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THE EFFECT OF URINE AND BLOOD METABOLIC RISK FACTORS ON CALCIUM STONE FORMATION

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ABSTRACT

In spite of vast improvements in urinary stone treatment (ESWL, PNL, ureteroscopy, etc.), metabolic workup concerning the existence of stone forming risk factors are of great importance and can lead to control and even prevention of urinary stone formation in these patients.

In this analytical case-control study performed on 266 persons [110 normal persons (56 males and 54 females), 76 patients with one episode of stone formation (40 males and 36 females), and 80 patients with recurrent stone formation (40 males and 40 females)] aged between 30 to 45 (with an average of 37.6) in Shahid Doctor Labbafinejad Medical Center from May to July 1999, serum parameters and 24-hour urine parameters have been investigated and compared among the three groups. Results of this study revealed considerable differences in urinary calcium levels of these three groups, with and without considering sex ($p<0.05$). Averages of 24-hour urinary calcium calculated for normal, one episode and recurrent stone formers in male groups were 159 ± 43, 219 ± 71, and 283 ± 74 mg/24h respectively, and for normal, one episode and recurrent stone formers in female groups were 124 ± 37, 190 ± 58, and 287 ± 152 mg/24h respectively. Although 24-hour urine citrate in females obviously showed higher values than males, there was no significant difference among the studied groups of the same sex. Levels of serum calcium, potassium and magnesium between groups of females and 24-hour urine magnesium and phosphate levels between groups of males had statistical differences also ($p<0.05$ for all of the cases mentioned above).

According to the results obtained from this study, it was realized that in the studied society levels of 24-hour urinary calcium which are higher than 200 mg/24h (sensitivity 80%, specificity 94% and FPR 6.4%) and calcium creatinine ratios of 24-hour urine which are higher than 0.17 (sensitivity 7.5%, specificity 88.1% and FPR 11.9%) can be regarded as hypercalciuria. However, the results of this study should be confirmed by more general and extended studies.

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Keywords: Kidney stone, Hypercalciuria, Hypocitraturia, Hypomagnesuria.

INTRODUCTION

Urinary stone disease has afflicted humankind since

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antiquity.[1] Nephrolithiasis is a common disorder and about 12% of the population will develop urinary stones during their lifetimes.[2] The highest incidence is between 30-50 years old.[3] The incidence of this problem is increasing[4] and the probability of recurrence without treatment for calcium oxalate renal stones is 10% at 1 year, 35% at 5 years and 50% at 10 years.[5]

Some metabolic abnormalities have been identified as risk factors: hypercalciuria, hyperoxaluria, hyperuricosuria and hyperphosphaturia.[1,6,7]

A very important role in the lithogenic process was attributed to a defective production of urinary inhibitors of stone formation, mainly hypocitraturia and hypomagnesuria.[8] Several studies have shown that a combination of factors provides a better separation than any individual parameter.[9,10,11]

The aim of this investigation was to compare the metabolic risk factors between normal and stone forming people (single and recurrent).

MATERIAL AND METHODS

In this analytical case-control study, metabolic evaluation was performed in 30 to 45 year old individuals living in Tehran and referred to Labbafinejad Hospital from May through July of 1999. According to history and primary workup (KUB and urinalysis) the studied population were divided into 3 groups:

Group I: Control group (without history of stone formation and normal primary workup)

Group II: Single stone formers

Group III: Recurrent stone formers

Gravindex was performed before KUB in females. Pregnant females, those with urinary infection, and cases with abnormal kidney function were excluded from the study. None of them were taking any vitamin D or calcium supplementation, antacids, diuretics, allopurinol or ascorbic acid.[1] Only calcium stone formers were included in group II and III.

The number of samples was calculated on the basis of Varier's dispersion used in various references.[13,19]

A total of 226 persons were evaluated: 110 normal persons (56 males and 54 females), 76 patients with one episode of stone formation (40 males and 36 females) and 80 patients with more than one episode of stone formation (40 males and 40 females).

With the patient on a random diet and on a holiday, one 24-hour urine sample was collected and analyzed for phosphate, calcium, pH, potassium, magnesium, chloride, sodium, uric acid, citrate, oxalate, creatinine and volume. A fasting venous blood sample (minimum 10 hours) was drawn with a vacuum tube (Venoject) and analyzed for creatinine, magnesium, phosphate, calcium, potassium, sodium, uric acid, chloride and HCO_3^-.[7]

Group differences in prevalence of discrete baseline variables were evaluated by Student's t-test for unpaired results and ANOVA, an analysis of variance program that applies Tukey's studentized range test. ($p<0.05$ as the significance level).

RESULTS

Table I shows some of the quantitative measurements in different studied groups.

Table I. The summary of quantitative variables and standard deviation indices in different studied groups.

