INCREASED RISK OF URINARY STONE DISEASE BY PHYSICAL EXERCISE

Pote Sriboonlue[1], Vitoon Prasongwatana[1], Piyarat Tosukhowong[2], Kriang Tungsanga[3] and Sombat Bovornpadoongkitti[4]

[1]Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [2]Department of Biochemistry and [3]Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [4]Urologist, Khon Kaen Provincial Hospital, Khon Kaen

Abstract. Constituents of 6-hour (0900-1500 hours) urine collected during rest and exercise have been compared among 3 groups of male volunteers. Groups 1 and 2 (GI, GII) were normal controls residing in an urban area (n = 10) and rural villages (n = 9), respectively, and group 3 (GIII) consisted of 10 renal stone formers from the same location as GII. Exercise was performed by cycling on an electronic bicycle with three 150-watt loads and the duration of each load was 20 minutes. Collected usine was analyzed for volume, pH, PI (permissible increment) in oxalate, creatinine, calcium, sodium, potassium, phosphorus, oxalate, uric acid and citrate. The results showed that most urinary excretions during both rest and exercise periods were similar among the 3 groups. Only the following values were significantly different, *ie* in the rest period, calcium of GIII < GII ($p < .01$) and potassium of GII < GI ($p < .05$); in the exercise period, potassium of GIII < GI ($p < .02$) and phosphorus of GIII < GII ($p < .03$). In comparison between the rest and exercise periods within each group, the decreased total excretions during exercise were creatinine of GI ($p < .05$) and GIII ($p < .05$), calcium of GII ($p < .05$) and phosphorus of GIII ($p < .05$); only calcium of GIII ($p < .05$) was increased. However, when the concentration of each constituent was taken into consideration, most constituents increased in concentration during the exercise period due to the fall in urinary volume. Furthermore, during exercise both pH and PI in oxalate of urine decreased significantly. Thus the results of our study suggested that though most total urinary excretion patterns were similar between the rest and exercise periods, the risk of stone formation in the urinary tract during exercise could be enhanced. The enhanced risk is likely due to 3 main factors, *ie* (1) decrease in urinary volume, (2) increased propensity for crystallization of calcium oxalate (PI in oxalate decreased) and (3) decrease in urinary pH which will directly cause an increase in saturation level of uric acid. This increased risk of stone formation was consistently observed in all three groups of subjects.

INTRODUCTION

Regional differences in the occurrence rates of urolithiasis are usually demonstrated in most epidemiological surveys (Swift Joly, 1934; Frank *et al*, 1959; Anderson, 1973; Schneider, 1985). This strongly suggests an etiologic role of environmental factors such as diet, climate, occupation and water intake (Anderson, 1973). In studies among Israeli populations, Frank *et al* (1963) observed a relationship between the incidence of urolithiasis and the climatic temperature *ie* the incidence was highest in the hottest region. A major cause was probably inadequacy of fluid intake in compensating for the large extrarenal fluid loss from high temperature (Frank *et al*, 1959). This condition would inevitably cause low urine output and finally lead to an increase in saturation level of stone-forming salts. Unusually high prevalence of urinary tract stones was associated with subsets of the population whose activities may have caused excessive sweating, as observed in marathon runners (Milvy, 1981) and in lifeguards on beaches of the Mediteranean sea in Israel (Better *et al*, 1980). However, in the case of marathon runners, stone formation was probably not only a consequence of excessive sweat loss, but also strenuous exercise could bring about high production of uric acid from subclinical muscle damage. Increased uric acid excretion or hyperuricosuria is an important risk factor of urinary stone disease (Robertson and Peacock, 1985; Pak *et al*, 1980).

