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PATHOPHYSIOLOGY AND TREATMENT OF NEPHROLITHIASIS

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Abstract: Kidney diseases are among the most important causes of death and disability in many countries around the world. Among these diseases, nephrolithiasis stands out. Nephrolithiasis is a medical condition that affects the kidneys or urinary tract, characterized by the concentration of different mineral salts combined with an organic matrix that crystallizes in the upper urinary tract. The formation of kidney stones can be derived from various substances, such as calcium oxalate, calcium phosphate and uric acid. Considered a multifactorial disease, the factors that predispose people to the formation of kidney stones can be genetic, metabolic and environmental. It is now recognized that nephrolithiasis is a marker of systemic alterations and a predictor of metabolic and cardiovascular complications. This condition is responsible for intense cramps, unbearable pain, at first accompanied by nausea and emesis, and can cause obstruction of the urinary tract, leading to renal failure and, consequently, death. Over the decades, nephrolithiasis has become more common, occurring in around 6% to 15% of the Western population, affecting mostly men. The aim of this article is to analyze, through a literature review, the pathophysiology and treatment of nephrolithiasis, since, despite its relevance, it remains a complex disease with a significant impact.
Keywords: nephrolithiasis, kidney stones, pathophysiology, treatment

METHODOLOGY

This is a descriptive bibliographic study. The bibliographic search was carried out on November 28, 2024, comprising the following databases: SciELO, PubMed, BVS and Google Scholar, using a quantitative and qualitative data analysis. The data collected in this study met the following inclusion criteria: original articles published in Portuguese, English and Spanish between 2000 and 2024, which dis-

cussed the pathophysiology and treatment of nephrolithiasis. The exclusion criteria were: thesis articles, case reports that did not deal with specific relationships related to the topic.

DISCUSSION

Nephrolithiasis is a medical condition characterized by concretions of different mineral salts mixed with an organic matrix that form in the upper urinary tract [1] . As a stone moves from the kidney into the ureter, it can present with symptoms of renal colic and can cause urinary tract obstruction and/or infection [1] , people who have a sedentary lifestyle, unbalanced diet, poor fluid balance and genetic predisposition face a higher risk of developing the disease [5] . Most kidney stones are composed of calcium (calcium oxalate and/or calcium phosphate), either pure or in combination with uric acid. The most frequent kidney stones are those derived from calcium oxalate, which can be caused by hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and/or low urine volume 6. Idiopathic hypercalciuria (IH), the main cause of kidney stones without a proven metabolic cause, occurs due to an increase in the concentration of calcium in the urine, resulting from low renal retention of calcium and greater excretion of this element in the urine, which results in high urinary excretion of calcium, which consequently favors urinary salt saturation, crystallization of calcium urine and the formation of phosphate oxalate stones [7 8].

Hyperoxaluria is the formation of kidney stones based on the excessive formation or absorption of oxalate, a substance that cannot be processed by mammals and is excreted in the urine [9] . Depending on its etiology, it can manifest clinically in two ways: primary (rare) and secondary (common)[10] . The formation of oxalate occurs in three distinct phases, each of which is interconnected with each type of primary hyperoxaluria.

Primary hyperoxaluria is an autosomal recessive metabolic disease that disturbs body homeostasis through the excessive synthesis of calcium oxalate. In contrast, secondary hyperoxaluria is caused by excessive intake of oxalate-rich foods. Primary hyperoxaluria can be divided into types I, II and III. Type I is due to a vitamin B6 deficiency related to the AGXT mutation present on chromosome 2[10], of the enzyme alanine glyoxylate aminotransferase (AGT), which catalyzes, in the peroxisome within the liver parenchyma, the transformation of alanine and glyoxalate into pyruvate and glycine[Fig.1], leading to an increase in the concentration of glyoxalate inside the cells, which is transformed in the cytosol, by the enzyme lactate dehydrogenase (LDH), into oxalate, increasing the concentration of this compound in the tissues and can lead to renal insufficiency [11 12] [FIG 2].

