Epidemiology of Stone Disease in Northern India

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Raguram Ganesamoni and Shrawan K. Singh

Abstract

Urinary stone disease is highly prevalent in North India, a part of the stone belt in Asia. Two distinct "stone belts" have been identified in the northwestern region (NW); stone disease is less common in the southern and eastern regions. Calcium oxalate (CaOx) comprises a greater proportion of stones than seen in Western studies. While struvite stones were common in older series from NW, CaOx remains the predominant stone now, even in staghorns. First-degree relatives of stone formers are at higher risk of developing urolithiasis and have significantly higher urinary calcium excretion as compared to the spouses of the stone formers. Urinary tract infection was found to be one of the principal risk factors of urinary stones in North India. Metabolic acidosis is present in up to 45.2 % of stone formers as compared with 10.8 % in non-stone formers. Only dietary calcium correlated significantly with serum and urine calcium in stone formers. Stone patients from North India were shown to have a significantly higher intake of dairy products such as curd and cheese as compared to non-stone cases. Lower concentrations of urinary magnesium, copper, and manganese were noted in stone formers. Zinc excretion was significantly higher in stone formers. A significantly higher urinary urate excretion has been shown among stone formers from Delhi and Rajasthan.

Keywords

Incidence • Urinary stones • Oxalates • Urates • Prevalence • Geographical variation • Stone composition • Urine composition • Staghorn stones • Calcium oxalate stones • Calcium phosphate stones • Infection stones • Uric acid stones • Cystine stones • Practice patterns • Pediatric stones • Age-related stone formation • Recurrence • Stone site

Introduction

Urinary stone disease is highly prevalent in North India, which forms a part of the stone belt in Asia. Although shock-wave lithotripsy and endourological management of stone disease have revolutionized stone management, these modalities have not altered the risk of stone recurrence. The study of distribution and determinants of stone disease can help us in finding new ways of prevention of stone formation and its recurrence. Epidemiological studies including molecular epidemiology help in identification of risk factors for stone disease, which in turn aids in a better understanding of the pathophysiological processes leading to stone formation and how the individual factors interact in the individual stone-forming patient. Since epidemiology of stone disease varies widely in different geographic regions, a careful study of each region is important to guide stone prevention strategies and future research pertinent to the region.

R. Ganesamoni, MS, MRCS, MCh (Urology)
S.K. Singh, MS, MCh (Urology) (✉)
Department of Urology, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh, Chandigarh, 160012, India
e-mail: dr_raguramg@yahoo.co.in; shrawanksingh2002@yahoo.com

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Incidence and Prevalence

Stone disease has plagued mankind from time immemorial. Sushruta, hailed from Varanasi in North India, the pioneer in stone surgery, described vesicolithotomy about 2,800 years ago [1]. The prevalence of stone disease and the composition of stones vary widely across the world, highlighting the etiological role of different geographic and etiological factors. The overall probability of forming stones differs in various parts of the world and is estimated to 1–5 % in Asia, 5–9 % in Europe, and 13 % in North America [2]. In Asia, a stone-forming belt has been reported to stretch across Sudan, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, Indonesia, and the Philippines [3]. In India, upper and lower urinary tract stones occur frequently, but the incidence shows wide regional variation [4]. The pattern of occurrence of stone disease in northern India with respect to age and sex is not different from that reported in other regions of the world. Stone disease is more common in males, young adults, and the middle aged. The incidence of endemic bladder calculi was high in children living in rural areas of India until 1980. However, this incidence has decreased in the last few years due to improved socioeconomic status leading to better nutrition and diet. There is a simultaneous increase in upper urinary tract stones [5]. In urban centers, nearly 99 % of stone removal is done endourologically. In rural and semi-urban areas, where still general surgeons treat majority of patients with stone disease, open surgery is still commonly performed.

