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Nephrolithiasis and Gastrointestinal Tract Diseases: Can Diet Intervention Help?

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Nephrolithiasis is a disease whose prevalence is continuously rising in Western countries. The most common type is idiopathic calcium nephrolithiasis (80%), but gastrointestinal disease, especially inflammatory bowel disease (IBD), may represent a significant risk factor. Nephrolithiasis is indeed a frequent long-term extraintestinal complication of IBD. Dietary habits have a direct effect on urinary lithogenic risk factors and on the onset of kidney stones. The main dietary features that can help preventing and treating nephrolithiasis are high fluid intake, high consumption of fruit and vegetables, low intake of salt and proteins and a balanced amount of calcium, lipids and carbohydrates. In this review we briefly describe epidemiologic and physiopathologic aspects of intestinal disease-associated nephrolithiasis and the role of diet in contrasting onset and relapses of kidney stones.

INTRODUCTION

Nephrolithiasis is a disease whose prevalence is continuously rising (10% of the population),[1] with a total cost in the United States of about 2 billion dollars/year for hospital stays.[2] In some cases it is the consequence of well-known hereditary or acquired diseases, such as cystinuria, primary hyperoxaluria, medullary sponge kidney, primary hyperparathyroidism, and also infections or anatomical malformations of kidneys or urinary tract. However, the most frequent type is idiopathic calcium nephrolithiasis (ICN). There are several types of kidney stones even if the most common (80%) are those containing calcium (calcium oxalate, calcium phosphate, mixed calcium-oxalate/calcium-phosphate). The pathogenesis of ICN encompasses both genetic and acquired factors, resulting in urinary biochemical abnormalities that lead to stone formation. Important risk factors for urinary stone formation are hypercalciuria, hyperoxaluria, hyperuricosuria, hyperphosphaturia, hypocitraturia, alkaline pH and low urine volume. Among these, hypercalciuria is the most frequent. The distribution among genders shows a slightly higher incidence in males [3] with two peaks of incidence (between the age of 20 and 30 and between 50 and 60).[4]

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Table 1. GI Diseases and Medications Associated with Nephrolithiasis

GI Diseases	Medications
• Crohn' s disease and Ulcerative Colitis	• Sulfasalazine and sulfapyridine
• Celiac disease	• Amoxicillin
• Small Intestinal Bacterial Overgrowth (SIBO)	• Ciprofloxacin
• Chronic diarrhoea	• Norfloxacin
• Intestinal blind loop syndrome	• Proteases inhibitors
• Intestinal resection	• Magnesium trisilicate
• Ileostomy	
• Jejuno-ileal by-pass	
• Biliary diversion or obstruction	
• Hepatic Cirrhosis	
• Chronic pancreatitis	
• Prolonged fasting	

A higher risk and incidence of kidney stones are well described in patients with concurrent gastrointestinal (GI) diseases, particularly in patients with malabsorption, enteric resections and inflammatory bowel disease (IBD).[5] In this paper we briefly review epidemiological and physiopathological features of GI disease-associated nephrolithiasis and the role of diet in contrasting onset and relapses of kidney stones.

NEPHROLITHIASIS AND GASTRO-INTESTINAL DISEASE

Epidemiology

An association between GI disease and kidney stones has been reported in many studies.[5] Diseases and medications that are more closely related to nephrolithiasis are listed in Table 1. There are also other associations, though indirect, such as some cases of peptic ulcer in Zollinger-Ellison syndrome, that may effectively be associated to a Multiple Endocrine Neoplasia Type 1 (MEN1) syndrome including hyperparathyroidism and nephrolithiasis.

The prevalence of GI disease-related nephrolithiasis has been studied, especially in patients with IBD, and varies from 4 to 34%. These percentages are twofold the ones of normal subjects with the same age and sex. The stone formation rate seems to be higher in patients with Crohn's disease than in patients with ulcerative colitis. Moreover, patients with an involvement of both ileus and colon have higher prevalence. Finally, patients who underwent an intestinal resection have even higher prevalence of nephrolithiasis (about 30%), particularly if an ileal resection was performed. To confirm for the role of abdominal surgery, it is interesting to point out that similar prevalence data were obtained also in obese subjects who underwent bariatric surgery (intestinal bypass).[6]

The most common type of nephrolithiasis in patients with gastroenteric disease is calcium nephrolithiasis, similarly to general population. However, up to 30% of these patients may form mixed calcium-uric acid stones. Uric acid stones are more frequent in patients who also underwent colectomy. The age of kidney stone onset varies between 30 and 50 and generally the peak of incidence follows the diagnosis of IBD by 6-12 years.

