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Tubular Proteinuria in Renal Calcium Stone Formers

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ABSTRACT

The incidence of tubular proteinuria measured as urinary excretion of β_2-microglobulin was evaluated in 68 consecutive renal calcium stone formers, 14 of whom had impaired urinary acidification capacity. During normal conditions 13% of these stone formers had tubular proteinuria. There was no statistical difference in the incidence of tubular proteinuria between subgroups with proximal or distal acidification defects. During transient metabolic acidosis induced by an ammonium chloride load a pronounced increase in β_2-microglobulin excretion was noticed in all patient groups but especially in those with urinary acidification defects. In stone formers with normal acidification capacity the degree of acidosis-induced β_2-microglobulinuria was moderate but a small group of patients exhibited a large urine excretion of β_2-microglobulin. This finding may reflect a latent tubular defect of importance for stone genesis.

INTRODUCTION

Studies of urolithiasis disease usually have focused on physico-chemical urine investigations and mineral metabolic problems (8). The importance of renal function has not drawn much attention. Recently, however, some studies of renal function in renal calcium stone formers, particularly tubular function,were reported (1, 3, 11, 12).

Tubular proteinuria indicates tubular dysfuction (9). Such signs of tubular defects seem to be rather common among renal calcium stone formers (1).

The present study was carried out in order to investigate the incidence of tubular proteinuria in subgroups of stone formers with various urinary acidification ability. The aim was also to study if a transient metabolic acidosis could provoke a tubular proteinuria in these stone formers.

METHODS

Laboratory evaluation of the patients was performed according to our standard protocol (11). Urinary acidification was investigated with a short time ammonium chloride loading test. By this test different defects in urinary acidification can be indentified with a relatively simple protocol (1). Urinary β_2-microglobulin (reference value < 15 µg/h) was measured with a radioimmunoassay (Phadebas β_2-micro Test, Pharmacia Diagnostics AB, Uppsala,Sweden). The urinary excretion of β_2-microglobulin was studied during normal conditions and during a transient metabolic acidosis induced by the abovementioned ammonium chloride load. Hourly portions of the urine at maximal acidosis, most often during the second to the fourth hour after intake of ammonium chloride, were analysed for β_2-microglobulin. The samples were alkalinized immediately after collection.

MATERIAL

From our out-patient stone clinic we investigated 68 consecutive patients (mean age 44 years, 57 males and 11 females) with idiopathic renal calcium stone disease. As controls served 10 apparently healthy individuals (mean age 30 years, 7 males and 3 females) recruited from the medical staff. All patients and controls had normal glomerular filtration rate evaluated from serum creatinine and endogenous creatinine clearance. Informed consent was obtained from all subjects.

RESULTS

The ammonium chloride loading test revealed that 21% (14/68) of the investigated stone formers had some type of acidification defect. (Table 1). All of these defects were incomplete types of renal tubular acidosis with no systemic acidosis in basal state. During normal conditions no case of increased excretion og β_2-microglobulin was seen among the controls whereas 13% (9/68) of the stone formers showed β_2-microglobulinuria. There was an overrepresentation of β_2-microglobulinuria in stone formers with acidification defects but there was no statistical difference in the incidence of tubular proteinuria between the subgroups of stone formers (Table II). The mean values of β_2-microglobulin

TABLE I. Urinary acidification ability in renal calcium stone formers and healthy individuals (controls) after an ammonium chloride loading.

	Normal urinary acidification	Incomplete roximal RTA[1]	Incomplete distal RTA[1]
Stone formers (n = 68)	54	9	5
Controls (n = 10)	10		

1) RTA = renal tubular acidosis

excretion of the different subgroups of subjects were well within the normal range (Table III).

TABLE II. Subjects with increased urinary excretion of β_2-microglobulin (< 15 µg/h) during normal conditions.

	n
Controls	0/10
Patients with normal urinary acidification	6/54
Patients with pRTA	2/9
Patients with dRTA	1/5

Abbreviations:

RTA = renal tubular acidosis, incomplete form
pRTA = proximal type of RTA
dRTA = distal type of RTA

TABLE III. Urinary β_2-microglobulin in controls and subgroups of renal calcium stone formers.

