Acta Paediatrica Hungarica 30 (1), pp 63-71 (1990)

HYPERCALCIURIA AND POSTGLOMERULAR HEMATURIA IN CHILDREN. THE EFFECTS OF THIAZIDE ON CALCIUM EXCRETION, URINE SATURATION WITH RESPECT TO CALCIUM-HYDROGENPHOSPHATE AND HEMATURIA

G. REUSZ, A. SZABÓ

1st Department of Pediatrics, Semmelweis University Medical School, Budapest, Hungary

Received 13 May 1988

Calcium-hydrogenphosphate was considered as one of the main factors governing renal calculus formation. The degree of saturation (expressed as activity product=AP) with respect to this phase was therefore calculated in urines of 36 hypercalciuric children (20 absorptive, 16 renal subtype) with isolated hematuria and 30 healthy controls. The effect of thiazide treatment on the urine saturation and on the evolution of hematuria was also investigated. The results were compared to the urinary calcium excretion (expressed as Ca/cr ratio). Urines of both hypercalciuric groups were saturated on basal conditions (AP above 3.5 x 10^{-6} mol^2/l^2; -lgAP below 6.4), the values differed significantly from those of the controls (-lgAP = 6.78 ± 0.4 in the control-; 6.1 ± 0.25 in absorptive-, 6.03 ± 0.34 in renal hypercalciuria; $p < 0.001$). Thiazide normalized the activity product in all groups.

During thiazide therapy significant decrease in the occurence of hematuria was noted ($p < 0.001$ in both hypercalciuric groups). These data furnish further evidence on the relation of hypercalciuria and postglomerular hematuria. Simultaneous determinations of the state of saturation may provide further information on the "stone forming potential" of the urines investigated.

INTRODUCTION

Recently a number of studies based on epidemiological data examined the relationship between hypercalciuria and hematuria. According to their data, microscopic or even gross hematuria may preceed by years renal stone formation in hypercalciuric patients. The exact mechanism of hematuria is not known, although crystalluria is one of the supposed and plausible

Akadémiai Kiadó, Budapest

factors /4,10,14,16,18,20/. The state of urine saturation in terms of calcium and phosphate ions is probably essential for the development of renal stones, irrespectively of the mechanism of nidus formation and growth of the stone /3,11,17/. Urine saturation may be expressed as "activity product" (K_{AP}), the name deriving from "ion activity", serving as base for the calculus. The saturation limit of urine concerning one constituent is defined by two special values of the activity product, namely the solubility product and the formation product. The solubility product (K_{SP}) represents the limit above which the present stones may grow, but if no stone crystals are present, then precipitation will not take place (heterogenous nucleation). The formation product (K_{FP}) represents the limit of supersaturation, its value is defined experimentally, above this limit both new stones can be formed and old stones can grow (homogenous nucleation) /3,11,12,21/.

The aim of the present work was the simultaneous study of the evolution of the

a) urinary calcium excretion

b) state of saturation of urine to calcium hydrogenphosphate

c) hematuria

in hypercalciuric children with isolated, postglomerular hematuria - on basal conditions and during thiazide treatment and thus to provide further data on the mechanism of hematuria and stone formation in hypercalciuric children.

PATIENTS AND METHODS

Sixty-six children were investigated: 36 hypercalciuric, 30 normal controls. The 36 hypercalciuric children (mean age 8 years, range 4-15) were observed originally because of hematuria of postglomerular origin: the classification was based on the analysis of urinary red cell morphology by OPTON phase contrast microscope, and urinary protein pattern studies using SDS-PAGE /14/. Idiopathic hypercalciuria was diagnosed in the absence of known causes of hypercalciuria if urinary Ca/cr exceeded 0.6 mmol/mmol and/or urinary Ca excretion exceeded 0.1 mmol/kg/24h. Hypercalciuric children with Ca/cr below 0.6 on low calcium diet were considered as having absorptive hypercalciuria, while those having a ratio still above 0.6 were classified as cases of renal hypercalciuria /5/. Twenty of the

36 patients had absorptive hypercalciuria and 16 renal hypercalciuria.

Collected 24 h urines of 30 healthy children (mean age 10 years, range 5-15) served as control.

