

Comparison of 24 hours urinary citrate levels in urolithiasis patients and healthy controls

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Abstract

Objective: To identify the difference in urinary citrate excretion between Stone Formers (SF) and Healthy Volunteers (HV) as a metabolic risk factor, that predisposes to urinary stone formation and to compare levels of urinary citrate in (HV) with reference values.

Methods: The 24 hours urinary citrate was evaluated in 40 patients treated for renal citrate and declared stone free, and 40 age matched healthy adults taken as controls. Both the groups had a similar living environment, extrinsic factors, diet and similar genetic descent.

Results: There was no significant difference in urinary citrate excretion level among stone formers (mean 262 SD 197) and normal volunteer subjects (mean 269 SD 140). Using the previously defined normal values (200) of urinary citrate in the local population, 55% of stone patients in our study group were hypocitric. While using the same value, 45% of our normal volunteers were also hypocitric. If 320 was taken as normal limit, 70 % of the patient's population and 72 % of controls were hypocitric. The prevalence of hypocitraturia was similar in the age matched adult groups.

Conclusion: Certain intrinsic factors in our local subjects may account for the high prevalence of urolithiasis than in western population. Although the urinary citrate excretion of stone patients is similar to normal volunteers, uniformly low urinary citrate excretion may be a feature as a nation and not a predisposing factor for the lithogenesis. This supports the view that there may be more often prominent influences in stone formers possibly of genetic origin (JPMA 55:371;2005).

Introduction

Countries in the Afro-Asian stone belt falling within the tropical and subtropical regions have consistently reported a high incidence of urolithiasis.¹ The recurrence rate without treatment for calcium oxalate renal stones is 10% at 1 year, 35% at 5 years and 50% at 10 years.²

Several studies indicate that urinary stone disease has a high prevalence in our country. But unfortunately the epidemiology of urolithiasis remains poorly investigated in the region. Prevalence rates are mostly based on hospital admissions. The etiology of stone formation in a given population is reflected in the composition of calculi, metabolic studies, and dietary habits.¹ There are various extrinsic and intrinsic factors for renal stones in the different population groups in different provinces of Pakistani population. More than half the people live in rural areas and the climate is

moderate to hot.³ Poor nutritional status and inadequate health facilities are common in the region. However, there are few published studies objectively comparing the risk factors for urinary stone disease and its recurrence in local population. The most common type of urinary stone in our local population is calcium oxalate (60-65%), confirming that the composition of urinary stones in Sind, lower Punjab and Balochistan is inconsistent with international findings. Metabolic studies from the region show that the major risk factors are low urinary volume (20-30%), hyperuricosuria (20-60%), hyperoxaluria (50-60%), hypomagnesuria (20-30%) and hypocitraturia (30-40%).¹ These results suggest that dietary and environmental factors are more important in this region, as oxalate-rich and calcium-poor diets prevail with low intake of proteins. Furthermore, chronic diarrhea and malabsorption in the tropics could be a major causative factor for hyperoxaluria.⁴

It is now frequently recognized that hypocitraturia is a frequent biochemical disturbance among patients with nephrolithiasis. There is no consensus on the normal range for urinary citrate. Arbitrary but different values are used in western and local studies to define the lower normal limits. The purpose of this study was to identify urinary citrate levels in stone formers and normal individuals and to compare the prevalence with other published data.

Subjects and Methods

Between June and December 2004 adult patients who were diagnosed for urolithiasis in out patients department and were treated as inpatients at our hospital were selected for the study. After completion of treatment forty patients, declared completely stone free, were included in the study, after informed consent. They were classed as index subjects. By using non probability purposive sampling technique, equal number of age matched normal adult individuals among the hospital employees, who had no evidence of urolithiasis and were willing to consent as control subjects were included as control group. A thorough medical history was taken from each index subject and normal control, which included date of the first stone episode and the number of stones previously passed.

Each participant was given verbal and written instructions about the collection of urine sample. Subjects were also instructed to collect the sample while on their usual diet and to avoid any medical therapy that may alter the urinary citrate levels. The 24 hours urinary excretion of citrate was measured in both the groups. All samples were collected in a special jar containing fixed quantity of citrate preservative, Thymol. All samples were checked in the same laboratory. Citrate level was estimated by enzymatic citrate lyase analysis (Bergmeyer method). Improper collection of urine was excluded.

All data was analyzed by SPSS version 10.0 data files. Description statistics regarding age distribution of the subjects was calculated. Difference in the mean and median of urinary citrate of both groups was tested with student-t at the level of significance of p value <0.05.

Results

The mean age of the patients and the controls (23 males and 17 females, male: female ratio 1.4:1); was 38.1 ± 12.7 years and 37.5 ± 8.8 years respectively. All patients included in the study had their 24 hours urinary collection for citrate excretion (Table 1). There was no documented urinary tract infection.

As the urinary excretion of citrate did not differ significantly with gender, they were included as one group among patients, and a t-test used to assess the significance of any differences when comparing with the citrate levels of control subjects (HV) (Table 1); Mean urinary citrate excre-

tion among the patients was 262 ± 198 mg (median value 174 mg) compared to 269 ± 140.5 mg (median value 232 mg) in control subjects. This shows no significant differences of excretion of urinary citrate between patients and control population in the study Figure.

Table 1. Mean Urinary Volume and Mean Urinary Citrate.