Furthermore, metabolic acidosis associated with exercise may cause low urinary excretion of citrate (Simpson, 1964). The resulting hypocitraturia would enhance stone-salt activities in the urine (Robertson and Peacock, 1978). Hypercalciuria, another well known factor in urolithiasis, might be created due to an inhibitory effect of acidosis on calcium reabsorption (Sutton and Dirks, 1977). Low urinary pH resulting from metabolic acidosis would also increase undissociated form of uric acid and eventually increase its saturation level in urine. Investigation to assess the role of physical

exercise on urinary stone formation by Sakhee *et al* (1987) found that though the exercise was only moderate, if performed without increased fluid intake to compensate for excessive sweating, could increase risk indices of urinary stone disease. In this extended study, we observed the effects of moderate exercise on urinary risk factors in three different groups of subjects: two groups with and without stone formation from a rural area, the third group being non-stone formers from an urban area. The diet and fluid intake of the subjects were well controlled thoughout the study period.

MATERIALS AND METHODS

Subjects

There were 3 groups of subjects involved in this study. Ten laboratory personnel comprised the urban control group 1 (GI), 9 villagers served as the rural control group 2 (GII) and group 3 (GIII) comprised 10 renal stone formers residing in the same rural villages as GII. The subjects of GIII included both ones having a history of stone surgery and those with stones retained at the time of investigation. All subjects were males aged 20-50 years old. They were aparently healthy without evidence of renal failure (serum creatinine ≥ 2 mg %), urinary tract infection (urine culture $\leq 10^5$ colony/ml urine), heart disease or any other detectable systemic illness. Characteristics of the subject groups were shown in Table 1.

Study methods

The study protocol comprised 3 days.

(1) First day-adaptation period : Subjects were brought to the laboratory site and had the whole 3 meals together. They had breakfast at 0800 hours of 2 boiled eggs and some sticky rice, lunch at 1200 hours of boiled rice noodles and a small amount of meat; dinner at 1800 hours with beef curry, some vegetables and some sticky rice. These meals, from estimation, would cause the subjects to receive calcium, phosphorus, potassium and sodium less than 400 g, 800 g, 60 meq and 100 meq per day, respectively.

Table 1

Characteristics of the subject groups.

	GI (n = 10)	GII (n = 9)	GIII (n = 10)
Age, year (X ± SD)	29.5 ± 3.37	26 ± 5.94	35.4 ± 6.29
range	20-35	20-37	25-43
Weight, kg (X ± SD)	65.2 ± 7.33	62.7 ± 6.69	61.6 ± 7.6
History of stone surgery	-	-	9
Bilateral stone	-	-	2

(2) Second day-rest period : After bringing the subjects to the laboratory as on the first day, most of their activity was at rest, watching TV. The same meals as the first day were taken at the same times and 300 ml of deionized water was given every 3 hours starting from 0800 hours. Urine specimens (6 hours) were collected without preservative and chilled on ice during 0900-1500 hours.

Third day-exercise period : Meals and water were taken similar to the procedure in the rest period. Exercise was performed by cycling on an electronic bicycle with three 150 watt loads and each load lasted for 20 minutes. The first 2 cyclings were performed during 0900-1200 hours and the third after a lunch break. A period of about 1 hour or more was allowed for a rest between each load. Urine specimens were also collected in the rest period.

Urinary analysis : Volume and pH of urine were measured after the specimens were warmed to 37°C. Prior to further analysis, aliquots of urine specimens were centrifuged to remove debris.

(A) *Biochemical analysis :* The determination of calcium was carried out by atomic absorption spectophotometry. Sodium and potassium were determined by ion-selective electrodes. Color reaction of Fiske and Subbarow (1925) was used for phosphorus determination. Uric acid was analyzed by an enzymatic method (Makino and Konno, 1967), oxalate by the color reaction of Hodgkinson and Williams (1972). Citrate was determined by citrate lyase (Welshman and McCambridge, 1973) and creatinine was done by the Jaffe reaction (Tietz, 1970).

