The tubular maximum for calcium reabsorption in patients with chronic active thoracic sarcoidosis

P.D. Broulik*, V. Votava**, V. Pacovsky*

The tubular maximum for calcium reabsorption (TmCa) was evaluated in 52 patients with chronic active thoracic sarcoidosis. Hypercalcaemia was found in five patients (9.6%). The mean serum calcium value of 2.54±0.18 mmol l⁻¹ in patients with sarcoidosis was significantly higher than that obtained in the control group (2.42±0.11 mmol l⁻¹). The mean TmCa in patients with sarcoidosis (2.11±0.26 mmol l⁻¹ glomerular filtrate (GF)) was not statistically different from the mean TmCa for the group of healthy subjects (2.18±0.23 mmol l⁻¹ GF). Urinary sodium corrected TmCa in both groups of patients was affected in a similar way. Our study demonstrates for the first time that there is no increase in TmCa in patients with chronic active thoracic sarcoidosis. Hypercalcaemia is not a result of an increased TmCa.


Hypercalcaemia, with or without hypercalciuria, is a well-known complication of sarcoidosis. The reported incidence of hypercalcaemia associated with sarcoidosis varies from 2-63% [1]. Hypercalcaemia tends to be transient in subacute sarcoidosis, but in chronic sarcoidosis, depending on the activity of the disease, the serum level of calcium may fluctuate [2]. Hypercalciuria is considerably more common [3]. Absorptive hypercalciuria is related to the development of sarcoidosis and can be explained by high free 1,25-dihydroxy vitamin D₃ (1, 25(OH)₂D₃). Resorptive hypercalciuria seems to be linked with disease extension [4, 5].

The plasma calcium concentration is determined by the relationship between three factors: 1) the rate of flow of calcium into the extracellular space from gut or bone; 2) the rate of filtration of calcium through the glomeruli; and 3) the rate of tubular reabsorption of calcium. In spite of the growing knowledge about sarcoidosis the mechanism of hypercalcaemia has rarely been investigated.

We have used a method which has been developed for measuring the tubular maximum for calcium in man [6]. The tubular maximum relative to the glomerular filtration rate (GFR) can be calculated in any subject [7] based on the known relationship between the plasma and urine calcium before and during calcium infusions in normal subjects.

The purpose of the present study was to examine the tubular maximum for calcium in an unselected group of patients with chronic active thoracic sarcoidosis.

Patients and methods

The subjects were 52 patients with chronic thoracic sarcoidosis (25 men and 27 women, aged 20-71 yrs) who had been followed-up for varying periods (mean 4.2 yrs). The diagnosis of sarcoidosis was based on clinical, radiographic and laboratory features consistent with the disease and was supported by a tissue biopsy showing noncaseating epithelioid-cell granulomas. Diagnosis of thoracic active sarcoidosis was related to presence of prolonged respiratory symptoms and to duration of findings on chest X-ray pulmonary examination (more than two years) with a slow progression. The biological marker of activity that was considered was the lymphocyte percentage, i.e. the percentage of lymphocytes in bronchoalveolar lavage fluid. No subjects in either the observation or the control group used any medical treatment to affect calcium and phosphorous metabolism. No patient was taking corticosteroids at the time of the investigations.

To minimize dietary influences the patients were fasted overnight and urine samples (collected over 2 h) and blood samples were obtained. Each sample was analysed for calcium, phosphate, sodium and creatinine content. The calcium/creatinine ratio was calculated according to NORDIN [8]. Fasting calcium excretion (Cₐ) was calculated from the formula: Cₐ = Uₐ × (Pₐ Uₐ). The tubular maximum for calcium reabsorption was calculated according to NEED et al. [6], from the formula: TmCa = ((0.56 Pcₐ-Caₐ) - (1.08 logc(0.56 Pcₐ Caₐ))) mmol l⁻¹.
glomerular filtrate (GF). The term (0.56 Pca) is an approximation to the plasma ultrafilterable concentration. The tubular maximum for calcium reabsorption was also calculated after correction for urinary sodium [6]. The renal phosphate threshold concentration (TmPO/GFR) was calculated using the nomogram of WALTON and BUVOR [9]. Inorganic phosphate in the serum and urine was determined photometrically [10]. Serum and urine creatinine were measured by the method of HARE [11]. Serum and urine calcium were determined by a complexometric method [12]. A control group matched for age and sex was selected from the original health screening register. Group data are expressed as mean±sd and a comparison made using Students t-test for unpaired data [13].