Geography

The geographic distribution of stone disease tends to roughly follow environmental risk factors; a higher prevalence of stone disease is found in hot, arid, or dry climates such as the mountains, desert, or tropical areas [6]. In India, two distinct "stone belts" have been identified in the northwestern region. One stone belt starts from Amritsar in the North, passes through Delhi and Agra, and ends up in Uttar Pradesh. The other belt starts from Jamnagar in the West Coast and extends inward toward Jabalpur in Central India (Fig. 4.1). Stone disease is less common in the southern and eastern regions of India. Hot climate is considered to be one of the factors for the difference in this distribution [7]. The northwestern parts of India have extremes of temperature (temperature reaches up to 45 ° C or even more during summer), while the southern parts have a relatively uniform warm climate throughout the year. The relative inability of the body to adapt to these changes in weather of different seasons and the lack of drastic changes in fluid intake may play a role in causing the increased incidence of stone disease in northwestern parts of India.

Socioeconomic Status

The incidence of stone disease is more common in lower and middle socioeconomic strata, in particular in those subsisting on a monotonous diet. Endemic bladder stones, which were once common in low socioeconomic groups of eastern Uttar Pradesh and Bihar, probably due to malnutrition and vitamin A deficiency, have become very uncommon now. Low socioeconomic status is associated with lack of health awareness and delay in access to optimal health care. A significant number of patients in North India present with renal insufficiency (15 %) as compared to their counterparts in the West (1.7 %) [8]. Of the 222 million households in India, the absolutely poor households (annual incomes below $1,000) accounted for 15.6 % of them (about 35 million). About 48 % have annual income of more than $2,000. The average family size in India is 4.8 [9]. Though the incidence of stone disease has been found to be higher in lower socioeconomic strata, data regarding average income of stone formers are not available. The burden of healthcare costs frequently pushes people of lower socioeconomic status into further poverty especially if the earning male member of the family is affected.

Site of Occurrence

Similar to Western studies, a reducing trend for bladder calculi has been noted in North India, albeit a little later. The proportion of bladder calculi had significantly decreased from 30.5 % during 1965–1968 to 8.4 % during 1982–1986 [10]. In late 90s also, stones in the bladder have been reported from Satpura belt of Central India and Mumbai in the pediatric age group [11–13] (Fig. 4.2). The consumption of a protein-rich diet has shifted the stone occurrence from the lower to upper urinary tract [6].

Composition

As compared to Western studies where calcium oxalate accounts for 66–72 % of all stones, Indian studies reveal a higher percentage of this stone constituent. Ansari et al. [14] analyzed 1,050 stones (900 renal, 150 ureteric) and found that 977 (93 %) were composed of calcium oxalate, out of which 80 % were calcium oxalate monohydrate and 20 % were calcium oxalate dihydrate. Only a small percentage of the stones contained struvite (1.4 %), apatite (1.8 %), and uric acid (0.95 %). The remaining 2.76 % were mixed stones. A total of 89.9 % of staghorn stones were made of oxalates and only 4.0 % of struvite. This finding is also in contrast to Western studies where staghorn stones more often are composed of struvite. The predominance of