(B) *Crystallization study of urine specimens :* Only calcium oxalate crystallization was studied and the permissible increment (PI) in oxalate as described by Nicar and coworkers (1983) was employed due to the convenience in practice and east of interpretation. In brief, a urine specimen was adjusted to pH 6.4 and recentrifuged to remove

debris. Ten milliliter portions of clear urine were pipetted into various tubes to which 100 µl of sodium oxalate solution of different concentrations (0-60 mM) were added. After incubation with stiring at 37°C for 3 hours, the tube with lowest concentration of added sodium oxalate and that with the appearance of white precipitation of calcium oxalate was recorded. This amount of added sodium oxalate would reflect both the levels of oxalate and inhibitors of calcium oxalate crystallization that already exist in that urine specimen. It indicated the propensity for spontaneous nucleation of calcium oxalate, where a decreasing value (small amount of sodium oxalate added) represented an increased propensity.

RESULTS

Comparision of biochemical composition of urine among the 3 groups

Urine composition during rest and exercise periods is shown in Tables 2 and 3, respectively. Most constituents of rest period urine were similar among the 3 groups, except that calcium of GII was higher than that of GIII (GII = 68.7 ± 9.90, GIII = 34.4 ± 5.68 mg/6 hours; $p < .01$) and potassium of GI was higher than that of GII (GI = 9.34 ± 1.14, GII = 5.39 ± 1.04 mg/6 hours; $p < .05$). This degree of consistency in composition was observed also for urine collected during exercise where only 2 values were significantly different, *ie* potassium between GI and GIII (GI = 11.7 ± 1.77, GIII = 6.2 ± 0.72 meq/6 hours; $p < .02$) and phosphorus between GII and GIII (GII = 174 ± 26.1, GIII = 108 ± 10.6; $p < .03$).

Table 2

Biochemical composition of 6 hours urine during rest period (X ± SEM).

	GI (n = 10)	GII (n = 9)	GIII (n = 10)
Volume, ml	795 ± 125	760 ± 165	845 ± 98
Creatinine, mg	575 ± 86.0	430 ± 29.5	433 ± 21.1
		p < 0.01	
Calcium, mg	49.9± 9.00	68.7± 9.90	34.4± 5.68
Sodium, meq	42.5 ± 7.13	44.5± 11.5	36.4 ± 4.24
	p < 0.05		
Potassium, meq	9.34 ± 1.14	5.39 ± 1.04	7.30 ± 1.06
Phosphorus, mg	162 ± 32.1	163 ± 25.1	192 ± 33.9
Uric acid, mg	175 ± 20.6	190± 22.9	155± 27.4
Oxalate, mg	6.41 ± 1.62	8.78 ± 2.89	7.95 ± 2.92
Citrate, mg	60.3 ± 19.6	48.8 ± 8.97	30.2 ± 10.7

Table 3

Biochemical composition of 6 hours urine during exercise period (X ± SEM).

	GI (n = 10)	GII (n = 9)	GIII (n = 10)
Volume, ml	345 ± 98	330 ± 92	370 ± 81
Creatinine, mg	398 ± 23.0	414 ± 33.4	353 ± 40.7
Calcium, mg	48.8± 11.6	46.2± 5.76	53.8± 6.80
Sodium, meq	36.4 ± 4.50	37.6± 6.55	29.7 ± 8.03
	p < 0.02		
Potassium, meq	11.7 ± 1.77	8.42 ± 1.31	6.20 ± 0.72
		p < 0.03	
Phosphorus, mg	166 ± 27.8	174 ± 26.1	108 ± 10.6
Uric acid, mg	177 ± 34.3	152± 31.9	123± 15.9
Oxalate, mg	5.76 ± 1.29	7.58 ± 1.93	6.96 ± 1.13
Citrate, mg	32.3 ± 7.82	41.0 ± 9.49	25.4 ± 9.10

Comparison of biochemical composition of urine between rest and exercise periods within the same groups

In comparison within groups, between rest and exercise periods, the results are shown in Table 4 for total excretion and in Table 5 for concentration of the constituents. The results showed that almost all total excretions were the same between rest and exercise periods for GI and GII, only creatinine of