### Table 1. Mean values±sd of measured variables in fasting blood and urine collected from 52 patients with sarcoidosis and 40 healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>Sarcoïdosis</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>n=52</td>
<td>n=40</td>
</tr>
<tr>
<td>Age yrs</td>
<td>45.6±13</td>
<td>44.5±8</td>
</tr>
<tr>
<td>Serum calcium mmol·l⁻¹</td>
<td>2.54±0.18*</td>
<td>2.42±0.11</td>
</tr>
<tr>
<td>Serum creatinine mmol·l⁻¹</td>
<td>0.08±0.013</td>
<td>0.08±0.011</td>
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<tr>
<td>Urine Ca/Cr mmol-mmol⁻¹</td>
<td>0.31±0.28</td>
<td>0.28±0.11</td>
</tr>
<tr>
<td>Ca₄₆ mmol·l⁻¹ GFR</td>
<td>0.027±0.019</td>
<td>0.025±0.011</td>
</tr>
<tr>
<td>Na₄₆ mmol·l⁻¹ GFR</td>
<td>1.08±0.84</td>
<td>0.89±0.45</td>
</tr>
<tr>
<td>TmCa mmol·l⁻¹ GFR</td>
<td>2.11±0.26</td>
<td>2.18±0.23</td>
</tr>
<tr>
<td>TmCa/Na corr. mmol·l⁻¹ GFR</td>
<td>2.40±0.25</td>
<td>2.44±0.20</td>
</tr>
<tr>
<td>TmPO₄ mmol·l⁻¹ GFR</td>
<td>1.16±0.28*</td>
<td>1.01±0.14</td>
</tr>
</tbody>
</table>

Ca: calcium; Cr: creatinine; Ca₄₆: calcium excretion; Na₄₆: sodium excretion; GFR: glomerular filtration rate; TmCa: tubular maximum for calcium reabsorption; TmCa/Na corr.: sodium corrected TmCa; TmPO₄: tubular maximum for phosphate reabsorption; *: p<0.01.

### Results

The mean values of the measured variables are shown in table 1. At the time of investigation all 52 patients had chronic active thoracic sarcoidosis. The mean serum calcium value of 2.54±0.18 mmol·l⁻¹ in patients with sarcoidosis was significantly higher than that obtained in the group of healthy subjects (2.42±0.11 mmol·l⁻¹). Five patients were unmistakably hypercalcaemic. Hypercalcaemia was diagnosed if serum calcium levels were equal to or greater than the mean of the control group (2.42±0.11 mmol·l⁻¹). Serum calcium values plus three standard deviations. The mean tubular maximum for calcium reabsorption (TmCa) in patients with sarcoidosis, 2.11±0.26 mmol·l⁻¹ GF (range 1.72–2.64), was not statistically different from the mean TmCa for the group of healthy subjects, 2.18±0.23 mmol·l⁻¹ GF (range 1.72–2.64). The range is mean±sd. The range of TmCa was reduced by taking urinary sodium into account. Thus urinary sodium corrected TmCa in patients with sarcoidosis was affected in a similar way to TmCa uncorrected. The values were within the normal range without significant differences between the means of the groups.

Renal function as measured by the serum creatinine was normal in all of the patients with sarcoidosis. In seven patients the fasting urinary calcium/creatinine ratios were above the normal range (0.40). Measurement of this ratio minimizes dietary influences. Increased values indicate either, increased bone resorption of calcium or, less commonly, decreased renal tubular reabsorption of calcium.

The mean TmPO₄/GFR in sarcoidosis was significantly higher than in controls (p<0.01), but still within the normal range for TmPO₄/GFR (0.8–1.25 mmol·l⁻¹ GF). Fourteen patients with sarcoidosis had functional hypoparathyroidism as measured by the renal phosphate threshold concentration, the TmPO₄/GFR was increased above the normal range 1.25 mmol·l⁻¹ GF (1.34±0.24 mmol·l⁻¹ GF).

