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ROLE OF SEX HORMONES AND OTHER FACTORS IN PREDOMINANCE OF STONE FORMATION IN MALES AS COMPARED TO FEMALES

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ABSTRACT

Urolithiasis is the formation of stones in the urinary system. It has been observed that occurence of stones is more in males as compared to females. The male- to- female ratio in stone formation in the reproductive age is 3:1. This difference is mainly because of the enhancing effect of testosterone in males and inhibitory or protective effect of estrogen. Estrogen also influences the amount of citric acid secreted, citric acid being an inhibitor of stone formation. With reference to the effect of climate it was found that although both men and women sweat to same extent women are better at replenishing the losses as compared to males and this might agin explain the higher incidence of stones in men.

KEYWORDS: Testosterone and estrogen in stone formation, sex hormones in urolithiasis, promoters and inhibitors of stone formation, citric acid and urolithiasis.

INTRODUCTION

Urolithiasis (UL) is the formation of stones in the urinary system. Urolithiasis has worldwide distribution but it is particularly common in some countries like United States, South Africa, India and South East Asia.[1] Around 12% of global population suffers from urolithiasis. The major challenge is reoccurrence of stones post treatment in urolithiasis. Reoccurence rate in males is 78-81% and 47-60% in females.[2] Urinary stones are typically classified by their location or by their composition. When it occurs in kidney it is called as nephrolithiasis. When stone occurs in ureter it is called as ureterolithiasis. Occurrence of stones in urinary bladder and urethra is termed as Cystolithiasis.[3] The aim of the review was to study the causes behind males being more susceptible to formation of kidney stones as compared to

females. Although incidence is more in males in recent years it has been seen that women are becoming increasingly prone because of changes in diet and lifestyle. The increase in susceptibility in males is because of testosterone which promotes stone formation whereas in females estrogen provides a protective effect. In females there is also an increase in citric acid excretion in urine during the reproductive ages. Citric acid is an inhibitor of stone formation and thereby leads to less chances of women developing stones.

A literature search of Pubmed and Google Scholar was done with the topic factors affecting stone formation in males and females or gender difference in formation of stones.

Etiology

Stone formation is considered as a medical challenge as the etiology and pathophysiology is still widely unknown and governed by a number of factors.[3] An imbalance between promoters and inhibitors leads to precipitation and formation of stones. It has also been found that the formation of renal stones and also the composition varies with gender of the patients. In recent times though there is a change in incidence with respect to gender.

Gender difference

Studies have reported that prevalence of nephrolithiasis is higher in males than females. However in recent years there has been an increase in the percentage of women developing nephrolithiasis. Male predominance in occurrence of urolithiasis is seen usually in the middle aged patients where it is 2.8 times more common than among women. Diet and lifestyle changes have led to variations in stone disease prevalence and an apparent increase in nephrolithiasis in women.

Role of testosterone and estrogens

The male-to-female ratio in stone formation in the reproductive stage is approximately 3:1 as stated above, although there is no gender difference in childhood or climacterium. This is because of enhancing capacity of testosterone and inhibitory capacity of oestrogen in stone formation. Studies have shown that testosterone promotes renal crystal deposition because glycolic acid oxidase is involved in the metabolism of ethylene glycol (EG) to oxalate and the activity may be enhanced by testosterone.[4] Estrogens may influence several key steps in kidney stone formation, including the urinary excretion of kidney stone constituents, urinary promoters and inhibitors of kidney stone formation. Postmenopausal estrogen production is primarily influenced by body weight but not by age. Estrogen has been shown to inhibit bone

resorption and enhance renal tubular calcium re-absorption. In females low level of estrogen increases the sensitivity of bones to parathyroid hormone, leading to a net increase in bone resorption and increased urinary calcium excretion.[6] Estradiol has protective effect in premenopausal women compared with menopausal women in reducing urolithiasis development.[7] Urinary excretion of calcium, oxalate, and uric acid is higher in male and that of citrate an inhibitor of stone formation, is lower, as compared to females.[8] Kohri et al reported that middle-aged women had milder metabolic acidosis and alkaline urine, while the elderly had a similar normal acid base balance as men. Studies of stone forming patients also showed that men did excrete more calcium and oxalate (two important promoters of lithogenesis) and less citrate (an important inhibitor of lithogenesis) as compared to women. Compared with men urinary calcium was lower in women until age 50 years, when it equaled that of men. The excretion of urinary citrate varies with serum estrogen during the menstrual cycle. Menopause is associated with loss of the hypocalciuria and hypercitraturia effect of estrogens and itmay describe the second peak age of onset for nephrolithiasis in women. Estrogen deficiency at menopause in women is associated with reduced calcium absorption and increased calcium oxalate saturation, which is reversed by estrogen replacement. These discoveries support a connection of serum estrogen status with the propensity for calcium oxalate nephrolithiasis. It has been seen that the excretion of urinary citrate varies with serum estrogen during the menstrual cycle. These studies are compatible with the assumption that menopause is associated with loss of the hypocalciuria and hypercitraturia effect of estrogen and it may explain the second peak age of onset for nephrolithiasis in women. Estrogen deficiency during menopause in women is associated with reduced calcium absorption and increased calcium oxalate saturation, which is reversed by estrogen replacement. These findings show a connection of serum estrogen status with the liability for calcium oxalate nephrolithiasis. In experimental animal studies, Lee, Lguchi, Yoshioka and Fan also found extensive crystal deposition in intact male rats and testosterone administered males and females, whereas relatively few crystal deposits were observed in intact females, castrated females, castrated males and estradiol - administered males. In addition, castration of male rats dramatically decreased the incidence of renal stones. Their findings showed that testosterone is a promoter and estradiol an inhibitor of crystal deposition.[9]

