# Metabolic syndrome as a risk factor for nephrolithiasis

## Síndrome metabólica como fator de risco para nefrolitíase

Thiago Milani da Costa[1], Fabíola de Azevedo Mello[1],Juliana Machado Avila[2], Maria Julia Demattei de Melo[2], Marina Schroeder Iglesias[2], Sarah Duarte Silveira[2], Gabriela Reigota Blanco[1], Marcus Vinícius Pimenta Rodrigues[1], Renata Calciolari Rossi[1]


### ABSTRACT

**Objective:** To elucidate the main characteristics of the patient considered to be at high risk for the formation of nephrolithiasis for better targeting in the prevention of this disease. **Methods:** From September 2019 to October 2020, a prospective study of 112 patients considered to be at high risk for the formation of urinary tract stones was carried out, through the collection of clinical data and complete metabolic investigation. For data analysis, the Minitab 18® statistical program was used. **Results:** The mean age was 46.76±13.53 years, and most were overweight/obese with a mean BMI of 29.37±6.14 kg/m$^2$. The Caucasian race prevailed (68.75%) and 66.07% had a family history. The most prominent metabolic alterations were: low urinary volume (77.68%), hypercalciuria (40.18%), hypocitraturia (39.29%), and hyperuricosuria (33.04%). The study identified that the male gender (p=0.02; OR=2.10), BMI (p=0.00; OR=3.50), SAH (p=0.007; OR=1.53), DM (p =0.003; OR=4.99) and dyslipidemia (p=0.002; OR=2.84) represented a strong probability of contributing to the lithiasis event and the main correlations and odds ratio were between hypercalciuria and altered BMI (p=0.001; OR=3.28), hypocitraturia and staghorn calculi (p=0.003; OR=2.21), hyperuricosuria and altered BMI (p=0.017; OR=2.01), hyperoxaluria and altered BMI (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), altered parathyroid hormone and altered BMI (p=0.008; OR =2.69) and hyperphosphaturia and altered BMI (p=0.021; OR=1.99). **Conclusion:** In this study, it was observed that the metabolic syndrome is an important trigger of metabolic changes in kidney stones, and consequently, nephrolithiasis, emphasizing the need to promote or assist public health policies in this population.


**Keywords:** Nephrolithiasis, Urolithiasis, Urinary calculus, Metabolic syndrome.


### RESUMO

**Objetivo:** Elucidar as principais características do paciente considerado de alto risco para a formação de nefrolitíase para melhor direcionamento na prevenção desta doença. **Métodos:** De setembro de 2019 a outubro de 2020, foi realizado um estudo prospectivo de 112 pacientes considerados de alto risco para a formação de cálculos no trato urinário, por meio de coleta de dados clínicos e investigação metabólica completa. Para análise dos dados, foi utilizado o programa estatístico Minitab 18®. **Resultados:** A média de idade foi de 46,76±13,53 anos, e a maioria apresentava sobrepeso/obesidade com IMC médio de 29,37±6.14 kg/m$^2$. Predominou a raça caucasiana (68,75%) e 66,07% tinham histórico familiar. As alterações metabólicas mais destacadas foram: baixo volume urinário (77,68%), hipercalciúria (40,18%), hipocitratúria (39,29%), hiperuricosúria (33,04%). O estudo identificou que o sexo masculino (p=0,02; OR=2,10), IMC (p=0,00; OR=3,50), HAS (p=0,007; OR=1,53), DM (p=0,003; OR=4,99) e a dislipidemia (p=0,002; OR=2,84) representou forte probabilidade de contribuir para o evento litíase e as principais


[1]University of West Paulista, Presidente Prudente, (SP), Brazil
[2]Medical School of Presidente Prudente, Presidente Prudente, (SP), Brazil



https://doi.org/10.11606/issn.2176-7262.rmrp.2024.203849

correlações e odds ratio foram entre a hipercalciúria e IMC alterado (p=0,001; OR=3,28), hipocitratúria e cálculo coraliforme (p=0,003; OR=2.21), hiperuricosúria e IMC alterado (p=0,017; OR=2,01), hiperoxalúria e IMC alterado (p=0,002; OR= 2,81), infecção urinária e DM (p=0,005; OR=1,73), infecção urinária do trato urinário e cálculo coraliforme (p=0,003; OR=1,77), paratormônio alterado e IMC alterado (p=0,008; OR =2,69) e hiperfosfatúria e IMC alterado (p=0,021; OR=1,99). **Conclusão:** Neste estudo, observou-se que a síndrome metabólica é um importante gatilho de alterações metabólicas em cálculos renais e, consequentemente, nefrolitíase, enfatizando a necessidade de promover ou auxiliar políticas de saúde pública nessa população.