	Total (n)	Urinary Volume mls/24hrs	Urinary Citrate mg/24hrs
Cases	40	2214 ± 934	262 ± 197
control	40	1568 ± 1044	269 ± 140

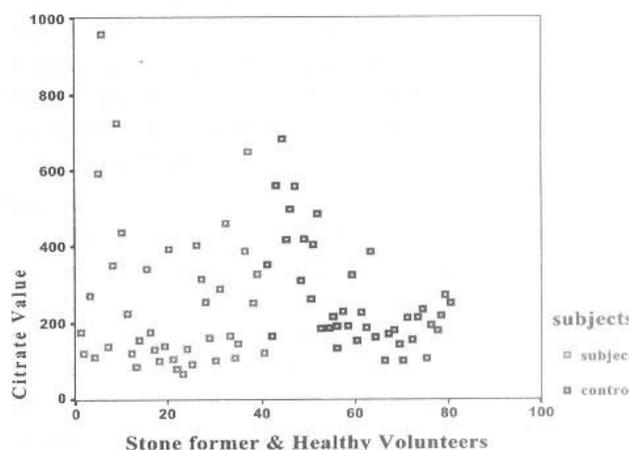


Figure. Citrate Values of Stone formers and Health Volunteers.

Using the previously defined normal value 200 mg⁵ (Table 2) of urinary citrate in the local population, 55 % of stone patients in the study group and 45% of the controls had hypocitraturia. While using 320 mg⁶ as normal limit, 70% of the patients and 72% of the controls had hypocitraturia. The level of hypocitraturia was similar in the age matched adult groups.

Table 2. Stone formers and normal volunteers with urinary citrate levels below reference levels.

	Reference levels for 24 hrs Urinary Citrate	Hypocitraturic Stone Formers n = (%)	Hypocitraturic Controls (HV) n = (%)
Nabeel ⁵	200 mg	22 (55%)	18 (45%)
Rizvi ¹	300 mg	27 (67%)	28 (70%)
Talati ⁶	320 mg	28 (70%)	29 (72.5%)

Discussion

Despite advances in treatment methods, urinary stone disease remains a major source of morbidity. The understanding of pathophysiology of stone disease remains limited and stone recurrence continues to be a significant clinical problem. The rates of stone recurrence are reported-ly 22.6-51% at a mean follow-up of 2-7.1 years.⁷

Several extrinsic factors, e.g. geography, climate, water intake, diet, metabolic disorders and occupation, are considered risk factors for stone formation and recurrence. Diet constitutes a major component of the environmental factors for urolithiasis. Rizvi et al have reported a low protein and calcium diet with an increased consumption of oxalate-rich foods and a low intake of fluids in our population.⁸ Other factors with undefined roles in stone formation are heredity, age and sex. If there was a reliable prediction of which factor(s) were important in increasing the risk for stone formation and recurrence, efforts in both medical prevention and life-style changes could be preferentially directed towards those factors.

Urine could supersaturate with the crystals of salts (calcium, oxalate and phosphate) and in the absence/low concentration of urinary inhibitors. These inhibitors include small ions such as magnesium and citrate as well as polyanions of high molecular weight such as glyconaminglycans.⁹

In the present study, gender distribution was comparable with previous international data.⁷ Gender has some effects on urinary constituents; normal women have higher urinary citrate and lower urinary calcium than normal men.¹⁰ Because of the gender difference we compared the mean of the excreted urinary citrate between men and women in the patients. Mean urinary citrate in male stone forming patients was 259 mg (median value 170 mg) and among females 265.8 mg (median value 255 mg). There was no age difference between the genders in the two groups.

Dehydration and low urinary volume are widely accepted risk factors for urinary stone disease. There was a higher level of high urinary output in the study patients $2214 \text{ ml} \pm 934$ compared to controls, 1568 ± 1044 (Table 1), probably because the patients group was told to drink more water during their post operative hospital stay or after lithotripsy sessions.

Hypocitraturia may be an ominous sign for stone formation and an obvious finding in our study when compared to other studies. The frequencies of the 24 hours urinary citrate excretion between the cases and the control groups (262 ± 197 and 269 ± 140 respectively) were statistically insignificant. Control group (HV) had no significant difference in mean urinary citrate excretion than patients group (SF). There was also only a minor difference in the excretion of any urinary citrate between men (259 mg) and women (265.8 mg) in patients groups.

There appears to be no consistency in deciding cut-off values for hypocitraturia. Different authors have used

different levels.^{1,5,6} Looking at the urinary citrate excretion values at the different cut off of 200 mg, 300 mg and 320 mg, there was equal distribution of patients and normal subjects. Consistency of the results at different cut off levels, also supports the finding that there is no significant difference in the mean urinary citrate excretion. However as there is no consistency in lower acceptable levels, true frequency of hypocitraturia in subject and control population is difficult to determine.

Overall there was not a major difference between the two groups in urinary citrate as risk factors that predispose to stone formation.

Conclusion

Despite intensive research the knowledge of stone pathogenesis, which is the basis of stone prevention and metaphylaxis, has remained scanty. Targeting the hypocitraturic population for stone metaphylaxis requires uniformity in definition of hypocitraturia and consistency in urinary citrate levels. To label our local population as hypocitraturic is difficult in light of this study as even the controls have same levels. How they would respond to therapeutic measures is even a bigger question. Further prospective studies are required to establish the value of urinary citrate determination in patients consuming an uncontrolled diet in an out-patient setting.

References

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