Etiopathogenesis

Diarrhea, malabsorption, steatorrhea, surgery and pharmacotherapy (particularly steroid drugs) play an important role in the onset of kidney stones during a

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gastroenteric disease. These occurrences may actually lead to: 1) loss of water, sodium, potassium, bicarbonate and magnesium; 2) lower citrate absorption; 3) increased oxalate absorption. Table 2 shows the prevalence of these factors related to the type of stone. Many studies have confirmed these pathogenetic hypotheses, showing significant differences between urine composition of IBD patients and controls as regards urinary factors of lithogenic risk.[5]

THE ROLE OF DIETARY HABITS IN PREVENTION AND TREATMENT OF NEPHROLITHIASIS

Diet plays an important role in kidney stone onset; some authors affirm that dietary changes in industrialized countries over the last decades may have substantially contributed to the rise of the prevalence of nephrolithiasis. The basis of an anti-lithogenic diet must be founded, as we explain below, on an adequate intake of water, proteins, salt, fruit and vegetables, milk and dairy products, carbohydrates, fats and vitamins. These aspects are particularly important in an intestinal disease setting, both for the dietary prescriptions gastroenterologists make in some disease stages (for example, low-fiber diets) and for some spontaneous habits of patients. Regarding the latter aspect, for instance, it has been demonstrated that IBD patients are prone to restricting their dietary intake thinking that certain foods can lead to symptom onset.[7]

Role of Water

With a diuresis < 1 L/day, even the urine of a normal subject reaches extremely high supersaturation levels; promoting spontaneous crystallization of the lithogenic salts.[8] On the other hand, if the volume is maintained > 2.5 L/day, the urine becomes undersaturated for calcium phosphate and uric acid and only slightly supersaturated for calcium oxalate, making spontaneous crystallization impossible.[9,10] The rise in urinary volume, moreover, does not modify the activity of lithogenesis inhibitors. The ability of crystal aggregation after an oxalate load is lower in diluted urine than in concentrated urine.[11,12]Even if for many years the only advice given to patients with nephrolithiasis was to raise their water intake, there is only one randomized controlled study that addressed this practice. It demonstrated a significant reduction in relapse rate and a prolongation of the relapse interval in patients whose urinary volume was constantly > 2 liters/day.[13,14] However, big epidemiologic studies have stated that a high urinary volume is an effective measure for prevention in general population, able to diminish the risk by 29-39%.[15-17]

Table 2. Physiopathological Factors for Nephrolithiasis in GI Diseases

Type of Stone	Physiopathological factors
Calcium oxalate & Calcium phosphate	Low urine volume
	Low urine pH
	Hyperoxaluria
	Hypocitraturia
	Hyperoxaluria
	Hypercalciuria (steroid use)
Uric acid	Low urine volume
	Mild metabolic acidosis due to bicarbonate loss
	Sodium and potassium loss
	Low urine pH
Any	Urinary tract infections
	Bowel obstruction

Role of Other Beverages

There is no full consensus in the literature on the role of hydration with other beverages. Most studies have actually evaluated a surrogate end-point (i.e. urinary lithogenic risk factors) and there are very few data from epidemiologic studies evaluating the impact on the onset or relapse of kidney stones.[18]

We can generically say that some beverages have a positive effect as they make pH and/or citrate and/or volume rise, such as juices, lemonade, coffee, green tea, beer and wine. A beverage that is particularly useful in infectious nephrolithiasis is cranberry juice, also for its acidifying ability.[19] On the other hand, there are some beverages that raise the oxalate intake, such as tea, or act as pro-lithogenic factors with a not fully understood mechanism, such as grapefruit juice, apple juice, cola. To this end, for their diffusion, we must cite soft drinks: recent studies have identified a higher risk of stones, probably because of their content in fructose, sucrose and phosphoric acid.[20-23] Sport and

Table 3. Dietary Considerations in Patients with GI Disease Associated Nephrolithiasis

1. Correct sodium, potassium and magnesium losses
2. Maintain urinary volume over 2 liters/day
3. Do not excess 3-4 serving per week of red meat and poultry
4. Eat at least 40 grams per day of vegetable proteins
5. Eat fruit and vegetables every day avoiding those rich in oxalate
6. Consume milk and dairy products to target a 1000 mg/day calcium intake
7. Follow guidelines for carbohydrate intake
8. Consume fresh or frozen foods avoiding parboiled or preserved foods
9. Limit saturated fatty acid intake, substituting long-chain triglycerides with middle-chain triglycerides
10. Evaluate pyridoxine (vitamin B6) status and consider supplementing if deemed deficient

energy drinks deserve a separate discussion. There are only few data in literature, often contradictory.[24, 25] These beverages, especially the ones with a higher content of sodium, carbohydrates and caffeine, may raise the risk of nephrolithiasis. However, more studies are needed.