**Palavras-chave:** Nefrolitíase, Urolitíase, Cálculos urinários, Síndrome metabólica.

## INTRODUCTION

Urinary tract lithiasis corresponds to the third most prevalent condition in men aged 20 to 40 years, Caucasian, 1 to 15% lifetime prevalence, varying according to age, gender, race and geographic location, having a recurrence of 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%). In this sense, the main metabolic alterations are hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, low urinary volume, urinary tract infection, primary hyperparathyroidism, renal tubular acidosis, cystinuria[2].

In this scenario, uric acid (UA) stones account for about 5-10% of all kidney stone formation, making them the third most common cause of kidney stones after calcium oxalate and struvite stones. Prevalence is highest 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 clarified[3].

Another reason could be a high prevalence of the metabolic syndrome characterized by obesity, diabetes or insulin resistance, dyslipidemia and systemic arterial hypertension (SAH), which 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 stone-forming patients with type 2 diabetes had UA stones compared with only 6.2% among non-diabetic stone formers. Furthermore, recent epidemiological findings highlight a specific role of dietary acid load in dysregulation of glucose metabolism and insulin resistance[6].

There are different factors that influence the formation of stones depending on their composition. Regarding UA 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 the urea is mandatory. They generate ammonia ions with the ability to damage the urothelium and, mainly, to form ammonium or magnesium phosphate lithiasis. In relation to cystine, it started to be classified as type A and B depending on the silenced gene, being more useful to perform direct measurement of 24-hour urine than screening tests that have low sensitivity[7].

In addition, drug-induced stones 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. There are also drugs that cause urinary stone formation because of their metabolic effects on urinary pH and/or excretion of calcium, phosphate, oxalate, citrate, uric acid, or other purines. Examples of metabolically induced stones are those formed in patients who take 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 stones and metabolically induced stones[8]. Studies have shown that in inflammatory bowel disease (IBD), kidney stones can arise from chronic inflammation, changes in intestinal absorption due to inflammation, surgery, or intestinal malabsorption [9].

There are concepts of uric acid metabolism that affect the renal parenchyma and current therapies to reduce hyperuricemia (HiU) and prevent the progression of kidney disease[10].

In this sense, risk factors should be evaluated in all patients with urolithiasis. The type of assessment, simplified or extended, depends on the composition of the stone and, in patients with calcium lithiasis, on the clinical presentation. Patients with uric acid, infectious stones, and cystine require only a more abbreviated selective evaluation. In calcium lithiasis, an extensive metabolic assessment is performed in recurrent patients, as well as in single-episode patients, when they are at high risk of recurrence. There is still not enough clinical evidence on what would be the most convenient study methodology for an adequate metabolic assessment, and clinical guidelines are mainly based on expert committee opinions[11].

With the hypothesis that certain substances, when elevated in the body, have the capacity to promote the precipitation of salts in the urine and form urinary calculi and considering the social, economic and health impact of this population, the objective of this study was to elucidate the main characteristics of the patient considered to be at high risk for the formation of nephrolithiasis in order to better target the prevention of this disease.

## METHODS

### Characterization of the study

From September 2019 to October 2020, a prospective, observational and descriptive study was carried out with patients with urinary tract stones, whether or not undergoing surgical extraction of the stone(s), who attended the consultation at the Outpatient Clinic of Urology at the Hospital Regional de Presidente Prudente, located in the West of the State of São Paulo.

### Sample Description

Patients with a diagnosis of lithiasis in the urinary tract, confirmed by imaging tests and considered at high risk for the formation of nephrolithiasis, were included in the study, such as: recurrent history of lithiasis, multiple unilateral or bilateral calculi, staghorn calculus, anatomical alteration of the urinary tract and first episode in childhood and adolescence.

Patients who did not complete clini-

cal and laboratory data collection were excluded from the study.

## Ethical aspects

The research project was attached to the Plataforma Brasil for consideration and approved on 08/06/2019 by the ethics committee of UNOESTE-Universidade do Oeste Paulista, Presidente Prudente/SP under number 5588. The informed consent form was used for all patients under study. The data were kept confidential in accordance with the ethical principles that are in resolution 466/12 of the National Health Council.

## Procedures and Assessments

Information related to the urolithiasis event was collected, such as: anamnesis, physical examination, history of kidney stones, comorbidities, medications in use, habits and addictions, imaging methods that confirmed the presence of stones and anatomical changes in the urinary tract, family history of urolithiasis, weight, height, body mass index (BMI), schooling and monthly income.

Regarding laboratory tests, the following elements were requested and evaluated: Serum (urea, creatinine, sodium, potassium, uric acid, calcium, glucose, blood count, parathyroid hormone) and at least one 24-hour urine sample (calcium, uric acid, citrate, sodium, creatinine, oxalate, phosphate, cystinuria test, fasting urinary pH, urine volume and urine culture).