	Urinary β_2-microglobulin (µg/h) Normal conditions (mean ± SEM)	Metabolic acidosis (mean ± SEM)
Controls (n = 10)	5.1 ± 0.5	18.8 ± 7.4*
Patients without RTA (n = 54)	4.3 ± 0.9	32.6 ± 8.4*
Patients with pRTA (n = 9)	11.0 ± 4.6	63.9 ± 20.6**
Patients with dRTA	9.7 ± 3.6	69.9 ± 30.5*

*) $p < 0.05$ compared to normal conditions.
**) $p < 0.01$ compared to normal conditions.
Rank sum test, paired samples.

Abbreviations: see Table II.

During metabolic acidosis a marked increase in β_2-microglobulinuria was noticed in all subject groups (Table III, Figs 1-4). The mean values for all subgroups were in the pathological range of β_2-microglobulin excretion (Table III). The increase was most evident in patients with urinary acidification defects. However, there was no difference between the degree of acidosis-induced β_2-microglobulinuria in stone formers with incomplete proximal renal tubular acidosis (RTA) and those with distal RTA.

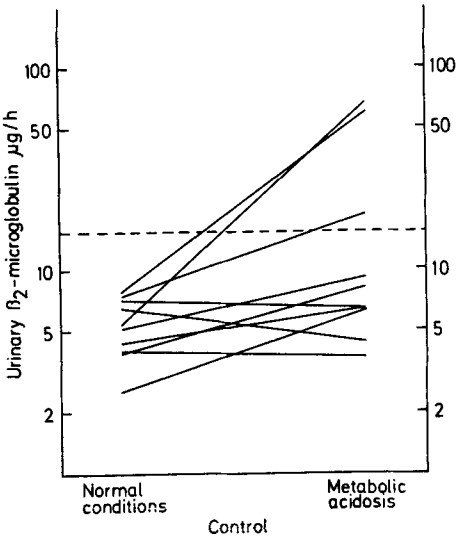

Fig. 1 Urinary excretion of β_2-microglobulin in controls. Samples drawn during normal conditions and during transient metabolic acidosis. Dashed line shows upper limit of urinary β_2-microglobulin excretion.
RTA = renal tubular acidosis, incomplete form.

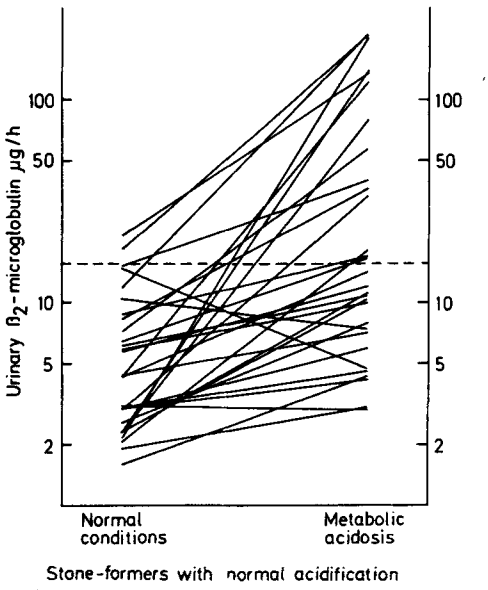

Fig. 2 Urinary excretion of β_2- microglobulin in stone formers with normal urinary acidification capacity.
See text Fig. 1.

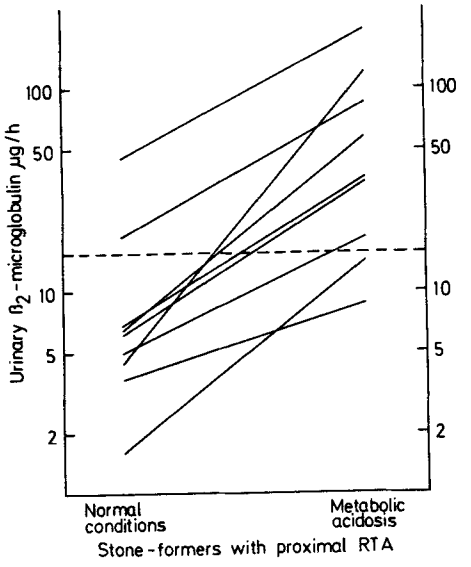

Fig. 3 Urinary excretion of β_2-microglobulin in stone formers with proximal RTA.
See text Fig. 1.