In the present work all children of the study groups were examined in 2 consecutive periods:

a) unrescricted diet

b) hydrochlorothiazide treatment for 7 days (daily dose 1 mg/kg)

All children of the control group were investigated on basal conditions only.

At the end of each period, 24 h urine collection was performed and blood sample was taken. Concentrations of creatinine, calcium, phosphate, sodium, potassium, uric acid were measured and the alkaline phosphatase activity was determined by routine chemical analysis on Technicon RA-1000 Autoanalyser and ISE module.

The Ca/cr was calculated in all urine specimens.

The activity product of $CaHPO_4$ was calculated using the following equation:

$$K_{AP} = a_{Ca^{2+}} \cdot a_{HPO_4^{2-}} = f[Ca^{2+}] \cdot f[HPO_4^{2-}]$$

where a is the activity, f represents activity coefficients, the brackets denote molar concentrations of free ions /11,12/. f was calculated from the Debye-Hückel law, the level of ionised calcium was calculated using: $[Ca^{2+}] \cong 0.5 \cdot Ca_T$ /15/; and HPO_4^{2-} was calculated from P_T according to the principles of complex equilibria /17/. Ca_T and P_T represent the concentrations of total calcium and inorganic phosphate in urine.

In 11 of the absorptive and 10 of the renal hypercalciuric children the evolution of the degree of hematuria was evaluated as follows:

The parents of the patients were supplied with "Medi-Test Combi 9" test strips (Macherey-Nagel labs.) including reagents for rapid determination of blood. The minimum sensitivity of the test strip is 5 to 10 erythrocytes/microliter urine. Collected urine was checked daily for blood and denoted by 1,2,3 according to the manufacturer's instructions (=degree of hematuria). After the control period on normal diet, hydrochlorothiazide was given in a daily dose of 1 mg/kg for 14 days.

On the basis of the urinary blood test results obtained from the parents, the control period (C), and the second week of thiazide treatment (H) were evaluated.

For each child a "weighted hematuric ratio" was calculated as follows:

[(degree of hematuria)/(number of patients)] /(number of days of the period)

(Dimension: degree of hematuria/child/day).

Statistical analysis was performed by Student's t-test.

Approval of this study was granted by the local Ethical Commettee and informed consent was obtained from the parents of each child before admitted to the study.

RESULTS

All children had normal serum calcium, phosphate and uric acid levels, and alkaline phosphatase activity, these values were normal at the end of thiazide treatment, too.

The evolution of values of Ca/cr, K_{AP} and of the WHR are shown on Figures 1,2 and 3, respectively.

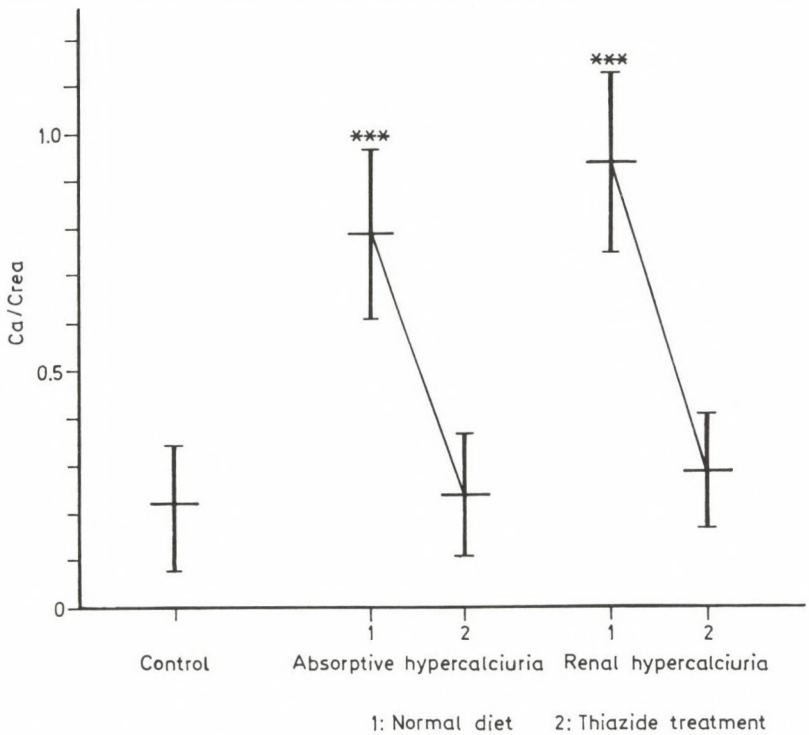

Fig. 1. Evaluation of the Ca/creatinine ratio (Ca/cr) in the control and study groups, *** $p < 0.001$