For serum dosages, the Vitros 5600 equipment from Ortho Clinical Diagnostics was used with immunometric methodology to measure parathyroid hormone and dry-chemical methodology for urea, creatinine, sodium, potassium, uric acid, calcium, glucose. The XE 2100 Sysmex hematology analyzer uses fluorescent flow cytometry to prepare a complete blood count.

For urine analysis, the Roche urisys 2400 System was used by the reflectance method to characterize the urine pH. The Vitros 5600 equipment from Ortho Clinical Diagnostics processed, by means of the dry-chemical methodology, Proteinuria, Natriuria, Calciuria, Phosphaturia and Uricosuria, by the enzymatic method Oxalaturia, Citraturia, by colorimetry the research of Cystinuria and HPLC (High Resolution Liquid Chromatography) for the quantification of cystinuria. Finally, the culture was performed by laminated culture (Uribac).

## Data analysis

For data analysis, a database was built in Microsoft Excel spreadsheet, which was exported to the statistical program Minitab 18® statistical program (version 18, Minitab, LLC, State College, Pennsylvania, USA)[12]. A common descriptive statistical analysis was performed with mean, standard deviation and minimum/maximum values of numeric general clinical data. Quantitative values were prepared both numerically and in percentage of all dichotomous variables (0;1) or those that presented 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 in the 95% confidence interval (CI) in relation to the reference group adopted for each variable. The calculation of the Odds Ratio (OR) was carried out to know the probability ratio between the analyzed groups, obeying the 95% CI.

## RESULTS

One hundred and twelve (112) patients who met the inclusion criteria were selected. The ages ranged from 10 to 83 years, with a mean of 46.76±13.53 years, and most were overweight/obese with a mean BMI of 29.37±6.14 kg/m$^2$, as shown in Table 1.

**Table 1.** Characterization of the patient sample with urinary tract stones, treated at the Urology Outpatient Clinic at the Regional Hospital in Presidente Prudente, from September 2019 to October 2020.

| Variables | X±DP | Minimum Value | Maximum Value | Amplitude |
|---|---|---|---|---|
| **Age (years)** | 46,76 ± 13,53 | 10,00 | 83,00 | 73,00 |
| **Weight (Kg)** | 80,40 ± 20,18 | 26,00 | 139,00 | 113,00 |
| **BMC (Kg/m$^2$)** | 29,37 ± 6,14 | 14,10 | 44,40 | 30,30 |

X±SD: mean ± standard deviation, Kg: kilograms, m$^2$: square meters, BMC: Body mass index

As for the demographic and clinical data, Table 2 shows that the number of genders was the same (50% for men and women), and the Caucasian race prevailed with 68.75%. Most of the patients analyzed were non-smokers (88.39%) and non-alcoholics (96.43%). It also reveals the presence of personal history such as diabetes mellitus in 25.89%, dyslipidemia in 17.86% and 16.07% having metabolic syndrome. In addition, 66.07% had a family history, 17.86% had staghorn calculi, 7.14% had hyperuricemia, and 4.46% had inflammatory bowel disease.

**Table 2.** Demographic and clinical data of the 112 patients selected at the Urology Outpatient Clinic at the Regional Hospital in Presidente Prudente, from September 2019 to October 2020, are presented below.

| Variables | Dichotomous Variable | n (%) |
|---|---|---|
| **Gender** | 1 | 56 (50) |
| | 2 | 56 (50) |
| **Color** | 1 | 77 (68,75) |
| | 2 | 1 (0,89) |
| | 3 | 30 (26,79) |
| | 4 | 4 (3,57) |
| **Education** | 0 | 5 (4,46) |
| | 1 | 41 (36,61) |
| | 2 | 51 (45,54) |
| | 3 | 13 (11,61) |
| | 4 | 2 (1,79) |

| | | |
|---|---|---|
| **Smoking** | 0 | 99 (88,39) |
| | 1 | 13 (11,61) |
| **Alcoholism** | 0 | 108 (96,43) |
| | 1 | 4 (3,57) |
| **SAH** | 0 | 67 (59,82) |
| | 1 | 45 (40,18) |
| **DM** | 0 | 83 (74,11) |
| | 1 | 29 (25,89) |
| **Dyslipidemia** | 0 | 92 (82,14) |
| | 1 | 20 (17,86) |
| **Hyperparathyroidism** | 0 | 110 (98,21) |
| | 1 | 2 (1,79) |
| **Metabolic syndrome** | 0 | 94 (83,93) |
| | 1 | 18 (16,07) |
| **CRF** | 0 | 111 (99,11) |
| | 1 | 1 (0,89) |
| **Inflammatory bowel disease** | 0 | 107 (95,54) |
| | 1 | 5 (4,46) |
| **Hyperuricemia** | 0 | 104 (92,86) |
| | 1 | 8 (7,14) |
| **Family history** | 0 | 38 (33,93) |
| | 1 | 74 (66,07) |
| **Staghorn calculus** | 0 | 92 (82,14) |
| | 1 | 20 (17,86) |
| **Kidney cyst** | 0 | 89 (79,46) |
| | 1 | 23 (20,54) |

