strategy

The bibliographic search process was conducted from June to August 2025 and developed based on the Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar databases, covering scientific articles from various periods up to the present day. The following descriptors (DeCS/MeSH Terms) were used: *"Lithiasis. Metabolism. Obesity. Metabolic syndrome. Diets. Proteins"*, using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was assigned to case reports, editorials, and brief communications, according to the GRADE instrument. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size) using Cohen's d test.

Participant Selection

Scientific articles were selected whose participants presented a diagnosis of urinary tract lithiasis, whether or not they underwent surgical extraction of the stones. Records without a history of urinary tract lithiasis and/or without metabolic evaluation were excluded.

Data Analysis

A database was created in a Microsoft Excel spreadsheet, which was exported to the statistical programs Stata 18 and Minitab 18®. Common descriptive statistical analysis was performed with mean, standard deviation, and minimum/maximum values of general numerical clinical data. As there are more than 15 data points, normality is not a problem. Quantitative values, both numerical and percentage-based, were developed for all dichotomous variables (0;1) or those with numerical codes ranging from 1 to 2 or from 1 to 4. Binary Logistic Regression analysis

was performed, with $p<0.05$, with statistical significance at the 95% confidence interval (CI) in relation to the reference group adopted for each variable. The Odds Ratio (OR) was calculated to determine the probability ratio between the analyzed groups, respecting the 95% CI.

Results

Summary of Findings

As a corollary to the literature search system, 137 studies were analyzed and submitted to eligibility analysis, and 21 of the final 42 studies were subsequently selected for this meta-analysis. The selected studies were of medium to high quality (Figure 1), considering, first, the level of scientific evidence of studies of meta-analysis, consensus, randomized clinical, prospective, and observational types. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneous results, with X^2 = 91.4% >50%.

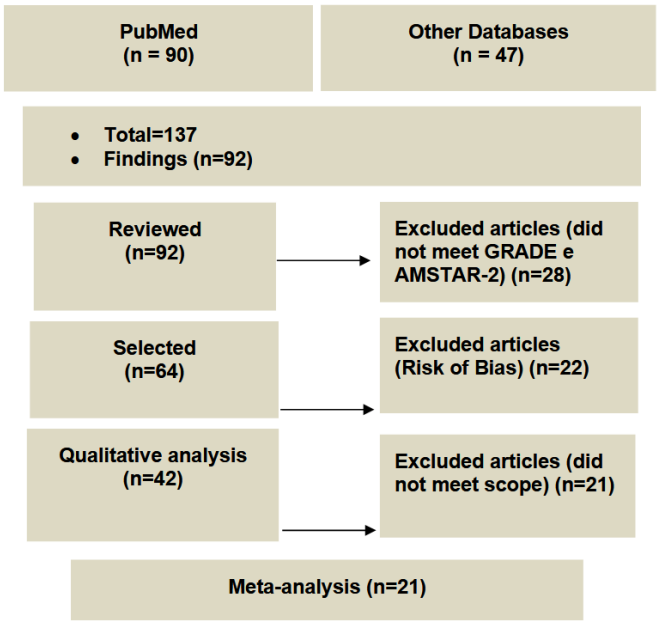

Figure 1. Flowchart showing the article selection process. Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d Test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), which are shown at the bottom of the graph, or among studies with large sample sizes, which are presented in the upper region.