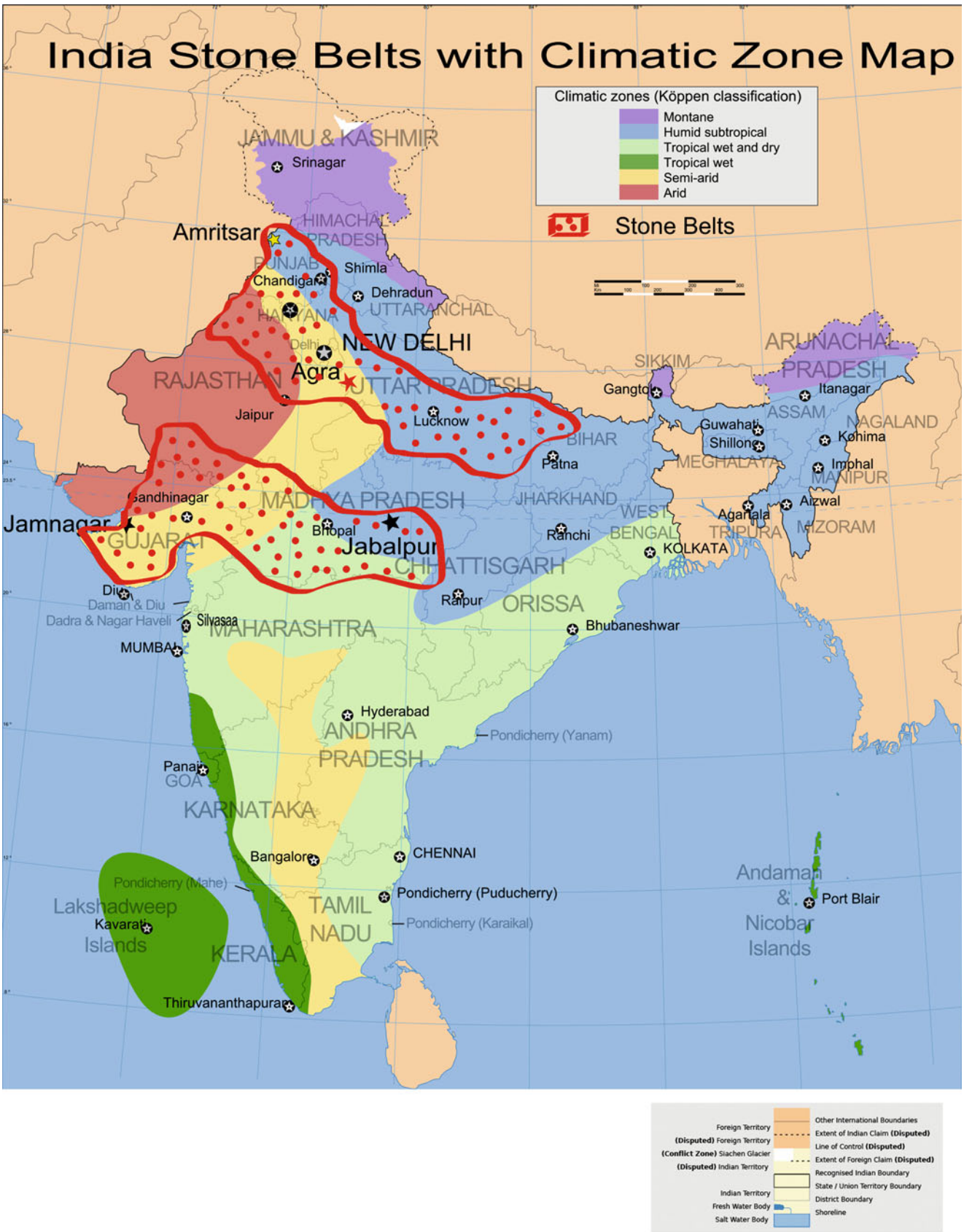

Fig. 4.1 The geographical distribution of the two stone belts in India (Modified with permission from http://commons.wikimedia.org/wiki/File:India_climatic_zone_map_en.svg, © copyright 2007, Saravask)