Role of Proteins

The results of big epidemiologic studies are conflicting: while in a large cohort of healthy males a protein intake higher than 76 g/day lead to a 33% increase in risk,[15] in NHS-II study, (about 100,000 healthy women), a daily protein intake higher than 78 g lead to a 16% risk reduction. The effect of animal proteins is different from those of vegetable proteins. The prevalence of nephrolithiasis in vegetarians is half than in general population.[26] There are two randomized controlled trials that addressed the effects of a low-protein diet with a long follow-up: the first[27] studied 99 stone formers for 4 years, randomized to receive only water therapy or low-protein, high-fibre diet. The relapse rate was surprisingly higher in the latter group than in controls. Nevertheless, this study presents some biases, such as a higher fluid intake in the control group, a scarce compliance to the low-protein diet and some differences in the calcium and fiber intake in the two groups. The second study,[28] by our research group, followed 120 patients for 5 years. They were randomized to receive a low-calcium diet or a low-protein low-salt normal-calcium diet; in the latter group the relapse rate was significantly lower (40% vs. 20%); however, in this study it is not possible to distinguish the protective effect of reduction of protein intake from the rise in calcium or the reduction in sodium intake.

Role of Salt

In literature there are contrasting data about the role of salt in nephrolithiasis. However, a direct relation between calciuria and sodiuria has been demonstrated and there is also a summation effect with proteins. We ourselves demonstrated that a mildly low-salt diet might correct hypercalciuria in hypercalciuric idiopathic calcium stone formers.[30] On the other side, the same salt reduction can normalize urinary oxalate excretion in patients with mild hyperoxaluria.[31]

Role of Fruit and Vegetables

Fruit and vegetables may exhibit an antilithogenic activity. The beneficial effects are linked to the particular physical, chemical and nutritional features. Fruit and vegetables in fact show a high water, potassium and magnesium content, a low content in sodium chloride and proteins and a high alkalinizing power due to the presence of citrate and bicarbonate. It has been well demonstrated that a high intake of potassium and magnesium may lower the risk of nephrolithiasis by 50%.[16,17]

We ourselves demonstrated in 2004 that fruit and vegetable deprivation causes a significant

Table 4. Rationale for Dietary Considerations in GI Disease Associated Nephrolithiasis

Intervention	Rationale
Adequate hydration	• Lowers urinary concentration of calcium, oxalate and uric acid, leading to a lower supersaturation of calcium oxalate, calcium phosphate and uric acid • Raises the urinary tolerance to an oxalate load • Lowers the urinary concentration of inhibitory molecules without affecting their inhibitory effect • Raises the clearance of crystals and post-ESWL stone fragments
Limit animal protein	An excess of proteins may cause: • Hypercalciuria through a rise in the calcium intestinal absorption, a rise in the skeletal calcium mobilization and a decrease in renal tubular calcium reabsorption • Hyperoxaluria through a rise in intestinal oxalate absorption and endogenous oxalate production • Hyperuricosuria for a rise in the dietary supply and in endogenous production of purine • Hypocitraturia and pH drop for the increased load of fixed acids
Limit salt consumption	An excess in salt intake may cause: • Hypercalciuria through a reduction of calcium tubular reabsorption both with a direct mechanism and in an indirect way, through extracellular volume expansion, mobilization of bone calcium and increase in intestinal calcium absorption • Hypocitraturia for cellular potassium depletion and rise of acid load (32-33).
Increase fruit & vegetable intake	Urinary deficit of alkaline potassium, magnesium and fiber may cause: • Hypercalciuria for reduction in tubular calcium reabsorption, excessive free intestinal calcium and bone calcium mobilization • Hypocitraturia for intracellular calcium depletion with a consequent mild intracellular acidosis • Strengthening of the tendency of calcium oxalate towards crystallization due to magnesium depletion with resulting hypomagnesiuria
Maintain normal calcium intake (1000-1200 mg/day)	Low dietary calcium intake may cause: • A lower calciuria because the intestinal absorption is lower • It may also cause a rise in calciuria for bone calcium loss • Finally, the lower calcium concentration in distal intestine causes a rise in oxalate which is free for absorption, and therefore hyperoxaluria