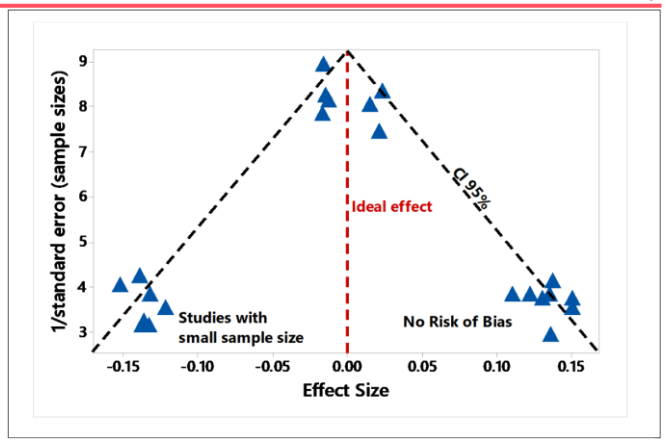

Figure 2. The symmetrical funnel plot suggests no risk of bias among the small-sample-size studies shown at the bottom of the graph. High-confidence and high-recommendation studies are shown above the graph (n=21 clinical studies). Source: Own Authorship.

Major Findings

One hundred and twelve (112) participants with nephrolithiasis were selected and evaluated from the articles selected in this meta-analysis. Table 1 shows the descriptive statistical values of mean, standard deviation, maximum and minimum values and range of the numerical quantitative variables, with a mean age of 46.76±13.53 years and a mean BMI of 29.37±6.14 kg/m^2.

Variables N total = 112	Mean	StDev	Minimum	Maximum	Range
Age (years)	46.76	13.53	10.00	83.00	73.00
Weight (kg)	80.40	20.18	26.00	139.00	113.00
BMI (kg/m^2)	29.37	6.14	14.10	44.40	30.30
Parathyroid hormone (pg/mL)	60.97	40.42	23.00	373.00	350.00

Table 1. Mean, standard deviation and minimum/ maximum values of general numerical clinical data.

Binary logistic regression analysis was performed to identify and quantify the association between each continuous predictor of patients with the event of lithiasis, with $p<0.05$ considered statistically significant (95% CI). Through this analysis, it was identified that the predictors male gender, with Chi-Square = 7.77, p-value = 0.02 and Odds Ratio = 2.10 in the CI (0.3919; 11.2638); BMI with Chi-Square = 26.34, p-value = 0.00 and Odds Ratio = 3.50 in the CI (0.3034; 0.6678); and alcoholism with Chi-Square = 6.25, p-value = 0.001 and Odds Ratio = 3.09 in the CI (0.0354; 270.6598); and hypertension with Chi-Square = 5.75. p-value=0.007 and Odds Ratio=1.53 in the CI (0.5758; 4.1061). DM with Chi-Square =6.18, p-value=0.003 and Odds Ratio=4.99 in the CI (1.2265; 20.3805). Dyslipidemia with Chi-Square =9.02, p-value=0.002 and Odds Ratio=2.84 in the CI (0.3029;

4.0556) and altered parathyroid hormone with Chi-Square =7.02, p-value=0.006 and Odds Ratio=1.69 in the CI (0.6980; 4.1273) represented, in this cohort of patients, a strong probability of contributing to the lithiasis event, according to Table 2.

Predictors	Reference (Lithiasis)	Chi-Square	p-value	Odds Ratio	95% CI
Age	1	3.81	0.051	1.0564	(0.9962; 1.1203)
Gender (Male=1; Female=2)	1	7.77	0.02	2.1009	(0.3919; 11.2638)
Ethnicity	1	0.13	0.718	0.8887	(0.4671; 1.6911)
Education	1	0.15	0.699	0.8408	(0.3472; 2.0361)
Monthly income	1	1.90	0.169	1.3619	(0.8120; 2.2841)
Weight (kg)	1	2.36	0.125	1.0754	(0.9781; 1.1823)
BMI (kg/m²)	1	26.34	0.000	3.5010	(0.3034; 0.6678)
Smoker	1	0.01	0.905	1.1168	(0.1808; 6.9005)
Etilism	1	6.25	0.001	3.0957	(0.0354; 270.6598)
HAS	1	5.75	0.007	1.5377	(0.5758; 4.1061)
Diabetes mellitus	1	6.18	0.003	4.9997	(1.2265; 20.3805)
Dyslipidemia	1	9.02	0.002	2.84	(0.3029; 4.0556)
Altered parathyroid hormone	1	7.02	0.006	1.6973	(0.6980; 4.1273)
Family history	1	1.48	0.223	0.5392	(0.1957; 1.4860)
Renal cyst	1	1.21	0.272	0.5240	(0.1651; 1.6632)

Table 2. Results of binary logistic regression analysis to identify and quantify the association between each predictor of general patient data and the event of lithiasis (p<0.05 with statistical significance; 95% CI).