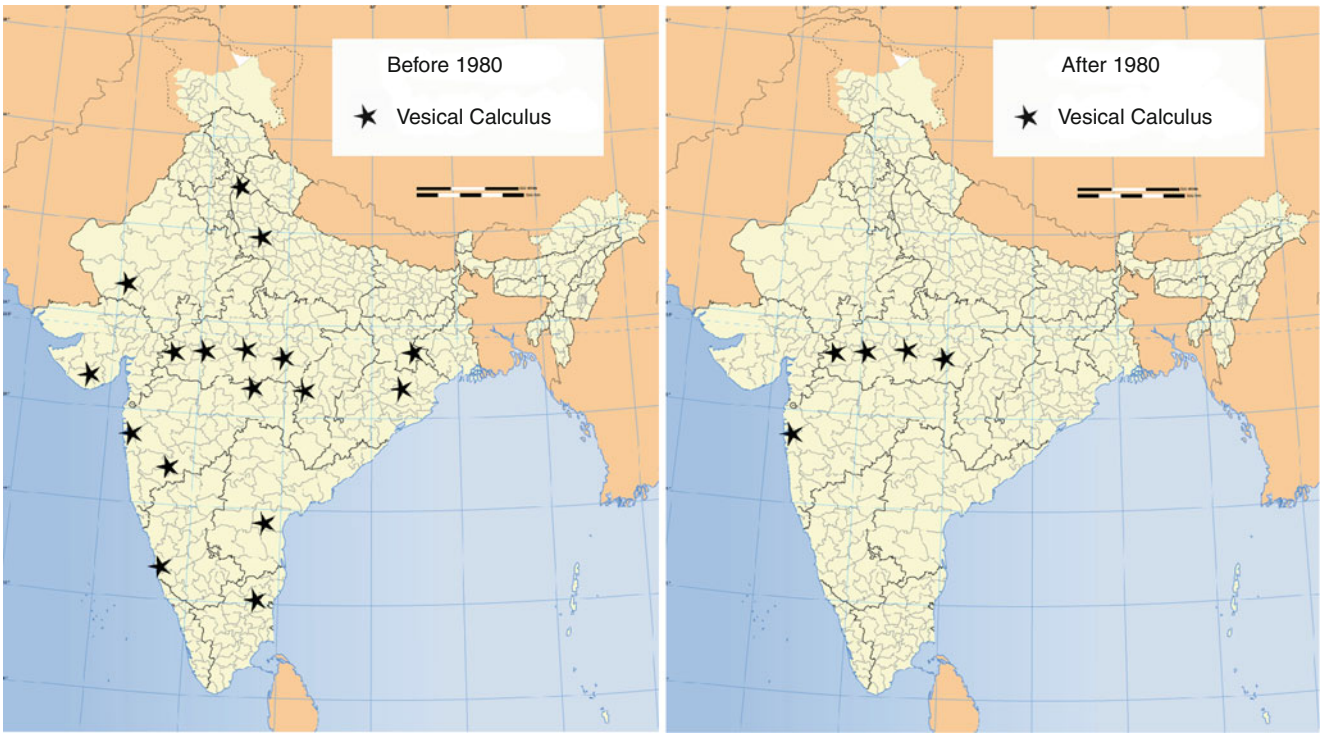

Fig. 4.2 The regions of occurrence of vesical calculi in India before and after 1980 (Modified with permission from http://commons.wikimedia.org/wiki/File:India_Lakshadweep_locator_map.svg. © copyright 2008, PlaneMad/Wikipedia)

Table 4.1 Stone composition in various studies

Author	Number	Method	Stone composition
Ansari et al. [14]	1,050	X-ray diffraction crystallography	Calcium oxalate monohydrate (COM) 74.4 %, calcium oxalate dihydrate (COD)18.6 %, struvite 1.4 %, apatite 1.8 %, uric acid 0.95 %, and mixed stones 2.76 %
Ahlawat et al. [15]	434	X-ray diffraction crystallography	COM 87.3 %, COD and mixed stones 9.7 %, struvite stones 1.4 %, uric acid and apatite stones less than 1 % each
Mittal et al. [19]	80	X-ray diffraction crystallography	COM 70.8 %, COD 18.6 %, COM + uric acid 6 %, COM + COD + uric acid 4.2 %
Sharma et al. [20]	501	Thermogravimetrc analysis	COM 81 %, COD 5 %, COM + phosphate 4.9 %, struvite 2.7 %, calcium phosphate 1.9 %, uric acid 1.2 %, other mixed stones 3.3 %

calcium oxalate stones also has been shown in various other studies [15, 16]. Older studies from the northwestern region of India revealed a higher proportion of struvite stones [7, 10]. Only anecdotal cases with 2,8-dihydroxyadenine, cystine, or xanthine stones have been reported [17, 18]. The stone composition reported in different studies is shown in Table 4.1.

Risk Factors

The various causes cited for the high prevalence of stone disease in North India include food habits, water quality, and the hot climate [11, 21]. The frequency of various urinary risk factors is shown in Table 4.2.

Genetic Factors

First-degree relatives of stone formers are at higher risk of developing urolithiasis [25]. These relatives, even without stone disease, have been found to have significantly high urinary excretion of calcium as compared to the spouses of the stone formers [26]. Hypercalciuria is a common abnormality found in 33 % of the patients with nephrolithiasis in northern India [25]. Intestinal hyper-absorption is predominantly seen in hypercalciuric subjects, and the only hormonal stimulus for the intestinal absorption of calcium is 1, 25 $(OH)_2$ vitamin D_3 and its receptor. The absorption of calcium is associated with vitamin D receptor (VDR) genotype [27]. In a study of VDR genotypes in the North Indian population, it was observed that both normocalciuric nephrolithiasis patients

Table 4.2 Frequency (%) of urinary metabolic abnormality in stone formers from India

Urinary risk factors	Teotia et al. [22]		Rai et al. [23]	Relan et al. [24]
	Male ($n=5,500$)	Female ($n=3,300$)	($n=100$)	($n=150$)
Hypercalciuria	26	27	31	38
Hyperoxaluria	29	29	25	–
Hyperuricosuria	18	15	18	15
Hypocitraturia	25	34	–	–
Hypomagnesuria	17	30	–	–
Hyperphosphaturia	30	15	–	–

and hypercalciuric nephrolithiasis patients who had the bb genotype with respect to Bsm I showed higher 24-h urinary calcium excretion than the homozygous BB patients [25].