Table 4

Comparision of 6 hours urinary excretions between rest (R) and exercise (E) periods within the same groups (only statistical p values are shown).

	p value of R *vs* E		
	GI (n = 10)	GII (n = 9)	GIII (n = 10)
Creatinine, mg	0.05↓	NS	0.05↓
Calcium, mg	NS	0.05↓	0.05↑
Sodium, meq	NS	NS	NS
Potassium, meq	NS	NS	NS
Phosphorus, mg	NS	NS	0.05↓
Uric acid, mg	NS	NS	NS
Oxalate, mg	NS	NS	NS
Citrate, mg	NS	NS	NS

↓ = E < R, ↑ = E > R

GI ($p < .05$) and calcium of GII ($p < .05$) decreased significantly during exercise. On the other hand, in GIII, 3 components were changed significantly, *ie* creatinine ($p < .05$) and phosphorus ($p < .05$) decreased during exercise whereas the reverse change was observed for calcium ($p < .05$). However, when volume of the urine was taken into account, most of the constituents showed a significant increase in their concentrations (Table 5). These were 5 changed values in GI, *ie* calcium ($p < .02$), sodium ($p < .03$), potassium ($p < .005$), uric acid ($p < .005$) and oxalate ($p < .05$); 3 changed values in GII, *ie* sodium ($p < .05$), potassium ($p < .02$) and phosphorus ($p < .01$) and 5 changed values in GIII, *ie* creatinine ($p < .02$), calcium ($p < .001$), sodium ($p < .02$), potassium ($p < .01$) and citrate ($p < .001$).

Table 5

Comparision of concentration of 6 hours urinary constituents between rest (R) and exercise (E) periods within the same groups (only statistical p values are shown).

	p value of R *vs* E		
	GI (n = 10)	GII (n = 9)	GIII (n = 10)
Creatinine, mg/dl	NS	NS	0.02↑
Calcium, mg/dl	0.02↑	NS	0.001↑
Sodium, meq/l	0.03↑	0.05↑	0.02↑
Potassium, meq/l	0.005↑	0.02↑	0.01↑
Phosphorus, mg/d	NS	0.01↑	NS
Uric acid, mg/dl	0.005↑	NS	NS
Oxalate, mg/dl	0.05↑	NS	NS
Citrate, mg/dl	NS	NS	0.001↑

↑ = E > R

Effect of physical exercise on volume, pH and PI in oxalate of urine.

Fig 1 shows the effect of exercise upon urine output, pH and PI in oxalate. These parameters, except for the urinary pH of GIII, decreased significantly in all groups during the exercise period.

DISCUSSION

The results of biochemical analysis of urine from similar three groups of subjects in the present study have been reported previously by Sriboonlue and coworkers (1991). Some of the main findings

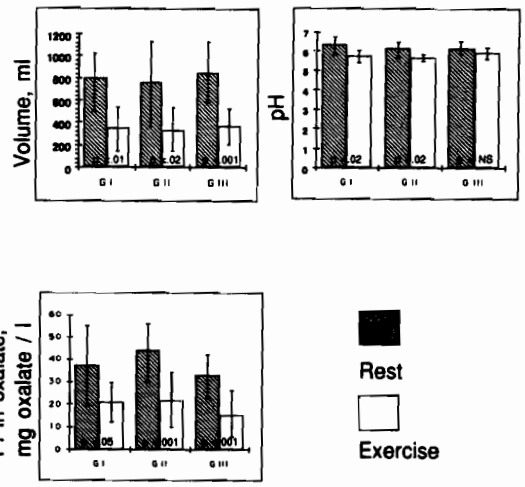

Fig 1–Comparision of urinary pH, volume and PI in oxalate between rest and exercise periods within the same groups.

were that subjects from rural areas who did not have or had stone disease (GII and GIII), excreted sodium, potassium and citrate similarly but, significantly less than that of urban control group (GI). This might reflect the environmental difference between the rural and urban subjects. However, in the present investigation we observed the similarity of most urinary excretions between subjects of rural and urban origins, both during rest and exercise. This was probably due to the fact that they were examined under the same environmental conditions, *ie* they consumed the same controlled diet, drank the same and equal amount of water as well as stayed under the same climatic temperature.