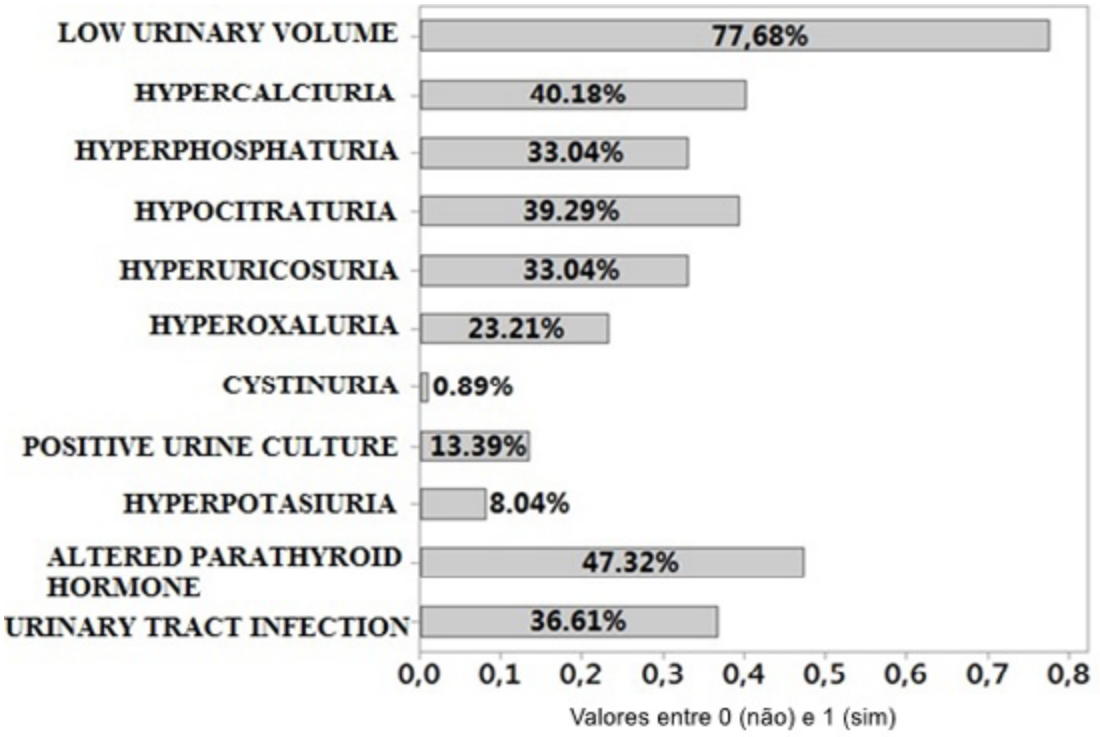
| | | |
|---|---|---|
| **Vicariant kidney** | 0 | 111 (99,11) |
| | 1 | 1 (0,89) |
| **Fanconi syndrome** | 0 | 111 (99,11) |
| | 1 | 1 (0,89) |
| **Nephrocalcinosis** | 0 | 111 (99,11) |
| | 1 | 1 (0,89) |

Dichotomous variables (Yes= 1 and No= 0 for the other variables). For the Color variable (1: White, 2: Yellow, 3: Brown and 4: Black). For the education variable (0: no education, 1: elementary school, 2: high school, 3: higher education, 4: graduate). SAH: systemic arterial hypertension; DM: Diabetes Mellitus; CRF: Chronic renal failure)

We did not find any patient in the research using lithogenic medication or with anatomical alterations in the urinary tract.

Among the metabolic alterations, the following stand out: 77.68% low urinary volume, 40.18% hypercalciuria, 33.04% hyperphosphaturia, 39.29% hypocitraturia, 33.04% hyperuricosuria, 23.21% hyperoxaluria, 47.32% altered parathyroid hormone, 36.61% urinary tract infection and 0.89% cystinuria, as shown in Figure 1.

**Figure 1**. Metabolic alterations found in patients selected at the Urology Outpatient Clinic of the Regional Hospital in Presidente Prudente, from September 2019 to October 2020.




