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Urinary Tract Stone Disease

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Preface

The surgical management of urinary stone disease has advanced quite dramatically since the introduction of shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), ureteroscopy (URS), and more recently retrograde intrarenal surgery (RIRS) with small, flexible fiber-optic ureteroscopes. As a result, "cutting for stones" has become a rare procedure. These minimally invasive techniques are now used in the pediatric population as well with great safety and success.

In the practice of medicine, it is far more important to prevent a disease than try to treat it once the symptoms have manifested. In this respect, our understanding on how stones form has also advanced significantly, particularly in the last decade. It is also being recognized that while it is possible to remove the stones with minimal morbidity, it is far better and more economical if stones can be prevented.

Given such advances, there is the need for a "text book" that brings together all aspects of urinary stone disease, and we have been fortunate to be able to recruit experts and opinion leaders from 15 countries across the globe to contribute. The book consists of 60 chapters divided into nine sections. The first three sections are devoted to basic sciences on subjects ranging from epidemiology of urinary calculi to shock wave physics. The fourth section deals with diagnostic, laboratory, and research methods in the diagnosis and investigation of stones. Stone disease in children is dealt with in Chap. 5 followed by three sections on surgical management of stones. Finally there is an entire section on medical management of stones. Most of the chapters are highly illustrated with diagrams, photographs, and X-rays.

We believe that this is the most comprehensive reference book on urinary stones currently available. In a work of this nature, there is bound to be some overlap between some of the chapters. However, this only enhances the information provided rather than being repetitive. We hope that this book would be of value and interest to urological surgeons, physicians with an interest in urolithiasis, scientists with a research interest as well as other health care professionals dealing with stones.

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Part X Medical Management

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Part
Basic Sciences

Epidemiology

1

Gary C. Curham

Abstract Substantial progress has been made in our understanding of the epidemiology of nephrolithiasis. Epidemiologic studies have quantified the burden of this common and painful condition, and they have expanded our understanding of risk factors for stone disease. A variety of dietary, non-dietary, and urinary risk factors contribute to the risk of stone formation, and the importance of these varies by age, sex, and body mass index (BMI). Scientifically, results from these studies have forced a reappraisal of our view of risk factors for stone disease. Importantly, the results from epidemiologic studies can be considered in the clinical setting when devising treatment plans for reducing the likelihood of stone formation.

1.1 Introduction

Nephrolithiasis is a common and complex disorder. Epidemiologic studies have quantified the burden of disease and have identified a variety of risk factors, which may help improve our understanding of the pathophysiology as well as lead to new approaches to reduce the risk of stone formation.

1.2 Prevalence

The prevalence of nephrolithiasis – defined as a history of stone disease – varies by age, sex, race, and geography. The prevalence increases with age, and the lifetime risk of stone formation in the USA exceeds 12% in men and 6% in women.[1,2] The prevalence appeared to be increasing in the last quarter of the twentieth century for men and women, whether black or white[2] (see Figs. 1.1 and 1.2). A history of stone disease in the USA is most common among older white males (~12%) and lowest in younger black females (~1%); frequencies for Asians and Hispanics fall in between.[2,3] Increased detection of asymptomatic stones resulting from the increasing use and sensitivity of radiologic studies may explain, in part, the rise in prevalence.

Few population-based studies of the prevalence of nephrolithiasis have been conducted outside of the USA. Prevalence of stone disease has increased in Japan[4] and Germany.[5]

A study of more than one million individuals found geographic variability with a north–south and west–east gradient; the highest prevalence of self-reported nephrolithiasis was in the Southeastern USA.[6]

A decrease in the male-to-female ratio was suggested by a recent study of hospital discharges.[7] Data from the Nationwide Inpatient Survey between 1997 and 2002 found