reduction in citraturia and a rise in calciuria, while the supplementation with fruit and vegetables in hypocitraturic stone formers can correct the deficit.[34] Two big cohort studies have recently confirmed this experimental evidence.[35,36] Taylor and colleagues have studied the dietary habits of almost 240,000 subjects enrolled in three large cohorts: Health Professionals

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Follow Up Study, NHS-I and NHS-II. These authors have defined a Dietary Approaches to Stop Hypertension (DASH) score based on eight components: high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and low-intake of sodium, sweetened beverages, and red and processed meats. Over a combined 50 years of follow up they documented that higher DASH scores were associated with a marked decrease in kidney stone risk.

In a 2010 paper, Taylor and co-workers found that a DASH-style diet was associated with an increased urinary output, independent of fluid intake. They speculated that higher urinary volumes were a result of the higher food water content and they reported that a high dietary intake of fruits and vegetables was linked to increased urinary citrate levels and raised urine pH.

Role of Milk and Dairy Products

It is well known that calcium intake causes an 8% rise in calciuria in controls and a 20% rise in stone formers .[37] However, a dietary calcium restriction is not advisable in stone formers because a low calcium intake increases oxalate intestinal absorption and oxaluria rise. Finally, imposing a reduction of milk and dairy product intake may lead patients to raise their protein intake.[38,39] Curhan and colleagues in the NHS-II study database evaluated almost 100,000 healthy women and documented a 35% reduction in risk of nephrolithiasis if the calcium intake was higher than 1098 mg/day. In our study cited above, we showed that the relapse rate was significantly lower in patients on a normal-calcium low-protein low-salt diet than in patients that were only on a low-calcium diet, both in high-risk and low-risk calcium stone formers.

Role of Carbohydrates, Fats, and Vitamins

It is well known that a glucose load leads to a rise in urinary calcium and the size of this rise is higher in stone formers and in their relatives than in healthy controls.[40]

The intake of simple carbohydrates has been linked to a rise in nephrolithiasis risk in women but not in men. It is possible that insulin plays a role in tubular calcium reabsorption. Insulin resistance, metabolic syndrome and type 2 diabetes have been associated to kidney stones, particularly from uric acid. Insulin resistance may cause a decrease in pH with concurrent citrate reduction and uric acid crystal precipitation. An optimal glycemic control in diabetic subjects may actually lead to a calciuria reduction.

A relationship between lipid intake and nephrolithiasis has also been suggested. Steatorrhea in chronic pancreatitis is linked to a high oxaluria. On the other hand, a good intake of fish oil, omega-3 fatty acids, may lower calciuria and oxaluria,[41-44] There are also some vitamins which have been suggested to be involved in lithogenic risk, such as vitamin D, vitamin C, vitamin B6 and vitamin A. It has been demonstrated that some subjects with idiopathic hypercalciuria show high levels of 25-hydroxy-vitamin D in blood with an increase in intestinal calcium absorption. However, epidemiologic studies with a long follow-up have not shown an association between intake of vitamin D and lithogenic risk; in Western countries a deficit of vitamin D is actually more common, due to the short time spent in the open air.[45-49]

In last decades vitamin C supplementation has become a widespread practice in Western countries. Ascorbic acid is indeed an oxalate precursor; therefore an excessive intake should be banned in nephrolithiasis (a dose up to 1500 mg/day is however considered safe).

Vitamin B6 plays a role in oxalate metabolism and its deficit may cause a rise in endogenous oxalate production. Its pharmacological and dietary supplementation may be considered in the treatment of hyperoxaluria.[47,48]

CONCLUSION

The interconnections between diet, nephrolithiasis and GI disease are complex. Nephrolithiasis may certainly be a severe complication and the clinician should educate patients to adhere not only to medical prescriptions but also to a safe lifestyle. A balanced antilithogenic diet may lead to a reduction of kidney stone onset and relapse. See Table 3 and 4 for dietary considerations and rationale respectively in patients with nephrolithiasis. ■

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