Variables	Normal		Single stone former		Recurrent stone former	
	Females Median(SD)	Males Median(SD)	Females Median(SD)	Males Median(SD)	Females Median(SD)	Males Median(SD)
24h urine volume	1467 (825)	1168 (464)	1666 (831)	1454 (740)	1871(1087)	1672 (847)
Serum potassium	4.02 (0.36)	4 (0.38)	4.06 (0.43)	4 (0.35)	4.2 (0.04)	4.1 (0.47)
24h urine potassium	43.5 (16)	39 (18)	36 (16)	38 (19)	28 (15)	28 (11)
Serum calcium	8.9 (0.75)	9.1 (0.89)	9.1 (0.83)	9.2 (0.8)	9.5 (0.77)	9.3 (1.1)
24h urine calcium	124 (37)	159 (43)	190 (58)	219 (71)	287 (152)	283 (74)
24h urine Ca/Cr ratio	0.130 (0.04)	0.12 (0.03)	0.20 (0.06)	0.18 (0.05)	0.3 (0.18)	0.22 (0.07)
24h urine phosphate	417 (125)	489 (139)	426 (162)	503 (170)	477 (129)	595 (208)
24h urine P/Cr ratio	0.42 (0.11)	0.38 (0.1)	0.44 (0.13)	0.4 (0.12)	0.5 (0.14)	0.45 (0.14)
24h urine uric acid	455 (124)	543 (138)	483 (144)	538 (143)	560 (197)	579 (202)
24h urine citrate	802 (296)	706 (267)	736 (302)	675 (364)	710 (371)	633 (386)
Serum magnesium	1.8 (0.31)	1.8 (0.33)	1.8 (0.26)	1.8 (0.38)	1.7 (0.16)	1.7 (0.24)
24h urine magnesium	60.3 (21.8)	64.6 (20.4)	50.7 (18.7)	53.9 (26)	54.9 (18.2)	51 (14.1)
24h urine Mg/Cr ratio	0.06 (0.03)	0.05 (0.02)	0.05 (0.02)	0.04 (0.02)	0.06 (0.02)	0.04 (0.01)

Table II. Comparison of the different studied groups for determining levels of urine and serum risk factors ($p<0.05$) [(+): Significant difference, (-): No significant difference].

Variables	Female			Male		
	I & II	I & III	II & III	I & II	I & III	II & III
24h urine volume	-	-	-	-	+	-
Serum potassium	-	-	-	-	+	-
24h urine potassium	-	+	+	+	+	+
Serum calcium	-	-	-	-	+	+
24h urine calcium	+	+	+	+	+	+
24h urine Ca/Cr ratio	+	+	+	+	+	+
24h urine phosphate	+	+	-	-	-	-
24h urine citrate	-	-	-	-	-	-
Serum magnesium	-	-	-	-	+	+
24h urine magnesium	+	+	-	-	-	-
24h urine Mg/Cr ratio	+	+	-	-	-	-

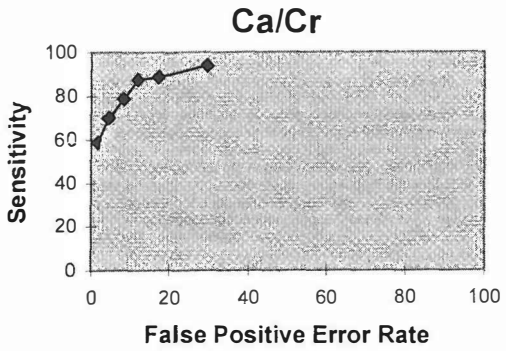

Fig. 1. ROC curve for Ca/Cr ratio (measurements on the curve from up to down are 0.14-0.16-0. 17-0. 18-0. 2-0.22 respectively).

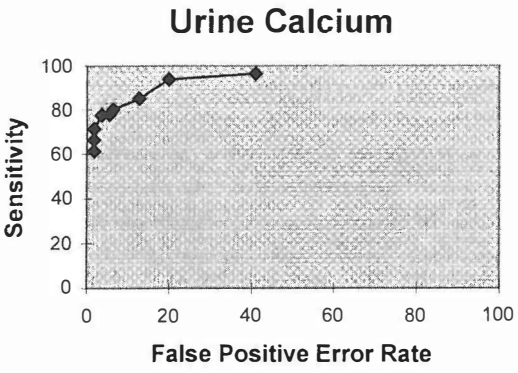

Fig. 2. ROC curve for urinary calcium (measurements on the curve from up to down are 150-180-190-200-210-220-230-240-250 mg/24h respectively).

The level of serum calcium in recurrent stone former females was significantly higher than single stone formers and normal females ($p<0.05$). Obviously 24h urine calcium levels in normal males were higher than normal females but such a difference was not seen between male and female stone formers.

The 24h urine calcium level in recurrent stone formers was higher than normal and single stone formers. Also, the urinary calcium level in single stone formers, in comparison with the normal group, was higher. These findings were confirmed with the results of urine calcium to creatinine ratios.