### Discussion

The present study revealed abnormal calcium metabolism in 12 (23%) patients. Five patients were hypercalcaemic and seven patients showed an abnormal calcium/creatinine ratio. The present data concerning the frequency of hypercalcaemia (9.6%) in sarcoidosis are consistent with those of LEBACQ et al. [14]. However, the whole group of patients with sarcoidosis had significantly higher plasma calcium levels than the group of healthy subjects. The bulk of calcium studies in sarcoidosis was essentially dedicated to the dearrangement of vitamin D metabolism. In this respect, two major steps were the demonstration that the serum 1,25(OH)₂D₃ level is elevated in sarcoidosis [15] and the evidence that sarcoid granulomas are able to elaborate 1,25(OH)₂D₃ or 1 alpha hydroxylase [16]. In spite of this growing knowledge, no attempts have been made to examine the tubular maximum for calcium reabsorption in patients with sarcoidosis. Increased TmCa is one of three variables which can contribute to the pathogenesis of hypercalcaemia. Using a very sensitive method, a range for TmCa in patients with sarcoidosis has been established for the first time. Our range of TmCa in the control group is in good correlation with the work of NEED et al. [6]. Because urinary sodium excretion has been reported to influence urinary calcium excretion we determined the effect of urinary sodium excretion on tubular reabsorption of calcium and derived a corrected TmCa in patients with sarcoidosis which takes into account the urinary sodium. Correcting the TmCa for urinary sodium excretion reduced the range of TmCa.

If hypercalcaemia is associated with a normal TmCa it must be due to increased entry of calcium into the plasma or a reduced glomerular filtration rate. In all of our patients with sarcoidosis renal functions were normal. From our results, it is obvious that there is no increase in TmCa in patients with chronic active thoracic sarcoidosis. Even the five patients with elevated serum calcium levels had normal TmCa. Thus, increased TmCa does not contribute to the pathogenesis of hypercalcaemia in sarcoidosis.

In seven patients the fasting urinary calcium/creatinine ratios were elevated. Mean TmCa of these seven patients
(1.95±0.37 mmol·l⁻¹ GF) was statistically different from mean TmCa for the group of healthy subjects (2.18±0.23 mmol·l⁻¹ GF); but still within the normal range for TmCa.

The mechanism for abnormally low calcium metabolism remains very complex. Among factors which might cause hypercalcæmia in sarcoidosis, parathyroid hyperplasia does not play a role [15]. When the data for all of our patients with sarcoidosis were considered as a whole, the mean TmPo4/GFR was within the normal range. Only 14 of these patients had functional hypoparathyroidism as measured by the TmPo4; the TmPo4/GFR was increased to 1.34±0.24 mmol·l⁻¹ GF. However, from TmPo4/GFR it is very difficult to assess whether serum parathormone (PTH) levels are in the low-normal range or renal phosphate excretion is augmented in response to the elevation of the serum calcium concentration. Any additional influence of PTH on the tubular handling of calcium in the majority of our patients with sarcoidosis remained negligible.

At present the factors causing the inappropriate elevation of 1,25(OH)₂D₃ in serum are sarcoïd granulomas which are able to elaborate 1,25(OH)₂D₃, or 1 alpha hydroxylase [16]. Whereas the effects of 1,25(OH)₂D₃ on the skeleton and intestine have been well documented as measured by the TmCa, the intrinsic effects of vitamin D on the kidney remain unclear [18].

Ninety nine per cent of the calcium filtered by the kidney is reabsorbed even in vitamin D deficiency, rendering any influence of vitamin D on calcium reabsorption of questionable physiological importance [19]. Our data support evidence that circulating active vitamin D metabolites have little or no influence on the TmCa.

Hypercalcæmia in patients with chronic thoracic active sarcoidosis is not a result of an increased tubular reabsorption of calcium.

References


Le maximum tubulaire pour la réabsorption calcique chez les patients atteints de sarcoïdose thoracique chronique active. P. Brouil, V. Yotava, V. Pacovsky.

RÉSUMÉ: Le maximum tubulaire de réabsorption calcique (TmCa) a été évalué chez 52 patients atteints de sarcoïdose thoracique chronique active. Une hypercalcémie a été trouvée chez 5 patients (9.6%). La valeur moyenne du calcium sérique de 2.54±0.18 mmol·l⁻¹ chez les patients atteints de sarcoïdose, s’avère significativement plus élevée que celle obtenue dans le groupe contrôle (2.42±0.11 mmol·l⁻¹). La TmCa moyenne chez les patients atteints de sarcoïdose (2.11±0.26 mmol·l⁻¹ GF) n’était pas statistiquement différente de la TmCa moyenne dans le groupe des sujets sains (2.18±0.23 mmol·l⁻¹ GF). La TmCa corrigée pour le sodium urinaire, a été affectée de façon similaire dans les deux groupes. Notre étude démontre pour la première fois que chez les patients atteints de sarcoïdose thoracique chronique active, il n’y a pas d’augmentation de TmCa. L’hypercalcémie n’est donc pas la conséquence d’une augmentation de TmCa.

Eur Respir J., 1990, 3, 447-449