Activity product is expressed as $-\lg K_{AP}$ (Fig.2). On normal diet the Ca/cr and K_{AP} values of hypercalciuric children differed significantly from the reference values of the control group.

Sixteen children out of the 20 with absorptive hypercalciuria had their urine saturation values in the metastable zone on basal conditions. All but one of the 16 values of the renal hypercalciuric children on normal diet

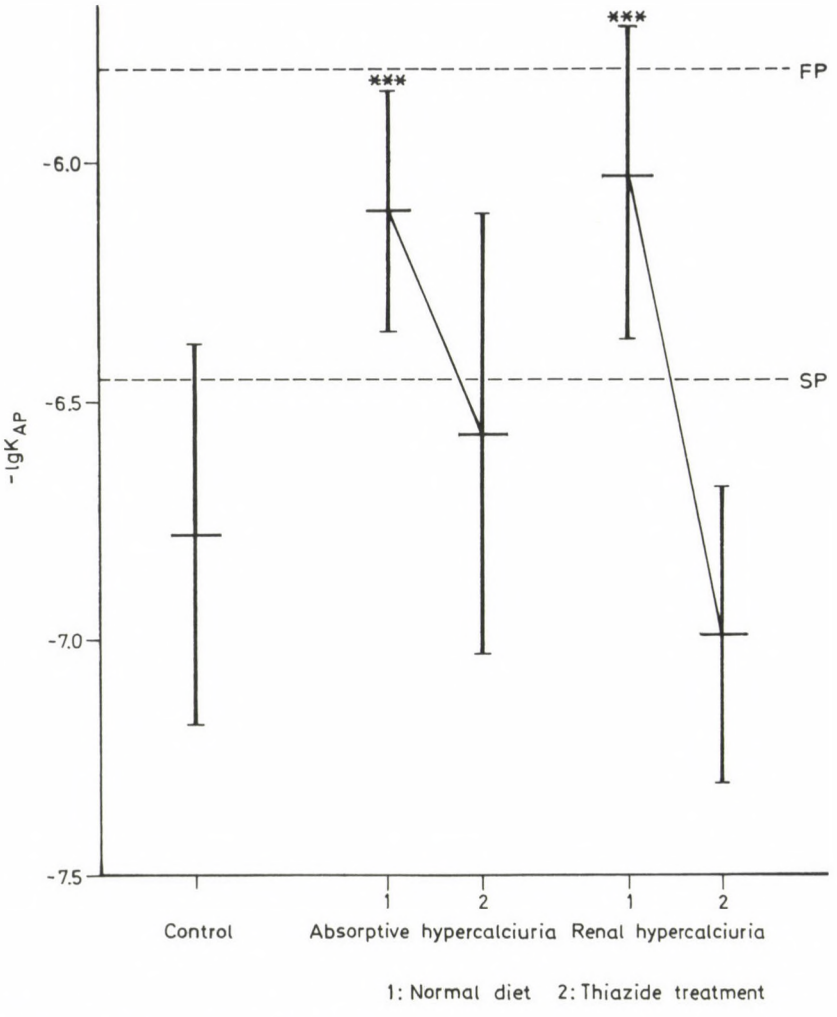

Fig. 2. Evolution of the activity product of $CaHPO_4$ (K_{AP}) in the control and study groups, *** $p < 0.001$
SP: solubility product
FP: formation product

were in the saturated zone. During thiazide administration K_{AP} values were similar to those of the control group. (Fig. 2).

Hydrochlorothiazide induced a significant decrease of WHR in the hypercalciuric groups (Fig. 3).