Primary hyperoxaluria type ll is the result of a diet rich in oxalate or due to intestinal pathologies that increase oxalate absorption[9] . The development of primary hyperoxaluria type ll occurs due to the loss of functionality of the enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR), which increases the synthesis of glyoxylate due to a decrease in the processing of glycolate, producing, and under the influence of the enzyme lactate dehydrogenase (LDH), a higher concentration of oxalate.[11] (Fig. 3)

Primary hyperoxaluria type 3 is caused by a mutation in the gene that codes for the enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA1), which leads to the accumulation of 4-hydroxy--2-oxoglutarate (HOG), and it is not yet known how this results in excess oxalate in the body, but there are 2 existing theories. The first posits that HOG can be transformed directly into glyoxylate by cytosolic alkalosis (Fig. 4). The second theory postulates that a deficit in HOGA1 may lead to increased production of HOG and this compound inhibits glyoxylate reductase/

ELEMENT	END PRODUCT	CATALYZING ENZYME	LOCAL:
GLYOXYLATE L-ALANINE	GLYCINE PYRUVATE	ALANINE: GLYOXYLATE AMINOTRANSFERASE (AGT)	PEROXISOME HEPATOCYTES

Fig.1

ELEMENT	END PRODUCT	ENZYME:	LOCAL:
GLIOXYLATE	OXALATE	LACTATE DEHYDROGENASE (LDH)	CYTOSOL

Fig.2

ELEMENT	PRODUCT END	ENZYME	LOCAL
GLYCOLATE	GLIOXYLATE	LOSS OF FUNCTION OF ENZYME glyoxylate reductase/hydroxypyruvate reductase (GRHPR), LACTATE DEHYDROGENASE (LDH)	CYTOSOL

Fig. 3

ELEMENT	PRODUCT END	REACTION	ENZYME CHANGED	LOCAL
4- hydroxy-2-oxoglutarate(HOG)	Glyoxylate	Aldalose c+itosolic	4- hydroxy-2- oxoglutarate aldolase (HOGA1)	Mitochondria

Fig.4

ELEMENT	PRODUCT END	ENZYME CHANGED	INHIBITED ENZYME	LOCAL
GLIOXALATE	GLICOLATE	4- hydroxy-2- oxoglutarate aldolase (HOGA1)	glyoxylate reductase/hydroxypyruvate reductase (GRHPR	Mitochondria

Fig.5

hydroxypyruvate reductase (GRHPRR), which converts glyoxylate to glycolate (a substance less toxic to the body), if glyoxalate is not being properly metabolized, conversion to oxalate will be increased by lactate dehydrogenase (LDH), creating an imbalance in the metabolic pathway, since oxalate is toxic to the human body and can accumulate in parts of the body forming crystals. [11] [13] (Fig 5)

Hypocitraturia is a common condition in kidney stone formers, affecting around 60% to 90% of patients, characterized by urinary citrate excretion in adults of less than 320 mg (1.67 mmol) per day for adults [14] . Citrate plays an important role in preventing lithogenesis, as it helps when it binds to calcium phosphate or oxalate, increasing their solubility. The bond between citrate and calcium limits supersaturation, preventing the nucleation and subsequent aggregation of crystals [14] [15] .

Hyperuricosuria is a determining factor in the formation of calcium-derived stones, conceptualized as uric acid excretion greater than 800 mg/day in men and 750 mg/day in women[1] . There are three mechanisms by which uric acid can assist in the formation of calcium stones. Firstly, monosodium urates serve as a deposition site for calcium oxalate crystals, which creates a mixed calculus, a process known as heterogeneous nucleation. 2) Colloidal urate particles disintegrate natural inhibitors of calcium oxalate crystallization, causing them to group together more easily and form calcium oxalate stones. 3) The increase in urate concentration favors the precipitation of calcium oxalate, a concept known as Salting-Out [1].