Testosterone appears to elevate stone formation by suppressing osteopontin expression in the kidneys and increasing urinary oxalate excretion, while estrogen appears to act inversely. It is postulated that lower serum testosterone levels is regarded as protective for women and

children against oxalate stone disease. Higher mean of plasma oxalate concentration and kidney calcium oxalate deposition in men are influenced by androgens.[10] Active dihydrotestosterone (DHT) is developed from testosterone by cytosolic enzyme, 5α-reductase and has been considered to be partially responsible for exaggerated hyperoxaluria observed in the rat ethylene glycol model of urolithiasis.[11] In the liver, oxalate is developed from glycolate via glyoxylate in the hepatic peroxysomes, and this oxidation is catalyzed by glycolate oxidase (GO), lactate dehydrogenase and xanthine oxidase. Simultaneously, glyoxylate is metabolized to glycine by serine pyruvate aminotransferase/alanine: glyoxylate aminotransferase (SPT/AGT), which is thought to inhibit oxalate synthesis.[12]

Role of citric acid

Urinary citric acid is assessed to be an inhibitor of stone formation because it shows a chelating activity against Calcium ions. The urinary excretion of citric acid is distinctly less in stone formers than that in healthy adult. The urinary excretion of citric acid has been established to vary with the estrus cycle and is markedly increased in postovulatory or later periods when the level of estrogen secreted increases. The urinary excretion of citric acid was most influenced by the variation of the acid-base equilibrium.[13] Citric acid plays an important role as an "Inhibitor" in preventing supersaturation with respect to the creation of calcium oxalate. The urinary citrate levels are really subject to wide variations and depend to some extent on dietary habits. Larger intake of animal protein and sodium usually reduces the urinary citrate level. It is observed that there is severe hypocitraturia in almost all stone patients and this might be because all these patients are nonvegetarians and are in the habit of eating non-vegetarian food frequently. Citrate excretion also increases with increase in body weight. Citrate chelates calcium in the urine, helping to prevent precipitation of calcium salts, particularly in alkaline urine. Under normal conditions as much as 70% of the calcium in the urine may be bound to citrate when citrate excretion is reduced, less calcium is chelated and nephrolithiasis formation is promoted.[14] Furthermore, urine in males has significantly less citrate in comparison to female. Hypocitraturia due to malabsorption or other reasons may be one of the liable factors for crystallization and urolithiasis. Citrate seemingly inhibits saturation, crystallisation and further growth of already formed Calcium Oxalate and Calcium Phosphate crystals.[15]

Effect of climate on urolithiasis

Significant human migration (from rural areas to warmer, urban locales beginning in the last century and projected to continue) may have a greater impact than global warming on the observed worldwide increasing prevalence rate of nephrolithiasis. In a follow-up analysis by Soucie et al the relation between stone prevalence and specific risk factors such as mean temperature, sunlight index, and beverage consumption was examined. For males, sunlight exposure explained more of the regional variation than mean annual temperature or beverage consumption. For women, beverage consumption, average temperature, and sunlight index each explained regional variation more or less equally, but even after adjustment for differences in all three risk factors, the regional variation in the odds of stones was still largely unexplained, unlike in males. It is noted that men and women probably sweat to a similar degree as evidenced by their reduced urine sodium excretion, but women are better at replenishing losses. Another possible clarification for the different gender response to temperature is the different stone composition in men versus women. As struvite stones are related to infection, rather than to the urinary supersaturation of calcium salts, one would not expect them to be associated with environmental factors. Although struvite stones are only 10% of all stones, women suffer from them proportionally more often than men. This may partially explain the gender difference in relation to changes in stone prevalence rates with respect to temperature. The odds ratio for stones was almost twice as high in the hottest, most sunny parts of the country than in the coldest, least sunny parts. In a healthy individual, during the residence time of urine in the urinary tract, crystals either do not form or are so small they are eliminated; it also appears that heat does play a role in pathogenesis in certain populations. The role of heat is much greater in men than in women.

CONCLUSION

The present review reveals that occurrence of stones is lesser in females as compared to males because of the protective role of female sex hormones. Also other factors like citric acid and environment play a crucial role in higher incidence of stones in men.

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