Y=1947 + 0,1094 X (Y= valor do teste. X= valor do p)

When analyzing the association between each predictor and the event of lithiasis, Table 3 identified that the predictors male gender (p=0.02; OR=2.10), BMI (p=0.00; OR=3.50), alcohol consumption (p=0.001; OR=3.09), SAH (p=0.007; OR=1.53), DM (p=0.003; OR=4.99), dyslipidemia (p=0.002; OR=2, 84) and altered parathyroid hormone (p=0.006; OR=1.69) represented, in this cohort of patients, a strong probability of contributing to the event of lithiasis.

**Table 3**. Binary logistic regression analysis was conducted to identify and quantify the association between each predictor of overall patient data with the lithiasis event.

| Predictors | Reference (Lithiasis) | Chi-Square | p-value | Odds Ratio | 95% CI |
|---|---|---|---|---|---|
| Age | 1 | 3,81 | 0,051 | 1,0564 | (0,9962; 1,1203) |
| Gender (M=1; F=2) | 1 | 7,77 | 0,02* | 2,1009 | (0,3919; 11,2638) |
| Race | 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/m$^2$) | 1 | 26,34 | 0,000* | 3,5010 | (0,3034; 0,6678) |
| Smoker | 1 | 0,01 | 0,905 | 1,1168 | (0,1808; 6,9005) |
| Alcoholic | 1 | 6,25 | 0,001* | 3,0957 | (0,0354; 270,6598) |
| SAH | 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 parathormonium | 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) |

* Significance level: p<0.05

The main correlations and odds ratios of the variables BMI, DM and staghorn stone with metabolic alterations were between hypercalciuria and altered BMI (p=0.001; OR=3.28), hypocitraturia and staghorn stones (p=0.003; OR=2.21), hyperuricosuria and altered BMI (p=0.017; OR=2.01), hyperoxaluria and altered BMI (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), alteration of parathyroid hormone and altered BMI (p=0.008; OR=2.69) and hyperphosphaturia and altered BMI (p=0.021; OR=1.99 ), as shown in Table 4.

**Table 4.** Correlation and odds ratio of the variables BMI, DM and Staghorn Calculi with metabolic alterations.

| Variable / references | Hypercalciuria | Chi-Square | p-value | Odds Ratio (OR) | 95% CI |
|---|---|---|---|---|---|
| Bmi (kg/m$^2$) (1; 2; 3)* | 2 and 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 calculi | 1 | | | | |
| | | 0,00 | 0,975 | 1,0177 | (0,3424; 3,0244) |
| | Hypocitraturia | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 1 ,2 and 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 calculi | 1 | 2,06 | 0,003* | 2,2176 | (0,7422; 6,6257) |
| | Hyperuricosuria | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 2 and 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 calculi | 1 | 0,01 | 0,910 | 1,0654 | (0,3561; 3,1880) |
| | Low Urinary Volume | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 1, 2 and 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 calculi | 1 | 0,05 | 0,825 | 0,8738 | (0,2653; 2,8775) |
| | Hyperoxaluria | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 2 and 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 calculi | 1 | 1,08 | 0,300 | 0,5273 | (0,1529; 1,8180) |
| | Urinary Infection | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 1, 2 and 3 | 0,30 | 0,582 | 0,8559 | (0,4912; 1,4915) |