Systemic Disorders

Diabetes and obesity are known risk factors for urolithiasis. Since the prevalence of these two risk factors is increasing in Indian population [28], urolithiasis may show an upsurge in the future.

Environmental Factors

North India has a hot climate with the Thar Desert located in Rajasthan. A higher incidence of urolithiasis has been demonstrated in tribal people working in a mining environment [29]. One study from the Delhi region of North India could not demonstrate any significant correlation between occupation and stone formation [30]. Lack of access to drinking water or bathroom facilities are real problems in many parts of North India. This may lead to lower fluid intake and a higher risk of stone formation.

Urinary Tract Infection

Urinary tract infection was found to be one of the principal risk factors of urinary stones in North India [7]. The prevalence of positive stone culture has been found to range from 33 to 47 % [30, 31]. Unusual microorganisms like *Ureaplasma urealyticum* have also been isolated from stones [31].

Nanobacteria

Nanobacterium is an extremely small nano-sized microorganism that has been isolated from human renal stones. In a study from Chandigarh, nanobacteria were isolated from 62 % of stones removed by open surgery. These bacteria were shown to be apatite forming. Nanobacteria have been shown to facilitate crystallization and biomineralization, and they thus may play a role in the pathophysiology of renal stone formation [32, 33]. Moynihan's statement that "a gallstone is a tombstone to the memory of the organism within it" probably holds true for renal stone as well [32].

Oxalobacter formigenes

Oxalobacter formigenes is an oxalate-degrading bacterium which has been demonstrated in 65 % of normal individuals and in 30 % of calcium oxalate stone formers from North India [34]. In patients with three or more than three stone episodes, these bacterial colonies were present only in 5.6 % of patients. Oxalate excretion was less in patients colonized with *O. formigenes* as compared to those with no colonization. Hyperoxaluria associated with deficient colonization with *O. formigenes* may be contributing to the risk of urolithiasis in this population.

Metabolic Acidosis

Metabolic acidosis is a risk factor for urolithiasis. It causes calcium mobilization from bone leading to hypercalciuria and decreases urinary excretion of citrate. The incidence of distal renal tubular acidosis defect detected by acid loading test was 22.2 % in a series of recurrent stone formers in North India [35]. The status of metabolic acidosis in idiopathic stone formers has also been studied. Sakthivel et al. found that the prevalence of metabolic acidosis was 45.2 % in stone formers as compared to 10.8 % in non-stone formers [36].

Dietary Factors

Some of the reasons for the high incidence of calcium oxalate stones in northwestern India might be as follows: (1) vegetarian diet (with high oxalate content); (2) high carbohydrate intake (especially rice), which provides an acidic milieu in urine favoring calcium oxalate stone formation; and (3) water quality, its mineral contents, and high fluoride levels [37–39].

In a study from Rajasthan, which has a hot environment, there was no influence of dietary intake of protein, carbohydrate, fat, fiber, calcium, and oxalic acid on urinary excretion of calcium, oxalate, urate, inorganic phosphorus, magnesium, and citrate [40]. But stone formers had higher urinary excretion of oxalate and calcium, lower excretion of citrate, and excreted more saturated urine. A difference in dietary habits does exist between the North and South Indian populations. Tartaric acid content of tamarind, which is used in cooking South Indian dishes such as *sambhar*, might play an inhibitory role against stone formation [41].

Protein

The amount of daily protein intake and the source of protein influence the type and site of stone formed. Endemic bladder calculi are common in regions where dietary protein is derived from plant sources [42]. It has been shown that stone formers from an urban area in India have a significantly higher intake of animal protein curd and cheese in comparison with non-stone-forming subjects [29]. The same study also revealed higher urinary urate excretion in those stone formers.