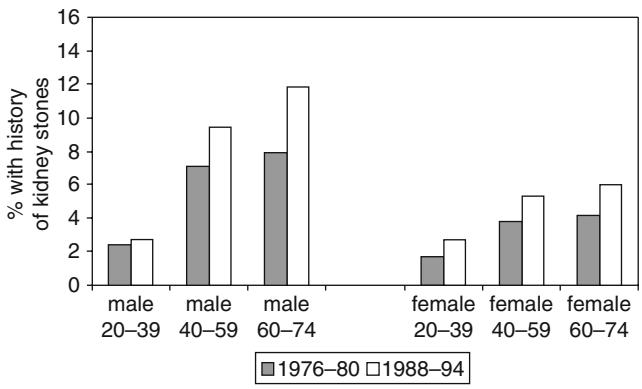

Fig. 1.1 Prevalence of stone disease by sex and age (Adapted and reprinted from Ref.[2] Copyright 2003, with permission from Nature Publishing Group)

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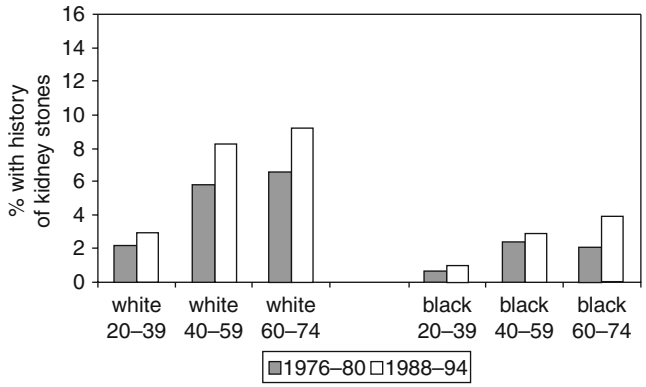

Fig. 1.2 Prevalence of stone disease by race and age (Adapted and reprinted from Ref.[2] Copyright 2003, with permission from Nature Publishing Group)

a male to female ratio 1.3:1; substantially lower than the commonly reported ratio of 2–3:1. Population-based studies of this interesting observation are needed.

1.3 Incidence

The incidence of nephrolithiasis – defined as the first stone event – varies by age, sex, and race. As with prevalence, white males have the highest incidence rates. In men, the incidence begins to rise after age 20, peaks between 40 and 60 years at ~3/1,000/year and then declines.[1,8,9] In women, the incidence is higher in their late twenties at 2.5/1,000/year and then decreases to 1/1,000/year by age 50, remaining at this rate for the next several decades.[1,9–11]

A recent study from Rochester, Minnesota, raised the possibility that incidence rates may be decreasing. Using the same methodology as a study performed 30 years earlier, the recent study reported incidence rates since 1990 may be falling in men and have leveled off in women.[12] Because there were only 157 cases in men and 91 in women, additional larger studies are needed to explore this important issue.

1.4 Recurrence Rates

Few studies provide reliable information on recurrence rates. Case series suggested 30–40% percent of untreated individuals will form another stone within 5 years after the initial episode.[1] Obviously, the risk of recurrence is influenced by a variety of factors including stone type and urinary composition. Fortunately, randomized trials demonstrated that interventions can reduce the likelihood of recurrence by 50% or more.[13–16] These interventions emphasize that prevention of stone recurrence is possible.

1.5 Risk Factors

Information on the importance of a variety of risk factors for stone formation has increased substantially over the past several decades. Risk factors are generally divided into non-dietary, dietary, and urinary.

1.5.1 Non-dietary

1.5.1.1 Family History

Studies of twins and populations have demonstrated that the common forms of stone disease are heritable.[17] The risk of stone formation is twofold higher in individuals with a family history of stone disease.[18] The increased risk is likely due to both genetic predisposition and similar environmental exposures (e.g., diet). Genetic causes of rare forms of nephrolithiasis (e.g., cystinuria, Dent disease) have been identified, but information is still limited on genes that contribute to risk of the common forms of stone disease.

1.5.1.2 Race/Ethnicity

In a cross-sectional Canadian study, individuals of Arabic, west Indian, west Asian, and Latin American descent were more likely to be stone formers than those of European descent.[19] Overall, in the general population, African-Americans have a lower frequency of stones; however, among individuals with end-stage renal disease, African-Americans had a higher than expected prevalence of stone disease.[20]

1.5.1.3 Systemic Disorders

There is substantial evidence that nephrolithiasis is a systemic disorder. Well-known conditions associated with calcium-containing stones include primary hyperparathyroidism, renal tubular acidosis, and Crohn's disease.