According to the results in Table 3, the main correlations and odds ratios of the variables BMI, DM, and staghorn stone with metabolic alterations were hypercalciuria and BMI in categories 2 and 3 (p=0.001; OR=3.28); hypocitraturia and staghorn stone (p=0.003; OR=2.21); hyperuricosuria and BMI in categories 2 and 3 (p=0.017; OR=2.01); hyperoxaluria and BMI in categories 2 and 3 (p=0.002; OR=2.81); urinary tract infection and diabetes mellitus (p=0.005; OR=1.73); urinary tract infection and staghorn stone (p=0.003; OR=1.77). Changes in parathyroid hormone and BMI in categories 2 and 3 (p=0.008; OR=2.69) and hyperphosphaturia and BMI in categories 2 and 3 (p=0.021; OR=1.99).

Variables	Hypercalciuria	Chi-Square	p-value	Odds Ratio (OR)	95% CI
BMI (kg/m²) (1;2;3)*	2 e 3	8.84	0.001	3.2851	(0.7503; 4.2012)
Diabetes mellitus	1	0.93	0.335	0.6371	(0.2524; 1.6079)
Staghorn stone	1	0.00	0.975	1.0177	(0.3424; 3.0244)
	Hypocitraturia				
BMI (kg/m²) (1;2;3)*	1 .2 e 3	0.00	0.976	0.9918	(0.5744; 1.7125)
Diabetes mellitus	1	0.50	0.480	1.3878	(0.5592; 3.4446)
Staghorn stone	1	2.06	0.003	2.2176	(0.7422; 6.6257)
	Hyperuricosuria				
BMI (kg/m²) (1;2;3)*	2 e 3	5.70	0.017	2.0176	(1.1178; 3.6419)
Diabetes mellitus	1	0.00	0.973	0.9840	(0.3846; 2.5173)
Staghorn stone	1	0.01	0.910	1.0654	(0.3561; 3.1880)
	Low Urinary Volume				
BMI (kg/m²) (1;2;3)*	1. 2 e 3	2.16	0.142	0.6134	(0.3171; 1.1866)
Diabetes mellitus	1	0.69	0.405	0.6498	(0.2380; 1.7741)
Staghorn stone	1	0.05	0.825	0.8738	(0.2653; 2.8775)
	Hyperoxaluria				
BMI (kg/m²) (1;2;3)*	2 e 3	9.46	0.002	2.8199	(1.3978; 5.6887)
Diabetes mellitus	1	0.05	0.818	1.1287	(0.4051; 3.1446)
Staghorn stone	1	1.08	0.300	0.5273	(0.1529; 1.8180)
	Urinary Tract Infection				
BMI (kg/m²) (1;2;3)*	1. 2 e 3	0.30	0.582	0.8559	(0.4912; 1.4915)
Diabetes mellitus	1	1.41	0.005	1.7397	(0.6974; 4.3399)
Staghorn stone	1	1.04	0.003	1.7789	(0.5873; 5.3875)
	Cystinuria				
BMI (kg/m²) (1;2;3)*	3	0.20	0.632	0.9559	(0.5312; 1.5915)
Diabetes mellitus	1	1.51	0.335	1.1457	(0.5974; 5.3399)
Staghorn stone	1	1.34	0.408	1.2413	(0.5462; 5.4683)
	Parathyroid hormone alteration				
BMI (kg/m²) (1;2;3)*	2 e 3	2.94	0.008	2.69	(0.9303; 2.7221)
Diabetes mellitus	1	0.15	0.701	0.8386	(0.3410; 2.0626)
Staghorn stone	1	0.16	0.686	1.2517	(0.4206; 3.7248)
	Hyperphosphatemia				
BMI (kg/m²) (1;2;3)*	2 e 3	5.35	0.021	1.9906	(1.0964; 3.6141)
Diabetes mellitus	1	0.20	0.654	1.2383	(0.4873; 3.1465)
Staghorn stone	1	0.38	0.535	1.4128	(0.4750; 4.2021)