Analysis of the correlation between Ca/cr and K_{AP} in the different groups on normal diet shows significant positive correlation in the control group ($r=0.58$, $p < 0.01$), while a

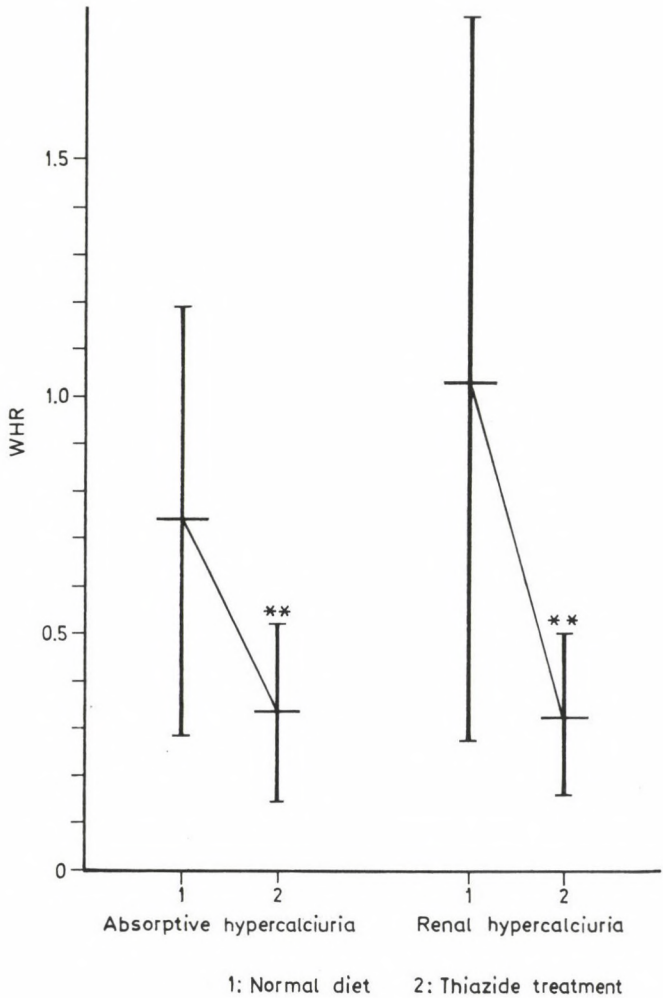

Fig. 3. Evolution of the degree of hematuria (WHR) during thiazide treatment, ** $p < 0.01$

significant negative one in renal hypercalciuria ($r = -0.54$, $p < 0.05$). There was no correlation between the two values in absorptive hypercalciuria ($r = 0.18$).

DISCUSSION

The pathogenesis of a renal stone represents a dual process of nidus formation and the subsequent development of the nidus into a stone. The nidus may form spontaneously by precipitation from supersaturated urine by homogenous nucleation, or organic matrix may facilitate the precipitation of inorganic salts. According to recent studies homogenous nucleation of calcium oxalate is almost improbable /3/, the kidney is incapable of creating sufficient supersaturation. The initial nidus of calcium containing stones is usually calcium phosphate. The deposition of calcium-oxalate, calcium-hydrogenphosphate or both occurs over the nidus /3,11,12/.

In the present work the relationship between the urinary calcium excretion (expressed as Ca/cr ratio) /5/, the state of saturation of urines concerning calcium-hydrogenphosphate and the evolution of hematuria were studied in the well defined patient groups of hypercalciuric children and controls.

We found that hypercalciuric children not only excreted calcium in significantly higher amounts than controls, but also their urine also had a high "stone forming potential". Positive correlation was found between Ca/cr and K_{AP} in the control group of healthy children. However, in the patient groups no such correlation could be determined. That means urinary calcium excretion is only one (important) factor of urine saturation, but there is no direct relation between urine saturation and urinary Ca/cr ratio.

Hypocalciuric effect of thiazide diuretics is known since 1959 /6/: in contrast to other diuretics, the chronic administration of these drugs diminishes urinary calcium excretion /6,7,9,19/. This hypocalciuric effect has made thiazides useful in the management of recurrent calcium nephrolithiasis and idiopathic hypercalciuria in adults. It is the treatment of choice in renal hypercalciuria, but it is useful in absorptive hypercalciuria and normocalciuric nephrolithiasis too because of the complexity of mechanisms of renal stone formation /2,7,9/.