Several other common conditions, including obesity, gout, and diabetes mellitus (DM), have recently been convincingly linked to nephrolithiasis. Increasing body size, assessed by weight, body mass index (BMI), or waistline, increases the risk of stone formation independent of other risk factors including diet[21]; for unexplained reasons, the impact is greater in women than in men. For example, the risk of stone formation for individuals with a BMI ≥ 30 kg/m^2 compared to those with a BMI 21–23 was 30% higher among men but nearly twofold higher among women. Urinary composition by body size; for example, higher BMI, is associated with higher urine oxalate and lower urine pH, changes that would increase risk for calcium oxalate or uric acid stones.[22]

In a cross-sectional study, individuals with gout were 50% more likely to have a history of stones.[23] When examined prospectively, individuals with a history of gout had a twofold higher risk of incident nephrolithiasis, independent of diet, weight, and medications.[24] Possible mechanisms for this relation include insulin resistance and acidification defects.

Diabetes mellitus (DM) has also been associated with an increased risk of stone formation, independent of diet and body size.[25] Cross-sectionally, individuals with a history of diabetes were more than 30% more likely also to have a history of nephrolithiasis. Prospectively, a history of DM increased the risk of stone formation by 30–50% in women but not in men.[26,27] In support of these findings, a recent study based on National Health and Nutrition Examination Survey (NHANES) III data found that the risk of being a stone former increased with an increasing number of metabolic syndrome traits.[28]

1.5.1.4 Environmental Factors

Occupations or settings with higher insensible fluid losses, such as a hot environment, increase the risk of stone formation.[29] The risk will also be higher when individuals have restricted access to water or bathroom facilities, leading to lower fluid intake and lower urine volume.

1.5.2 Dietary Factors

Dietary intake influences urine composition, thereby modifying the risk of nephrolithiasis. Implicated nutrients include calcium, animal protein,[30] oxalate,[31] sodium,[32] sucrose,[33] fructose,[34] magnesium,[35] and potassium.[36] Care must be taken when interpreting studies of diet and stone risk. Retrospective studies may be biased because individuals who develop stones may subsequently change their diet. Results from studies that use change in urine composition as a surrogate for actual stone formation should be viewed with caution because the composition of the urine does not completely predict risk and not all the components that modify risk are included in the calculation of supersaturation (e.g., urine phytate). Thus, prospective studies that assess a variety of nutrients are best suited for examining the associations between dietary factors and risk of actual stone formation.

1.5.2.1 Calcium

The associations between dietary factors and the risk of incident stone disease have been examined prospectively in three large cohorts: Health Professionals Follow-up Study (HPFS) involving more than 45,000 male health professionals aged 40–75 years at baseline; Nurses' Health Study I (NHS I) involving more than 80,000 female nurses aged 34–59 at baseline; and NHS II involving more than 80,000 female nurses aged 27–44 at baseline.[8,10,11] Prior to these studies, higher calcium intake had been strongly suspected of raising the risk of stone disease. However, these studies demonstrated that individuals with a higher intake of dietary calcium actually had a *lower* risk of incident nephrolithiasis independent of other risk factors.[8,10,11] Although this may seem counter-intuitive, lower calcium intake increases dietary oxalate absorption and urinary oxalate excretion.[37] Another possible explanation is that there is some other protective factor present in milk (dairy products are the major source of dietary calcium in the USA). Even among individuals with a family history of nephrolithiasis, lower dietary calcium intake was associated with an increased risk of stone formation.[18]

Borghi and colleagues performed a randomized controlled study diet that confirmed these observational findings. Men with elevated urine calcium and a history of calcium oxalate stones were randomized to one of two diets: a low calcium diet (400 mg/day) or a diet containing 1,200 mg of calcium along with low sodium and low animal protein intake.[13] Men in the higher calcium intake group had a 50% lower risk of recurrence. The evidence is now overwhelming that calcium restriction is not beneficial and may in fact be harmful, both for stone formation and bone loss.