Table 3. Correlation and odds ratio of the variables BMI, DM, and staghorn calculus with metabolic alterations, with p<0.05 with statistical significance (95% CI).
*BMI from 14.1 to 24.9 =1 (normal); BMI from 24.9 to 31 =2 (obese); BMI from 31 to 44.4 =3 (overweight)

Finally, staghorn stone correlate 70% with altered BMI. Urinary tract infection correlates 64.94% with altered parathyroid hormone. Hypercalciuria correlates approximately 50% with altered BMI and staghorn stone, and approximately 47% with diabetes mellitus.

Discussion

In the context of nephrolithiasis, an ideal metabolic assessment strategy has not yet been defined. Thus, this meta-analysis study sought to contribute to a better understanding of the incidence and prevalence of lithiasis, in order to elucidate which were the main metabolic and epigenetic predictors for better targeting the treatment of this disease. In this sense, according to the results of this study, the metabolic profile of the 112 participants evaluated from the scientific articles with lithiasis highlighted 77.68% low urinary volume, 40.18% hypercalciuria, 33.04% hyperphosphaturia, 39.29% hypocitraturia, 33.04% hyperuricosuria, 23.21% hyperoxalaturia, 47.32% altered parathyroid hormone, and 36.61% urinary tract infection. This metabolic profile is similar to the data found in the literature **[14-16]**.

The use of mesalazine/sulfa, vitamins D and C was insignificant, not contributing significantly to the statistical results. This was a positive aspect of this study, given that the literature shows strong evidence of the influence of these drugs and vitamins on the formation of stone **[17,18]**. Furthermore, the use of home remedies and quebracho tea was the most frequently reported, with 61.61% and 54.46%, respectively. Other studies have shown possible benefits of these applications in attempting to reduce or eliminate stone **[19]**.

It was identified that the predictors male gender, altered BMI, alcoholism, hypertension, diabetes mellitus, dyslipidemia, and altered parathyroid hormone showed a strong probability of contributing to

the lithiasis event. These findings agree with the results of several scientific studies that showed significant evidence of these metabolic alterations and the emergence of lithiasis **[20-22]**.

This study revealed important correlations and odds ratios (OR) of the variables BMI, DM, and staghorn stone with metabolic alterations, highlighting hypercalciuria and BMI in categories 2 and 3 (p=0.001; OR=3.28). hypocitraturia and staghorn stone (p=0.003; OR=2.21). hyperuricosuria and BMI in categories 2 and 3 (p=0.017; OR=2.01). hyperoxaluria and BMI in categories 2 and 3 (p=0.002; OR=2.81). urinary tract infection and DM (p=0.005; OR=1.73). urinary tract infection and staghorn stone (p=0.003; OR=1.77). Parathyroid hormone alteration and BMI in categories 2 and 3 (p=0.008; OR=2.69) and hyperphosphaturia and BMI in categories 2 and 3 (p=0.021; OR=1.99). These findings of the influence of obesity and DM as important metabolic syndromes that lead to the metabolic alterations of nephrolithiasis are also strongly elucidated in the world literature **[21,22]**.