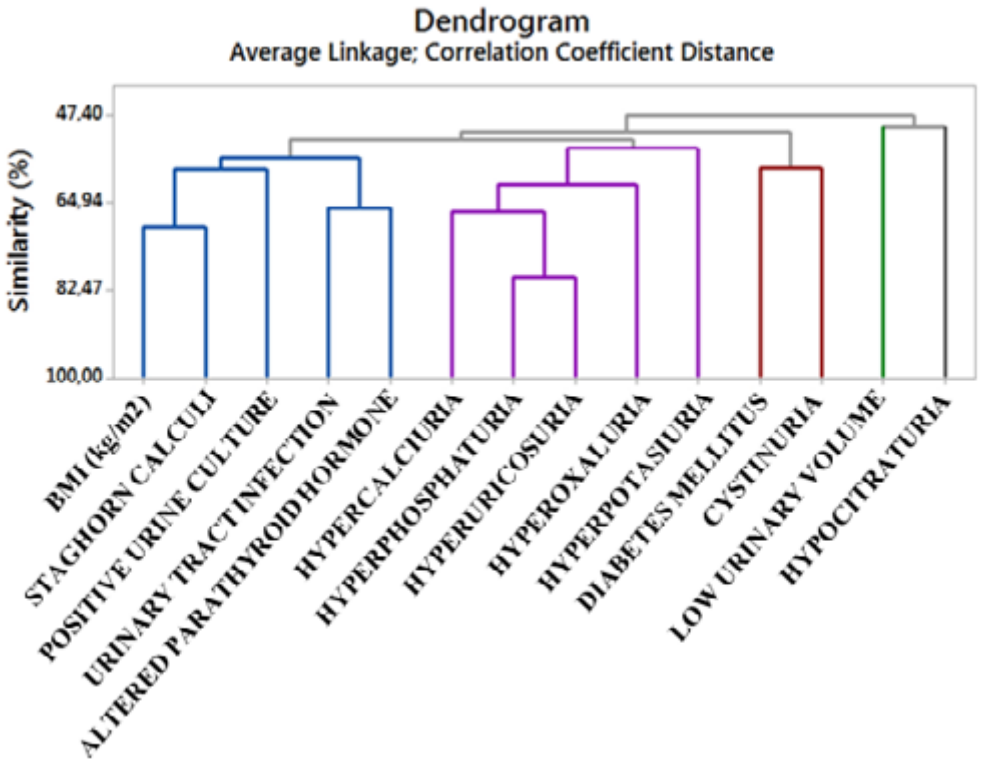
| | | | | | |
|---|---|---|---|---|---|
| Diabetes mellitus | 1 | 1,41 | 0,005* | 1,7397 | (0,6974; 4,3399) |
| Staghorn calculi | 1 | 1,04 | 0,003* | 1,7789 | (0,5873; 5,3875) |
| | Cystinuria | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 3 | 0,20 | 0,632 | 0,9559 | (0,5312; 1,5915) |
| Diabetes mellitus | 1 | 1,51 | 0,335 | 1,1457 | (0,5974; 5,3399) |
| Staghorn calculi | 1 | 1,34 | 0,408 | 1,2413 | (0,5462; 5,4683) |
| | Alteration in Parathyroid Hormone | | | | |
| Bmi (kg/m$^2$) (1;2;3)* | 2 and 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 calculi | 1 | 0,16 | 0,686 | 1,2517 | (0,4206; 3,7248) |
| | Hyperphosphaturia | | | | |
| Bmi (kg/m$^2$) (1;2;3)** | 2 and 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 calculi | 1 | 0,38 | 0,535 | 1,4128 | (0,4750; 4,2021) |

**BMI 14.1 to 24.9 =1 (normal); BMI from 25 to 29.9 =2 (overweight); BMI ≥ 30 =3(obese).

* Significance level: $p<0.05$

It can be inferred from the graph that staghorn calculi correlates 70% with altered BMI, urinary tract infection correlates 64.94% with altered parathyroid hormone, hypercalciuria correlates around 50% with altered BMI and staghorn calculi, and around 47% with DM, as shown by the similarity dendrogram (Figure 2).

**Figure 2**. Multivariate analysis of metabolic alterations, BMI, DM, staghorn calculi and low urinary volume in patients with lithiasis in the present study.




## DISCUSSION

Nephrolithiasis is an important public health problem that affects a large part of the economically active population, overcrowding emergency rooms, increasing absenteeism rates at work, not to mention the exorbitant expenses related to diagnosis and treatment. In this scenario, the definition of a strategy for ideal metabolic assessment is deficient. Thus, the present study sought to contribute to a better understanding of the incidence and prevalence of nephrolithiasis, in order to elucidate the main characteristics of the patient considered at high risk for the formation of nephrolithiasis, in order to better direct the prevention of this disease[13].

Nephrolithiasis preferentially affects the male population, in a ratio of 3:1[14]. In our research, the proportion of women with nephrolithiasis is equivalent to that of men, which can be attributed to changes in women's eating habits and lifestyle, leading to increased BMI and obesity[15]. Data from the 2021 VIGITEL Brasil survey reveal that almost 6 out of 10 Brazilians are overweight, with a higher percentage among men (59.9%) than women (55%). Regarding obesity, the percentage of women (22.6%) was higher than that of men (22%)[16].

We detected that the average age of the studied patients was 46.76 years and the predominance of the Caucasian race is close to the data in the literature[17].

Several studies demonstrate that the most frequent metabolic alterations are low urinary volume, hypercalciuria, hyperphosphaturia, hypocitraturia, hyperuricosuria, hyperoxaluria, similar to the results of the present study[18-20]. We believe that dehydration due to the hot climate in our region and the low fluid intake, associated with a high-protein and high-sodium diet, lead to such metabolic disturbances and contribute to the formation of stones.

Several scientific works show significant evidence that insulin resistance impairs the renal acidification process, decreasing urinary pH and citrate excretion, predisposing to urinary supersaturation of uric acid and calcium oxalate[21-23]. This corroborates the finding of the present study that DM and dyslipidemia are highly likely to contribute to the lithiasis event, and are also some of the main factors for the occurrence of the metabolic syndrome, which is based on resistance to insulin action and is associated with a greater number of cardiovascular events and the formation of kidney stones.