In contrast to dietary calcium, supplemental calcium does not appear to reduce risk in men or younger women[8,11] and may in fact increase the risk of stone formation in older women. In an observational study[10] and randomized trial,[38] calcium supplement users were ~20% more likely to form a stone than women who did not take supplements, after adjusting for dietary factors. However, the results from the randomized trial should be interpreted cautiously as the participants were instructed to take their supplements with meals, and the supplements contained both calcium and vitamin D. The timing of the supplemental calcium intake may account for the differences in risk. In the cohort studies, calcium supplements were typically not taken with meals, which would diminish binding of dietary oxalate in the intestine.

1.5.2.2 Oxalate

Urine oxalate is clearly an important risk factor for calcium oxalate stone formation; however, the role of dietary oxalate in the pathogenesis of calcium oxalate nephrolithiasis is less clear.[39] The proportion of dietary oxalate that is absorbed is estimated to range from 10% to 50%.[39] The factors influencing the absorption are incompletely characterized but likely include other dietary factors (e.g., calcium), genetic factors, and possibly intestinal flora. In addition, the bioavailability of oxalate in food is unknown. Urinary oxalate is also derived

from the endogenous metabolism of glycine, glycolate, hydroxyproline, and vitamin C. A recent study found individuals with a history of calcium oxalate nephrolithiasis were less likely to be colonized with *Oxalobacter formigenes*, an intestinal bacterium that degrades oxalate.[40] Prospective studies of dietary oxalate and stone risk were performed after modern approaches to measure the oxalate content of food provided information on the oxalate content of many foods.[41,42] Surprisingly the impact of dietary oxalate was minimal in men and older women and not associated with stone formation in younger women.[43]

1.5.2.3 Other Nutrients

A variety of other nutrients have been implicated in stone formation. Of note, the magnitudes of the associations often vary by age, sex, or body mass index. For example, higher animal protein intake may increase urinary calcium and decrease urinary citrate,[44] thereby increasing the risk of stone formation. However, when studied prospectively, animal protein was associated with an increased risk in men but not in women.[8,10,11] Further, the increased risk in men was only found among men with BMI < 25 kg/m^2.[45] Higher dietary potassium intake decreased risk in men and older women[8,10,45] possibly by reducing urine calcium excretion[36] or increasing urine citrate. Higher intake of sodium[32] or sucrose[33] increases urinary calcium excretion independent of calcium intake. In prospective studies, sucrose was associated with an increased risk in women and fructose increased risk in men and women.[10,11,34] Phytate, found in whole grains and beans, was observed to reduce risk of stone formation in younger women,[11] possibly by directly inhibiting calcium oxalate crystal formation.

Although magnesium may reduce dietary oxalate absorption, randomized trials of magnesium supplements did not find a protective effect on stone recurrence, though the drop-out rates were high. In prospective observational studies, higher dietary magnesium was associated with a lower risk of stone formation in men[45] but not women.[10,11]

Vitamin C (ascorbic acid) can be metabolized to oxalate. Consumption of 1,000 mg of supplemental vitamin C twice daily increased urinary oxalate excretion by 22%.[46] In a prospective observational study, men who consumed 1,000 mg or more per day of vitamin C had a 40% higher risk of stone formation compared to men who consumed less than 90 mg/day (the recommended dietary allowance).[45] While restricting *dietary* vitamin C is not recommended (because foods high in vitamin C contain inhibitory factors such as potassium), calcium oxalate stone formers should avoid vitamin C supplements.