Although serum magnesium in recurrent stone former females was significantly lower than normal and single stone former females, such findings were not seen in different male groups. Only in stone former males (groups II and III) was 24h urine magnesium significantly lower than normal males. No significant difference was seen between the level of urinary citrate in stone former and normal groups.

24h urine volume in normal females was lower than normal males, but only stone former females had significantly higher urine volumes than normal females and this difference was not seen between male groups.

Table I shows the important results. It should be mentioned that variables show no significant difference between the groups.

In our studies a Ca/Cr ratio higher than 0.17 (Sensitivity 87.5%, Specificity 88.1%, PPV: 84.3%, NPV: 90.6%) and 24h urine calcium higher than 200mg (Sensitivity 80%, Specificity 94%, PPV: 90%, NPV: 94%) indicated hypercalciuria (cut off points) (Fig 3. 1 and 2).

Determining cut off points for other variables-due to overlapping of findings between groups-was not statistically possible.

DISCUSSION

In this study, the age group of 30 to 45 years old has been selected to decrease the effects of age as much as possible. This age group was selected because most urinary stones are found in 30-50 year olds and for removing the menopausal factor in females.[3,4]

We showed that there was no considerable difference in serum calcium between males and females, but hypercalcemia is a risk factor of stone formation in recurrent stone former females. This can be explained by the higher incidence of hyperparathyroidism in females.[18,24] In this study if there was a possibility of hyperparathyroidism, complementary diagnostic tests were done and two cases of hyperparathyroidism in the recurrent stone former group were diagnosed.

In different references hypercalciuria has been shown with different measures. Some references would consider a level above 300 mg/24h[6] and others above 250 mg/24h[7] as hypercalciuria. Following this study it is proven that the average level of urinary calcium in our country is less than others, as also approved by Dr. MirSaeed Ghazi.[23] This would be explained by the lower level of calcium in our diet, as some references would explain hypercalciuria on the basis of the amount of calcium in the diet.[2]

Those who have experienced stone formation (single or recurrent) had a noticeably higher level of urine calcium than normal persons. Also, Tisellius revealed that there is a significant difference between the average excretion level of 24h urine calcium in normal and stone former males and females.[13] With respect to the calcium to creatinine ratio, our findings also had the same results.

For clinical use of our findings, the cut off point for 24h urine calcium level was determined and through statistical calculation, it was observed that the amount of 200 mg calcium in 24h urine is hypercalciuria. As the 24h urine calcium level was not significantly different in male and female stone formers, this cut off point can be used for both sexes. Then we determined the 24h urine calcium to creatinine ratio cut off point as 0.17.

It was shown that hypomagnesemia in females and hypomagnesuria in males is considerable in stone formation. The measurement of 24h urine magnesium to creatinine ratio confirmed this finding for males. Today, hypomagnesuria is an important known factor in stone formation.[12,13]

One of the considerable points of our study is the low incidence of hyperuricosuria in stone former patients. It should be mentioned that in other countries hyperuricosuria is commonly present.[3] In this research, the level of urinary phosphate in stone former males is considerably higher than normal males. The role of phosphate as a dependent or independent variable is important.[7] It must be mentioned that in some studies, hyperphosphaturia had no effect on stone formation[12,14,15] while in other studies it was effective.[13]

The role of urinary excretion of potassium in females is more noticeable. Although the urinary level of potassium is significantly low, in males this decrease is considerable only by the increase of stone formation episodes. The role of urinary potassium in stone formation has been mentioned in several studies, and has a direct relation to the acid and base variations.[18,19]

Although there was no noticeable difference in 24h-urine citrate between stone formers and the normal population in our study, the role of hypocitraturia in stone formation has been proven[12,14,15] and judgement about the role of hypocitraturia in our patients needs more studies.

Hyperoxaluria is an important factor in the formation of calcium stones[1,2,6] and the 24h urinary excretion level of oxalate was determined in this study, but because of the use of a qualitative process (Hodgkinson)[22] which has a low credit and was the only accessible measurement for us, the lack of significant differences between the groups was not reliable.

It seems that the low incidence of decreased urine output in our study is due to instructing stone formers to have high consumption of water. The role of the low level of 24h urine output in stone formation has been shown by Brown and colleagues recently.[12]

Enbon and colleagues have shown that the low level of urine output is a risk factor in 19% of patients with recurrent stone formation.[16] In Saudi Arabia, the low level of 24h urine output has been considered an important risk factor in stone former persons.[17]

Although different studies have shown that there is no difference between single or recurrent stone formation, in this study the urinary excretion level of calcium and potassium between the two groups was significantly different.

With regard to the results, we recommend:

1- Until an extensive study in our country, a 24h urine calcium level higher than 200mg and a 24h urine calcium to creatinine ratio higher than 0.17 to be considered as hypercalciuria.

2- Although in our study, hypocitraturia has not been shown as a risk factor, an extended study should be done.

3- Hypomagnesuria must be considered as a more important risk factor in stone formation.

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