According to the results represented by the dendrogram, it can be inferred that all variables and metabolic alterations are somehow correlated, with different levels of similarity, corroborating the complex process of formation of nephrolithiasis[23].

In addition, this study showed important correlations and probability ratios, highlighting urinary infection and staghorn calculus, hypocitraturia and staghorn calculus, explained by the fact that staghorn calculi are considered infection calculi, due to the presence of colonizing bacteria in the urine that produce urease, which increases the urinary concentration of ammonia, raising the urinary pH and by their consumption of urinary citrate[24]. The correlations between hypercalciuria, hyperuricosuria, hyperoxaluria, hyperphosphaturia and altered BMI, in addition to urinary tract infection and DM, are strongly elucidated in the world literature due to the influence of the acid load of obesity and DM that lead to the metabolic alterations of nephrolithiasis[22,23].

In this sense, there is an association between uric acid stones (UA) and insulin resistance, DM and obesity. 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[25].

More than half (66.07%) of the patients had a family history of nephrolithiasis, where genetic factors must be considered in the etiological diagnosis, in addition to dietary habits and behavior. A retrospective study between 2008 and 2018 with 60 patients determined the clinical and metabolic characteristics and the evolution of hereditary urolithiasis. There were 31 cases of cystinuria, 18 cases of type 1 primary hyperoxaluria and 11 cases of renal tubulopathy. Fourteen patients were affected with chronic renal failure, of which five were in end-stage renal disease. Thus, cystinuria was the most frequent etiology and primary hyperoxaluria the most serious condition[26].

Only five research patients had some type of inflammatory bowel disease. A systematic review study analyzed the relationship between urinary stones and intestinal diseases. Fifty-three articles were selected. Three types of urolithiasis are mainly involved in digestive pathologies such as calcium oxalate, uric acid and ammonium urate stones. The intestinal patho-

logies responsible for stones are divided into diseases of the small intestine, lesions of the colon 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 may be responsible for urolithiasis[27].

Based on this scenario of metabolic changes and lithiasis, a 2014 guideline gathered the main scientific evidence to evaluate the ideal strategy for evaluation and treatment of metabolic stones and to prevent recurrent urinary stones[28]. Reliable stone analysis and basic metabolic assessment are highly recommended in all patients after stone passage. Each patient should be assigned to either a low or high risk group for stone formation.

Finally, recurrent stone formers should undergo metabolic evaluation and chemical analysis of the stone. Current evidence proposes different approaches based on the metabolic disorder diagnosed. Diet can play a detrimental role in preventing recurrences. Prevention advice includes increasing the intake of fluids, vegetables and fruits, but decreasing the consumption of sugar, salt and animal protein[29].

The COVID-19 pandemic directly influenced the adherence of patients to the study, making it difficult both to perform the tests and to return to the outpatient clinic, which is a limitation for increasing the sample size. Although the sample was small, the study brought contributions to the scientific community with the knowledge of the predominant metabolic alterations in patients with nephrolithiasis, in order to direct disease prevention measures.

## CONCLUSION

Among the characteristics of the patient at high risk of developing nephrolithiasis, the present study showed that the metabolic syndrome such as obesity, SAH, DM, dyslipidemia, is an important triggers of metabolic changes, and consequently, of nephrolithiasis. In addition, this study made it possible to know how many times each predictor can influence these metabolic changes, thus representing important targets for the development of strategies aimed at preventing nephrolithiasis.

## REFERENCES


1 Sakhaee K. Epidemiology and clinical pathophysiology of uric acid kidney stones. J Nephrol; 27: 241–245,2014.

2 Carpentier X, Chabannes E, Traxer O. Update for the management of kidney stones in 2013. Prog Urol.;24(5):319-26,2014.

3 Scholz D, Schwille PO, Ulbrich D. Composition of renal stones and their frequency in a stone clinic: relationship to parameters of mineral metabolism in serum and urine. Urol Res; 7:161–170,1979.

4 Daudon M, Lacour B, Jungers P. High prevalence of uric acid calculi in diabetic stone formers. Nephrol Dial Transplant;20: 468–469, 2005.

5 Pak CYC, Preminger GM, Ekeruo W. Biochemical profile of stoneforming patients with diabetes mellitus. Urology; 61:523–527, 2003.

6 Della GL, Roggi C, Cena H. Diet-induced acidosis and alkali supplementation. Int J Food Sci Nutr.;67(7):754-61, 2016.

7 Arrabal-Martín M, Domínguez-Amillo A, Cózar-Olmo JM. Factores etiopatogénicos de los diferentes tipos de urolitiasis. Arch Esp Urol.;70(1):40-50, 2017.