Based on this scenario of metabolic alterations and lithiasis, a 2014 European guideline brought together the main scientific evidence to evaluate the ideal strategy for the assessment and treatment of metabolic stone and to prevent recurrent urinary stone **[26]**. Reliable calculus analysis and basic metabolic assessment are highly recommended in all patients after calculus passage. Each patient should be assigned to a low or high-risk group for calculus formation. It is highly recommended that low-risk calculus formers follow the general guidelines for fluid and nutrient intake, as well as preventive lifestyle measures to reduce the recurrence of kidney stones. Highrisk kidney stone formers should undergo specific metabolic evaluation with 24-hour urine collection.

There is strong evidence to recommend pharmacological treatment of calcium oxalate stones in patients with specific abnormalities in urine composition. Treatment of calcium phosphate stones with thiazides is highly recommended only when there is hypercalciuria. In the presence of renal tubular acidosis, potassium citrate and/or thiazide are highly recommended based on the relative urinary risk factor. Recommendations for therapeutic measures for other types of stones are based on low evidence. Therefore, assessment of metabolic stone is highly recommended to prevent stone recurrence **[26]**.

An association between uric acid (UA) stones and insulin resistance, diabetes mellitus, and obesity stands out. The development of UA stones depends on several risk factors, including genetic predisposition, geographic location, dietary indiscretion, and various metabolic characteristics. Low urinary pH is the most common factor, but the reason for this defect is unknown. There is evidence that there may be insufficient production of the urinary ammonium buffer. Many transport proteins participate in urate metabolism. with URAT1 and GLUT9 being the best characterized to date **[27]**.

Idiopathic hypercalciuria is defined as calcium excretion greater than 220 and 300 mg/day in women and men, respectively, or greater than 4 mg/kg of body weight. In women with osteoporosis, it is observed in 19% of cases, while in kidney stones, the cases vary between 50 and 70%. Thus, a study selected 206 hypercalciuric patients, with and without renal lithiasis, for whom there was an indication for a restricted diet. 122 patients with a diagnosis of diet-dependent hypercalciuria were considered (105 women and 17 men), who were followed with dietary control (800 mg of calcium, about 1 g of animal protein, and <100 mEq of sodium per day). After 17 months, all had their hypercalciuria controlled, and there were even 16 (13%) who, after 42 months of follow-up, they remained normocalciuric with diet alone. Therefore, the division of hypercalciuria is fundamental, according to its response to a restricted diet, in order to avoid or postpone the use of diuretics and their adverse effects, with proper diet management **[28]**.

In the setting of recurrent kidney stones, these are associated with loss of bone mineral density, altered bone remodeling markers, hypercalciuria, and increased fasting calcium/creatinine ratio. A cross-sectional study including 142 patients determined the biochemical changes in urine in patients with osteopenia/osteoporosis without calcium kidney stones compared to patients with calcium kidney stones. Group 1 (patients with recurrent calcium kidney stones) and Group 2 (patients with osteopenia/osteoporosis in the lumbar spine or hip). Patients in Group 2 showed greater loss of bone mineral density and higher levels of alkaline phosphatase, iPTH. phosphorus and β-crosslaps, when compared to patients in Group 1. However, Group 1 had higher urinary calcium, oxalate, and uric acid, and a higher proportion of hypocitraturia, hypercalciuria, and hyperoxaluria, compared to Group 2. Advanced age and β-crosslap levels are risk factors for bone mineral density loss, while low urinary calcium excretion was protective against bone demineralization **[29]**.

A cross-sectional study of 115 patients in eastern Andalusia, Spain, analyzed the importance of urinary citrate and the urinary calcium:citrate ratio in patients with calcium kidney stones and severe lithogenesis

compared to a control group of patients without lithiasis. Group A: 56 patients aged 25-60 years without calcium kidney stones; Group B: 59 patients aged 25-60 years presenting with calcium kidney stones and severe lithogenesis. In Group B, 32.2% of patients presented with hypocitraturia, compared with 14.3% of patients in Group A (p=0.02). Urinary citrate levels were lower in Group B than in Group A (p=0.001), and the calcium:citrate ratio was higher in Group B than in Group A (p=0.005). The results suggest that a urinary calcium:citrate ratio > 0.25 indicates severe lithogenesis. After linear regression analysis, it was found that the urinary citrate level is an independent factor associated with changes in bone densitometry values in patients **[30]**.