Heaton and Hodgkinson (1963) have shown that moderate physical exercise could affect renal excretion of calcium and magnesium but not of sodium, potassium, phosphorus and creatinine. Similar findings were seen in our study where excretion of sodium and potassium were not different between the periods of rest and exercise in all 3 groups. In the case of calcium excretion, however, physical exercise affected them differently. It ranged from no change in GI, decrease in GII and increase in GIII. It is recognized that physical exercise could bring about metabolic acidosis (Turrell and Robinson, 1942) and the condition has been shown to inhibit calcium reabsorption (Sutton and Dirks, 1977; Heaton and Hodgkinson, 1963). As a result, therefore, higher excretion of calcium in urine

should be expected during the exercise period. However, this was clearly observed only for GIII. Extracellular volume contraction due to excessive sweating is known to enhance renal proximal tubular reabsorption of some electrolytes and organic substances (Massry *et al*, 1969). Hence, for the excretion of calcium in GI and GII, this effect of extracellular volume contraction apparantly predominated over the inhibitory effect of metabolic acidosis on calcium reabsorption

Furthermore, oxalate, an organic acid, was less or only slighly affected by the condition of extracellular volume contraction, as its excretion was not different between rest and exercise in all 3 groups. Since urinary volume was decreased during exercise, this would bring about the further increase in urinary oxalate concentration and eventually lead to a rise in urinary saturation of calcium oxalate, especially in GIII. Low urinary output does not only increase concentration of stone-forming salts but should also increase concentration of inhibitors of crystallization such as citrate. However, this opposed effect of inhibitors appeared to be less than that of the urinary saturation effect, particularly for calcium oxalate as the propensity for crystallization was greater (PI in oxalate decreased) during the exercise period.

Physical exercise could increase the production and excretion of uric acid due to muscular damage. We, however, did not observe the increase excretion of this organic acid in any group of subjects. It was probably due to the enhance reabsorptive effect of extracellular volume contraction as mentioned earlier (Massry *et al*, 1969) or this exercise regimen might not rigorous enough to cause any damage to the muscle. A similar observation was also reported by Sakhee and coworkers (1987). Urinary pH declined significantly in GI and GII during exercise, probably due to metabolic acidosis. This decrease in urinary pH is well known to be the cause of an increase in the undissociated form of uric acid. Therefore acid urine would directly raise the degree of uric acid saturation despite no increase in total amount of uric acid. This condition is a major cause of uric acid/urate stone (Robertson and Peacock, 1985) and hyperuricosuric calcium urolithiasis (Pak *et al*, 1980). Renal tubular acidosis (RTA) in northeast Thailand is common and it has been reported to be a contributing cause of renal stone disease in this region (Nimmannit *et al*, 1988). Since the screen for RTA in GIII has not been made in this investigation, the nonsignificant drop in urinary pH during exercise in GIII was possibly due to some subjects having had RTA.

Though most urinary excretions were not different between the rest and exercise periods, most of them would automatically be increased in concentration during exercise due to low output of urinary volume. This condition would inevitably raise the degree of saturation of most stone-forming salts as clearly seen in case of calcium oxalate (PI in oxalate decreased).

In conclusion, the results of our present study showed that physical exercise may increase the risk of urinary stone formation primarily due to extrarenal fluid loss. The propensity for crystallization of calcium oxalate clearly increased during exercise as seen from the decrease in PI in oxalate. Though the excretion of uric acid during exercise was the same as that of the rest period, physical exercise may raise the level of saturation of this acid due to a fall of urinary pH resulting from metabolic acidosis. These conditions seemed to affect the subjects consistently in all three groups studied.

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