The dipstick chemical urinanalysis is an accurate

semiquantitative method for screening of hematuria /1,8,13/. Administration of thiazides not only lowered urinary calcium excretion and activity product of $CaHPO_4$ but also caused a simultaneous decrease of the hematuria. These data are further evidence supporting the theory of crystalluria as being the cause of isolated hematuria in these patients. Simultaneous determinations of the activity product may provide complementary data on the danger of renal stone formation and may help in the quantitative assessment of the therapies recommended.

REFERENCES

1. Bullock N: Asymptomatic microscopical hematuria. Brit Med J 292: 645, 1986.

2. Coe FL, Favus MJ: Disorders of stone formation. In: Brenner BM, Rector FC: The kidney. p:1403. W.B. Saunders Comp. Philadelphia. 1986.

3. Finlayson B: Physicochemical aspects of urolithiasis. Kidney Int 13: 344, 1978

4. Kalia A, Travis LB, Brouhard BH: The association of idiopathic hypercalciuria and asymptomatic gross hematuria in children. J Pediatr 99: 716, 1981

5. Kruse K, Kracht U, Kruse U: Reference values for urinary calcium excretion and screening for hypercalciuria in children and adolescents. Eur J Pediatr 143: 25, 1984

6. Lamberg BA, Kuhlbach B: Effect of chlorothiazide and hydrochlorothiazide on the excretion of calcium in urine. Scand J Clin Lab Invest 2: 351, 1959

7. Lemann J Jr: Nephrolithiasis. In: Massry SG, Glassock RJ: Textbook of nephrology. Williams and Wilkins. Baltimore/London 6: 266, 1983

8. Loo S, Scottolini A, Hodges CV: Dipstick chemical urinanalysis: an accurate cost-effective screening test. J Urol 132: 64, 1984

9. Massry SG: Renal handling of calcium. In: Massry SG, Glassock RJ. ed.: Textbook of nephrology. Williams and Wilkins/Baltimore/London. 3.54-3.59. 1983

10. Moore ES: Hypercalciuria in children. In: Berlyne GM. ed.: Contributions to nephrology. New York, Karger, pp: 20, 1981

11. Pak CYC: Physicochemical basis for formation of renal stones of calcium phosphate origin: calculation of the degree of saturation of urine with respect to brushite. J Clin Invest 48: 1914, 1969

12. Pak CYC, Holt K: Nucleation and growth of brushite and calcium oxalate in urine of stone-formers. Metabolism 25: 665, 1976

13. Ritchie CD, Bevan EA, Collier StJ: Importance of occult hematuria found at screening. Brit Med J 292: 681, 1986

14. Reusz G, Tulassay T, Szabó A, Tausz I, Miltényi M: Studies on the urinary calcium excretion in children with hematuria of postglomerular origin: effects of the variation of dietary calcium and sodium intake. Int J Pediatr Nephrol 7: 221, 1986

15. Robertson NG: Measurement of ionised calcium in biological fluids. Clin Chim Acta 24: 149, 1969

16. Roy S, Stapleton FB, Noe NH, Jerkins G: Haematuria preceding renal calculus formation in children with hypercalciuria. J Pediatr 99: 712, 1981

17. Sárközi L, Szabó A, Ors E, Beck MT: Calculated distribution of various inorganic phosphate constituents in body fluids, based on the principles of complex equilibria. Clin Physiol Biochem 2: 221, 1984

18. Stapleton FB, Roy S, Noe N, Jerkins G: Hypercalciuria in children with hematuria. N Eng J Med 310: 1345, 1984

19. Suki WN, Hull AR, Rector FC, Seldin WD: Mechanism of the effect of thiazide diuretics on calcium and uric acid (abstr.). J Clin Invest 46: 1161, 1967

20. Tulassay T, Reusz G, Öcsényi Z, Miltényi M: Isolated hematuria and idiopathic hypercalciuria in children. Helv Pediat Acta 44: 137, 1986

21. Weber DV, Coe FL, Parks JH, Dunn MSL, Tembe V: Urinary saturation measurements in calcium nephrolithiasis. Ann Int Med 90: 180, 1979

G. REUSZ, MD

Bókay J. u. 53.
H-1083 Budapest
Hungary