Another cross-sectional study, including 203 patients by the same authors, analyzed the differences in bone remodeling markers, lithogenic factors, and bone densitometry among 3 groups of patients (controls, patients with recurrent calcium kidney stones, and patients with bone mineral density loss without lithiasis). Patients in group 2 showed higher calcium excretion and lower citrate excretion in 24-hour urine samples compared to the other 2 groups. The proportion of hypercalciuria and hypocitraturia was higher in group 2. In addition, patients in group 2 showed less bone mineral density loss and altered bone remodeling markers compared to those in group 1. Patients in group 3 also showed alterations in urinary calcium and citrate excretion compared to the control group, with elevated fasting calcium and citrate levels and calcium to citrate **[31]**.

Also, genetic factors should be considered in the etiological diagnosis of urinary lithiasis. Thus. A retrospective study between 2008 and 2018 with 60 patients determined the clinical and metabolic characteristics and evolution of hereditary urinary lithiasis in our patients. Thirty-five men and twenty-five women were included in this study. The mean age at the time of diagnosis of the hereditary nature of urinary lithiasis was 28.6 years. The mean delay between the onset of lithiasis and the etiological diagnosis was 8 years. Thirty-one cases of cystinuria were observed, 18 cases of primary hyperoxaluria type 1 with two mutations (I244T in 14 cases, 33-34 Insc in 23 cases), and 11 cases of renal tubulopathy. Fourteen patients were affected with chronic renal failure, of whom five were in end-stage renal disease. Crystalluria was positive in 62% of cases. After a mean follow-up of 16 years, normal renal function was noted in 42 cases. Chronic renal failure in 7 cases. Hemodialysis in 10 cases. All with primary hyperoxaluria and transplantation in 1 case. Thus, cystinuria was the most frequent etiology, and primary hyperoxaluria was the most serious condition **[32]**.

A systematic review study analyzed the relationship between urinary stone and intestinal diseases. Fifty-three articles were selected. Three types of urolithiasis are mainly involved in digestive pathologies, such as calcium oxalate stone, uric acid, and ammonium urate stone. Intestinal pathologies responsible for stones are divided into small intestine diseases, colon lesions, and the absence of an oxalate-degrading bacterium (*Oxalobacter formigenes*) in the intestinal microbiota, resulting in decreased urinary output, pH, hyperoxaluria, hypocitraturia, or hypomagnesuria. Therefore, intestinal diseases can be responsible for urolithiasis **[33]**.

Finally, patients with recurrent kidney stone formation should undergo metabolic evaluation and chemical analysis of the stone. Current evidence suggests differentiated approaches based on the diagnosed metabolic disorder. Diet may play a detrimental role in preventing recurrences. Prevention advice includes increasing fluid intake, vegetables and fruits, but decreasing consumption of sugar, salt and meat **[34]**.

Limitations

Although this meta-analysis presents evidence of the main predictors of lithiasis, as well as nutritional risk factors (how to consume high protein), further analysis is needed from a nutrigenomic perspective on how precise nutritional management can impact the treatment of lithiasis. Furthermore, more robust randomized controlled clinical trials and epidemiological studies are lacking.

Conclusion

It was concluded that metabolic syndromes such as obesity, hypertension, diabetes mellitus, dyslipidemia, and altered parathyroid hormone, as well as epigenetic factors such as alcoholism and high-protein diets, have been shown to be important triggers of metabolic alterations in kidney stones and, consequently, lithiasis. Furthermore, this study allowed us to understand how many times each predictor can influence these metabolic alterations, thus representing important targets for the treatment of lithiasis.

CRediT

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