Although high-dose vitamin B6 (pyridoxine) may reduce oxalate production in selected patients with type 1 primary hyperoxaluria, it is unclear if there would be benefit from the use of vitamin B6 supplements to prevent common stone disease. In observational studies, higher intake of vitamin B6 was associated with a reduced risk of kidney stone formation in women[47] but not in men.[48]

1.5.2.4 Fluid Intake and Beverages

The main determinant of urine volume is fluid intake. Urine volume, and therefore fluid intake, is an important determinant of stone risk. When the urine output is less than 1 L/day, risk of stone formation is markedly higher. Higher fluid intake has been demonstrated to reduce the likelihood of stone formation in observational studies[8,10,11] and a randomized controlled trial.[49]

Patients with stone disease often ask which beverages they should drink and which they should avoid. Coffee, tea, beer, and wine were associated with a *reduced* risk of stone formation in prospective studies.[50,51] Although citrus juices theoretically could reduce the risk of stone formation by increasing urine citrate,[52] the prospective studies did not find an independent association with orange juice and grapefruit juice was associated with a significantly higher risk.[50,51] Grapefruit juice is known to affect several intestinal enzymes, but the mechanism for the observed increased risk of stone formation is unknown. Consumption of sugared soda was not associated with a higher risk of stone formation.[50,51] Milk intake reduces the risk of calcium kidney stone formation.

1.6 Urinary Factors

The 24-h urine collection is the cornerstone of the metabolic evaluation and the urine chemistries provide important prognostic information and guide preventive recommendations. Like many laboratory tests, urine results have traditionally been categorized into "normal" and "abnormal." However, recent data has revealed this grouping is unsatisfactory. Urine values are continuous so the dichotomization into "normal" and "abnormal" is arbitrary and potentially misleading. In addition, stone formation is a disorder of *concentration*, not just the absolute amount excreted. Although terms of abnormal excretion, such as "hypercalciuria" or "hypocitraturia" are often used clinically and in the scientific literature, the limitations of these terms should be acknowledged.

Hypercalciuria is commonly defined as urine calcium excretion ≥ 300 mg/day (7.5 mmol/day) in men and ≥ 250 mg/day (6.25 mmol/day) in women[53] on a 1,000-mg/ day calcium diet (but a variety of definitions are in use). Using these traditional definitions, approximately 20–40% of patients

with calcium stone disease will have hypercalciuria. Although possibly reasonable from a calcium balance perspective, there is insufficient justification for different thresholds for males and females. In fact, the sex-based definitions are particularly concerning because nephrolithiasis is a disorder of concentration and 24-h urine volumes are slightly higher in women than in men.[54]

Hyperoxaluria is typically defined as urinary oxalate excretion >45 mg/day (0.5 mmol/day), though here too a variety of thresholds are in use. Elevated urinary oxalate excretion is three to four times more common among men (~40%) than in women (~10%).[54] Mean urinary oxalate levels are only slightly higher in cases than in controls, but in multivariate models oxalate is clearly an important independent risk factor for stone formation.[54] Of note, the risk begins to rise well below the 45 mg/day level.

The relation between uric acid excretion and calcium stone disease is unsettled. Some early cross-sectional studies reported that *hyperuricosuria* (typically defined as greater than 800 mg/day (4.76 mmol/day) in men or 750 mg/day (4.46 mmol/day) in women) is more frequent in patients who form calcium stones than controls.[55] However, a recent study of more than 2,200 stone formers and 1,100 non-stone formers reported that a higher urine uric acid was associated with a lower likelihood of being a stone former in men, and there was no increase in risk for women.[54] A double-blind trial of allopurinol successfully decreased recurrence rates of calcium stones in patients with hyperuricosuria suggesting that uric acid is important,[16] but it is possible that the beneficial effect of allopurinol was through a mechanism unrelated to lowering of urine uric acid.

Hypocitraturia, often defined as 24-h excretion≤ 320 mg/day (1.67 mmol/day), increases risk of stone formation[56] and is found in 5–11% of first-time stone formers.[54] There is suggestive evidence that increasing urinary citrate into the high-normal range provides additional protection.[54]

Low urine volume, for which a variety of definitions have been used, is a common and modifiable risk factor. When defined as 24-h urine volume less than 1 L/day, 12–25% of first-time stone formers will have this abnormality.[54] Observational studies and a randomized trial have demonstrated the risk of stone formation decreases with increasing total urine volume.[49,54]

1.7 Conclusions

Epidemiologic studies have expanded our understanding of the magnitude and risk factors for stone disease. A variety of dietary, non-dietary, and urinary risk factors contribute to the risk of stone formation and the importance of these varies by age, sex, and BMI. Scientifically, results from these studies have forced a reappraisal of our view of risk factors for stone disease. Importantly, the results from epidemiologic studies can be considered in the clinical setting when devising treatment plans for reducing the likelihood of stone formation.