8 Daudon M, Frochot V, Jungers P. Drug-Induced Kidney Stones and Crystalline Nephropathy: Pathophysiology, Prevention and Treatment. Drugs;78(2):163-201, 2018.

9 Bianchi L, Cortegoso VP, Ruberto C. Renal

lithiasis and inflammatory bowel diseases, an update on pediatric population. Acta Biomed; 17;89(9-S):76-80, 2018.
10 Treviño-Becerra A. Uric Acid: The Unknown Uremic Toxin. Contrib Nephrol.; 192:25-33, 2018.
11 Lancina Martín JA. Estudio metabólico. Cómo hacerlo accesible, útil y generalizado. Arch Esp Urol.; 70 (1): 71-90, 2017.
12 Minitab®, Quality. Analysis. Results and the Minitab logo are registered trademarks of Minitab, Inc., in the United States and other countries. Additional trademarks of Minitab Inc. can be found at www.minitab.com. All other marks referenced remain the property of their respective owners.
13 Korkes, F, Da Silva JL, Heilberg, Ita P. Custo do tratamento hospitalar da litíase urinária para o Sistema Único de Saúde brasileiro. Einstein. 9 (1): 518-22, 2011.
14 Wang S, Zhang Y, Zhang X, Tang Y, Li J. Upper urinary tract stone compositions: the role of age and gender. Int. braz j urol., v. 46, n. 1, p. 70-80,2020.
15 Wanderley EM, Ferreira VA. Obesidade: uma perspectiva plural. Ciênc. saúde coletiva, v. 15, n. 1, p. 185-194,2010.
16 Vigitel Brasil 2021 : surveillance of risk and protective factors for chronic diseases by telephone survey : estimates on the frequency and sociodemographic distribution of risk and protective factors for chronic diseases in the capitals of the 26 Brazilian states and in the Federal District in 2021 / Ministry of Health , Secretariat of Health Surveillance, Department of Health Analysis and Surveillance of Noncommunicable Diseases. – Brasilia: Ministry of Health, 2021.
17 Hsi RS, Kabagambe EK, Shu X. Race- and Sex-related Differences in Nephrolithiasis Risk Among Blacks and Whites in the Southern Community Cohort Study. Urology.;118:36-42, 2018.
18 García Nieto VM, Perez Suarez G, Moraleda Mesa T. The idiopathic hypercalciuria reviewed. Metabolic abnormality or disease? Nefrologia. 39 (6):592-602, 2019.
19 Zhang GN, Ouyang JM, Shang YF. Property changes of urinary nanocrystallites and urine of uric acid stone formers after taking potassium citrate. Mater Sci Eng C Mater Biol Appl.;33(7): 4039-45, 2013.
20 Li X, Li B, Yang L. Treatment of recurrent renal transplant lithiasis: analysis of our experience and review of the relevant literature. BMC Nephrol.; 23;21(1): 238, 2020.
21 Cupisti A, D'Alessandro C. Características metabólicas e dietéticas em formadores de cálculos renais: uma abordagem nutricional. Braz. J. Nephrol., v. 42, n. 3, p. 271-272, 2020.
22 Arrabal-Polo MA, Arrabal-Martin M, Garrido--Gomez J. Calcium renal lithiasis: metabolic diagnosis and medical treatment. Sao Paulo Med J.;131(1):46-53,2013.
23 Letendre J, Cloutier J, Valiquette L. Metabolic evaluation of urinary lithiasis: what urologists should know and do. World J Urol.;33(2):171-8, 2015.
24 Schwaderer AL, Wolfe AJ. The association between bacteria and urinary stones. Ann Transl Med.;5(2):32,2017.
25 Pazos PF. Uric Acid Renal Lithiasis: New Concepts. Contrib Nephrol.; 192:116-124, 2018.
26 Kaaroud H, Goucha R, Ben Abdallah T. Lithiase urinaire héréditaire: expérience d'un service de néphrologie. Prog Urol;29(16):962-973, 2019.
27 Pradere B, Le Balc'h É, Bensalah K. Lithiases urinaires et pathologies digestives: une revue de la littérature. Prog Urol; 25(10): 557-64, 2015.
28 Skolarikos A, Seitz C, Türk C. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol.; 67(4): 750-63, 2015.
29 Kotsiris D, Adamou K, Kallidonis P. Diet and stone formation: a brief review of the literature. Curr Opin Urol.;28(5): 408-413, 2018.

**Corresponding Author:**
Renata Calciolari Rossi.
renatacalciolari@terra.com.br

Received: oct 26, 2022
Approved: sep 15, 2023
Editor: Prof. Dr. Felipe Villela Gomes