Calcium

In a study from Delhi, urine calcium correlated significantly to dietary intake of energy, protein, and fats (not carbohydrates) in stone formers only. Only dietary calcium correlated significantly with serum and urine calcium in stone formers. Thus, a dietary contribution of energy, protein, and fat to urinary calcium excretion in stone formers could be possible in this population [43]. Stone patients from North India were shown to have a significantly higher intake of dairy products such as curd and cheese as compared to non-stone cases [29].

Phosphate

In a study from North India, elevated urinary phosphate was shown to be the only factor that was significantly different when stone formers were compared with healthy controls [43]. That the elevated urine phosphate was not significantly correlated with any dietary intake probably indicates that that the metabolism of phosphate rather than its intake plays a role in stone formation [43].

Fluoride

In a study from Rajasthan, a chronic intake of fluoride has been shown to increase the risk of stone formation by a factor of 4.6 [39]. The prevalence of stone disease in endemic area was 750/100,000 as compared to 163/100,000 in non-endemic area for fluorosis. Fluoride is said to be a mild promoter of urinary stone formation by (1) increasing oxalate excretion in urine, by (2) excretion of insoluble calcium fluoride, and by (3) mildly increasing the oxidative burden [39]. The Rajasthani population has been shown to have a high excretion of oxalate, mainly due to defective nutrition [44]. Fluoride may indirectly increase oxaluria by enhancing the absorption of oxalate from the intestine due to low availability of calcium because part of the intestinal calcium is precipitated as calcium fluoride. Since fluoride also possesses the inherent property of being able to bind crystals strongly, which gives more hardness to bone [45], it has been postulated that formation of urinary stones will occur when the aforementioned conditions overwhelm the inhibitory forces present.

Magnesium

In a study from Rajasthan, though magnesium intake was normal in both normal subjects and stone formers, the mean excretion of magnesium was lower than normal in all the groups, suggesting its defective absorption in this population [16]. Lower concentration of urinary magnesium was found in stone formers from Chandigarh, suggesting its inhibitory role in urolithiasis [46].

Trace Elements

Serum levels of zinc, copper, and manganese have been reported to be similar among normal subjects and stone formers. Zinc excretion was significantly higher in stone formers. Copper and manganese excretions in stone formers were significantly lower than in normal subjects [47]. In another study, urinary concentrations of zinc and nickel were found to be significantly lower in stone formers. It suggests that these trace elements might inhibit the crystallization and crystal aggregation [46]. But it is not known whether the urinary excretion of these elements is influenced by dietary intake, environment, or body metabolism.

Drinking Water

In a large survey of 38,805 persons in Rajasthan with analysis of the total hardness of drinking water—Ca, Mg, Na, K, iP, SiO3, SO4, Cl, F, Cu, Zn, and Mn—no association was found between any of these constituents and stone disease [48].

Hyperuricosuria

A significantly higher urinary urate excretion has been shown among stone formers from the Delhi region of North India and Rajasthan [40, 49]. A significantly higher level of serum urate was found in stone patients as compared with non-stone cases, even though the values were within the normal range [49]. Children consuming wheat as a staple diet are at a greater risk of forming a stone because of the increased urine saturation and precipitation of urate [50].

Hypocitraturia

In a study from northwestern India, though urinary citrate excretion was not different between stone formers and normal controls, there was a significant circadian rhythm of urinary citrate excretion in the healthy males. That pattern was absent in stone-forming patients; the acrophase was located near noon in non-stone formers and near midnight in stone formers [13]. In another study of the same population, a significant hypocitraturia was demonstrated [40].

Glycosaminoglycans

Twenty-four hour urinary excretion of glycosaminoglycans (GAGs) was shown to be significantly lower in both male and female stone formers in North India. The 24-h urinary excretion of GAGs was not related to age or sex [51].

Conclusion

Epidemiologic studies of stone disease in North India, though limited in number, does show many important findings that are peculiar to this region. Calcium oxalate, mainly calcium oxalate monohydrate, is the major constituent of stones including staghorn calculi in North India. Fluoride content of water has been shown to be a significant risk factor in endemic regions. The role of nanobacteria and oxalobacter needs to be studied further.

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