URIC ACID STONES

Around 10% of nephrolithiasis is caused directly by the accumulation of uric acid crystals and the subsequent formation of kidney stones 16 . The main marker is aciduria (recurrently acidic urinary pH), but low urinary volume and hyperuricosuria (excessive urinary excretion of uric acid) are also valid signs[16 17] . This condition has congenital, acquired and idiopathic mechanisms [17] . Humans excrete uric acid by the final metabolization of purines into inosinic acid and hypoxanthine, which will be converted into xanthine and uric acid [16 18] . Persistently acidic urinary pH influences the solubility factor of urine, which is an important factor in knowing the solubility of uric acid, since it is a weak organic acid with an ionization constant of 5.5, so a urinary pH lower than 5.5 promotes the precipitation and crystallization of uric acid, forming calculi [18 19]. Urinary volume influences the formation of uric acid because reduced urinary production increases the concentration of uric acid, favoring uric acid precipitation and aggregation, forming kidney stones [18]. Hyperuricosuria is defined as uric acid excretion in women > 750 mg/day and in men > 800 mg/day [1 16] , hyperuricosuria favors supersaturation of the urine, because the concentration exceeds the solubility limit, uric acid precipitates and forms crystals, this situation is intensified when the urinary pH is persistently low because the acid becomes less soluble the lower the pH (<5.5). [16]

TREATMENT

It is essential to study the composition of kidney stones in order to determine the treatment method for each patient[1]. Current medicine is aware of a number of treatment methods for nephrolithiasis, the main ones being:

Non-pharmacological: Diet plays an important role in preventing the formation of kidney stones [20]. More industrialized countries have a diet with oxalate-rich foods such as figs, raspberries, dates, spinach, beans and beet. [1] Nutritional planning has a positive influence on the appearance of kidney stones. Fink et al (2009) proved that drinking more than 2 liters of water a day reduced the recurrence of kidney stones by 61% [21]

Pharmacological: Depending on the diameter and location, clinical expulsive therapy (TEC) can be used, the technique consists of analyzing the size of the distal stone, if they present a diameter of 5mm or less, the chance of spontaneous exit is between 50-70% , as the stones descend, renal colic, characterized by a pain with unexpected onset intense in the costovertebral angle lasting 15 to 45 minutes, Basically, it is a technique that consists of prescribing drugs to help expel the stones and improve colic with drugs that block ÿ1-adrenergic receptors or calcium channel blockers such as nifedipine to relax smooth muscle and facilitate the passage of stones through smooth muscle, reducing the need for more invasive therapies [23 and 24] .

Bergsland et al. (2013) [25] showed that in cases of hypercalciuria, thiazide diuretics are used to reduce calcium excretion in the urine, since their mechanism consists of maximizing calcium reabsorption in the distal nephrons and preventing stone recurrence [26]. There are more invasive procedures that are necessary when the stone does not regress using the methods mentioned above, one of which is extracorporeal shock wave lithotripsy (ESWL), which consists of degrading kidney stones by emitting shock waves that pass through the patient's body and fragment the kidney stones, which are eliminated during urination[22]. Another technique used is percutaneous nephrolithotripsy (PNL), which is recommended for stones measuring 2 cm that have not been degraded by LEOC, cystine stones, and stones associated with foreign bodies, where an imaging test such as radiography and ultrasound

of the urinary tract is carried out, anesthesia is administered and then the ureteral catheter is passed on the side homolateral to the kidney to be operated on, the patient is placed in dorsal decubitus for ascending pyelography, the best place to perform the pulsation is chosen and facial dilators are applied to perform the surgery [27 28].

CONCLUSION

The general aim of this article was to analyze the pathophysiology of nephrolithiasis and its treatment based on a review of the scientific literature. All the causes of nephrolithiasis and its treatment were comprehensively analyzed. Nephrolithiasis is a multifactorial disease, involving genetic, metabolic and environmental processes. Among the main results was that an intake of more than 2 liters reduces the recurrence of stones. With regard to diet, it was clear that a diet rich in oxalate-rich foods predisposes to the appearance of stones. With regard to genetics, it was clear that inheritance plays a fundamental role in the appearance of stones. In addition, the results of this research are significant in understanding the pathophysiological mechanism of each type of kidney stone-forming substance and consequently help in the clinical management and treatment of kidney stones formed by each element.

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