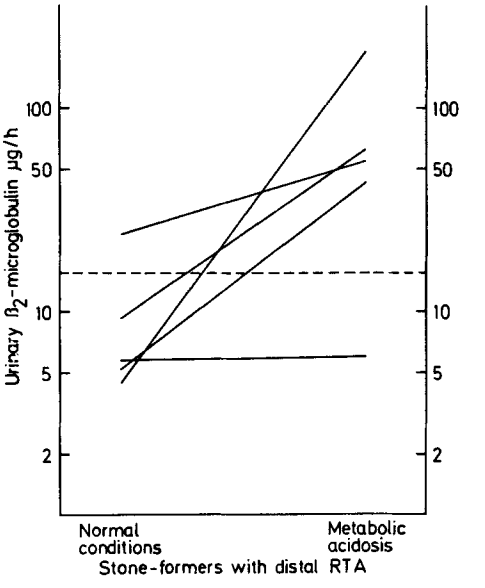

Fig. 4 Urinary excretion of β_2-microglobulin in stone formers with distal RTA.
See text Fig. 1.

In the group of stone formers with normal acidification ability the degree of acidosis-induced β_2-microglobulinuria was comparable to that of the controls but a small group of patients with a pronounced increase of β_2-microglobulin excretion during acidosis was noticed (Fig 2). These patients did not differ from the other stone formers regarding urinary calcium excretion or degree of maximal acidosis during the ammonium chloride loading test.

DISCUSSION

Serum proteins of low molecular weight (LMW) are freely filtered thought the glomerular membranes. These proteins are normally reabsorbed and catabolized by the cells in the renal proximal tubules (5). Subsequently, a dysfunction in this part of the nephron will give rise to tubular proteinuria. β_2-microglobulin, a LMW-protein of molecular weight 11,800, is the main component of tubular proteinuria and has been shown to be a suitable test substance for evaluation of the renal handling of LMW-proteins (9). Increased amounts of β_2-microglobulin in the urine are reported from patients with renal tubular disorders (4, 9).

In the present investigation the β_2-microglobulin excretion was evaluated in renal calcium stone formers during various conditions. During normal conditions 13% of the stone formers displayed tubular proteinuria. Previous studies have also shown abnormal β_2-microglobulin excretion in patients with recurrent renal stone disease (1,2,12). In other studies stone formers had normal excretion of β_2-microglobulin although the urinary excretion of other LMW-proteins was increased. This tubular proteinuria was interpreted as signsof a very specific alteration in tubular function (10).

The ammonium chloride loading test in the present study displayed urinary acidification defects in more than 20% of the stone formers. This finding correlates well to other studies from our stone clinic (1, 11). Stone formers with urinary acidification defects may be more prone to develop tubular proteinuria (12). RTA patients in the present study also showed an overrepresentation of tubular proteinuria during normal conditions (21%), although the number of RTA patients was too small to draw any firm conclusion from. During acidosis, however, a distinct pattern was with seen almost uniform tubular proteinuria in RTA stone formers.

In the group of stone formers with normal acidification ability an average moderate degree of acidosis-induced β_2-microglobulinuria was registrated. However, a notable collection of urine samples with large amounts of β_2-microglobulin during acidosis was seen in this group. The importance of this is unknown. One could speculate whether this might be an early sign of a latent tubular defect, e.g. RTA. Signs of tubular proteinuria may indicate a

risk for later development of clinical evident tubular damage described e.g. in hereditary tubular diseases. (6).

In our stone clinic three stone formers with a pronounced tubular proteinuria were tested with a second ammonium chloride loading 4-5 years after the initial ammonium chloride loading test. None of these patients showed signs of RTA at the second test (unpublished observations). This observation does not favour the abovementioned speculation. However, only further studies can elucidate this problem which may be important for urolithiasis pathogenesis since abnormalities in renal tubular functions are likely related to the genesis of urinary calculi (7).

ACKNOWLEDGEMENTS

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