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Genetics and Molecular Biology of Renal Stones

2

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Abstract Genetic studies of calcium kidney stones have hitherto assessed single candidate genes by testing for linkage disequilibria or associations between a locus and stone disease. They have identified the potential involvement of the calcium-sensing receptor (CaSR), vitamin D receptor, (VDR), and bicarbonate-sensitive adenylyl cyclase genes. In addition to research in humans, studies on different strains of knock-out mice have enabled us to include the phosphate reabsorption carrier NPT2 gene, the caveolin-1 gene, the protein NHERF-1 gene modulating calcium and urate reabsorption, osteopontin, and Tamm–Horsfall protein among the possible determinants. Interactions between genes, and between environmental factors and genes, are generally considered fundamental to calcium stone formation, however. To date, therefore, genetic studies have failed to significantly advance our understanding of the causes of calcium kidney stones, though they have enabled us to assess the dimension of the problem and establish criteria for facing it. Further progress in our knowledge of what causes calcium stones may derive from using the tools afforded to researchers by modern biotechnology and bioinformatics.

2.1 Introduction

Metabolic studies on patients have established that calcium kidney stones can be associated with various defects of mono- and bivalent electrolyte excretion. The most well known of these conditions is primary hypercalciuria, detected in 50% of patients with stones.[1] Others, such as hypo-citraturia, renal hypophosphatemia, hyperuricuria, and an elevated sodium and chloride excretion accompany stone-forming disease less frequently. It is consequently impossible to predict the onset of a calcium stone on the strength of these conditions alone, which leads us to assume that a number of factors interact and/or combine together to predispose an individual to calcium kidney stones.

In the last decade, nephrological research has focused on establishing the genetic causes of calcium nephrolithiasis. Our understanding of this topic has not improved substantially, however, and it has consequently not been possible to develop effective prevention and treatment criteria. Among the predisposing factors, we tend to consider those of genetic and environmental origin, though the distinction between the two is hazy because kidney stones are probably the outcome of an interaction between genes and environment.[1–4] Nephrolithiasis is consequently among the complex diseases with a multifactorial pathogenesis, like hypertension, diabetes, ischemic cardiopathy, and osteoporosis. Studying its causes is bound to be difficult, although advances in our biological/molecular knowledge and new biotechnologies have provided us with powerful analytical tools. These methods have certainly enabled progress to be made in genetic research, but our awareness of the complexity of the pathogenic picture, and of the commitment that will be needed to fully understand it, has likewise grown.

2.2 Genetic Linkage Studies

The genetic study of calcium kidney stones developed starting from the latter half of the 1990s. Early studies were conducted using linkage methods that assess the cosegregation of the nephrolithiasis with a chromosomal locus in members of stone-forming families. These methods are strong and

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accurate in pointing to the genes involved in a given disease, especially in monogenic diseases, which is why they were applied to nephrolithiasis.[5] Some studies also evaluated the phenotypes implicated in the disease, such as hypercalciuria.

Some linkage studies considered the loci of candidate genes believed to have a pathogenic role in the light of the prevailing pathophysiological hypotheses. This strategy was applied to a sample of more than 300 pairs of French–Canadian brothers suffering from kidney stones, whose chromosomal loci coding for renal 1α (alpha)-hydroxylase of 25(OH) vitamin D, the vitamin D receptor (VDR), or the calcium-sensing receptor (CaSR) were tested. Each region was assayed using specific polymorphic markers. The locus of the 1α (alpha)-hydroxylase of 25-dihydroxy-vitamin D (chromosomal locus 12q13.1-q13.3) was the first to be studied in this sample, but the results could confirm no role for it.[6] The locus of the VDR on chromosome 12q12–14 was analyzed using six different markers, four of which emerged in linkage disequilibrium with nephrolithiasis and only one with hypercalciuria, but with only a low significance.[7] Finally, no linkage was found between the locus of the CaSR (3q13.3–21) and the onset of nephrolithiasis in the series of French–Canadian brothers.[8]

Linkage studies have produced more significant results when members of stone formers' families were studied, by generation. One study reconsidered the locus of the VDR in Indian families and substantially confirmed the results obtained in the French–Canadian brothers.[9] Another confirmed the absence of CaSR gene mutations in seven European families.[10] Only one family-based study used chromosomal markers covering the whole genome (a genome-wide scan): this method enabled them to proceed without any preliminary pathogenic hypothesis or definition of a candidate gene. After exploring the whole genome with polymorphic markers, the results of the study suggested the loci where the genes implicated in nephrolithiasis could be found. In other words, a genome-wide scan enables a pathogenic hypothesis to be developed on the strength of the results obtained. Taking this approach, a linkage was identified between chromosome 1q23.3-q24 and hypercalciuria in three families suffering from absorptive hypercalciuria and kidney stones.[11] The interpretation of this finding was entrusted to a subsequent case-control study, which found an association between hypercalciuria and six polymorphisms of the soluble (bicarbonate-sensitive) adenylate cyclase (sAC) gene. The same polymorphisms were also associated with a low bone mineral mass.[12] The functional role of the sAC gene has yet to be clarified, though we know that it is expressed in the kidney, intestine, and bone cells, and that its function is activated by bicarbonate and modulated by bivalent cations.[13] The linkage between the sAC gene and hypercalciuria was not confirmed, however, in a European study of nine families.[14]

Despite the greater reliability of linkage studies, studies conducted using other strategies, such as analyzing the association between genotype and calcium nephrolithiasis, have been far more numerous. The reasons for this tendency lie in the numerous practical and theoretical problems involved. First, there is the difficulty of finding family groups covering at least three generations and numerically large enough to enable linkage studies. Another problem lies in the inability of linkage studies to identify genes with a scarce phenotypic effect.[3,5] This problem applies particularly to nephrolithiasis because stones may be caused not by a mutation in one or a few genes with a strongly predominant effect, but by compound changes induced by numerous genes, each incapable alone of giving rise to the disease.[15] This being the case, the causal substrate might be so variable and heterogeneous as to make it extremely difficult to conduct genetic studies and identify individual genes.

In addition to these specific problems, there is also the more general difficulty of classifying an individual as a stone-former; in fact, a kidney stone can develop at any age, and may even go unrecognized. It may also be that an individual possessing the predisposing genetic heritage forms no stones because other genes or nutrients with an antilithogenic effect prevail over the lithogenic factors.[16] A clear example of this phenomenon in the kidney stone setting is the low-sodium diet prescribed for hypercalciuric individuals. The lithogenic risk in these people is increased by their higher calcium excretion levels, but restricting their dietary intake of sodium and chloride reduces their stone-forming potential related to their hypercalciuria, which is known to have a genetic component.[17] It may also be that several genetic causes come into play in patients with recurrent kidney stones, but not in those who produce only one stone in a lifetime.[18]

2.3 Genetic Association Studies

The studies associating a genotype with calcium kidney stones are the most common alternative to genetic linkage studies. They assess whether an allele or a genotype is more or less common in patients with kidney stones than in those without them. The search for this association can involve analyzing of the whole genome or only a candidate gene. In the nephrolithiasis setting, only candidate genes have been tested to date,[2] but analyses with genome-wide markers represent the way forward.[19] In association studies, patients and controls are genotyped for single-base polymorphisms arranged along the sequence of candidate genes. These polymorphisms have a mean frequency of one for every 1,200 bases and contribute to the variability of the phenotype. They can be placed in coding regions and cause an amino acid change, or in untranscribed regions and leave the amino acid sequence in the protein unchanged. Their potential influence on the phenotype often remains unknown and this is a crucial drawback of such analyses.[20]