Vitamin D metabolism by alveolar immune cells in tuberculosis: correlation with calcium metabolism and clinical manifestations


ABSTRACT: The aim of this study was to investigate the relationship between the pulmonary vitamin D metabolism in tuberculosis and the calcium metabolism abnormalities and other clinical characteristics of the disease.

The metabolism of 25-hydroxyvitamin D₃ (25(OH)D₃) by alveolar immune cells recovered by bronchoalveolar lavage (BAL) was evaluated in parallel to the results of calcium metabolism, 25(OH) D and 1,25 dihydroxyvitamin D (1,25(OH)₂D₃) plasma levels and other clinical parameters obtained in 14 tuberculosis patients.

Whilst predominant metabolites produced by lavage cells in patients and controls were 5(E) - and 5(Z) -19-nor-10-oxo-25(OH)D₃, 1,25(OH)₂D₃ was produced by cells from all tuberculosis patients but not by cells from controls. Calcium metabolism abnormalities were observed in only some patients, but the production of 1,25(OH)₂D₃ by lavage cells was found to correlate both with 1,25(OH)₂D₃ levels (r=0.67) and post-load urinary calcium excretion (r=0.51). 1,25(OH)₂D₃ production by lavage cells was increased in patients of black origin, and those presenting with hilar adenopathy without pulmonary infiltrates, and was correlated with the number of lymphocytes recovered by lavage (r=0.87).

We conclude that 1,25(OH)₂D₃ production by alveolar immune cells makes a major contribution to the abnormalities in calcium metabolism seen in tuberculosis patients, and may be partly dependent on the clinical characteristics evaluated here.

Eur Respir J., 1994, 7, 1103–1110.

Patients with tuberculosis can produce 1,25 dihydroxyvitamin D₃ (1,25(OH)₂D₃) and other vitamin D metabolites at sites of disease activity [1–3]. The spontaneous production of vitamin D metabolites by granulomatous tissues could have both unfavourable and favourable clinical consequences [4].

The production of 1,25(OH)₂D₃ or other vitamin D metabolites could have deleterious effects, mediated through an endocrine pathway. Hypercalcaemia with increased levels of plasma 1,25(OH)₂D₃ has been observed in some tuberculosis patients, including several anephric patients [1, 5–8]. It has also been suggested that the production of 1,25(OH)₂D₃ by granulomatous tissue could contribute to the cachexia and fever seen in patients with tuberculosis [4, 9].

On the other hand, several lines of evidence suggest that 1,25(OH)₂D₃, operating through an autocrine/paracrine pathway, may be beneficial. Indeed, it has been demonstrated that cells obtained from sites of granulomatous reactions both convert 25 hydroxyvitamin D₃ (25(OH)D₃) into 1,25(OH)₂D₃ and express 1,25(OH)₂D₃ receptors [2, 3, 10]. Furthermore, in vitro studies indicate that 1,25(OH)₂D₃ may play an important role in the regulation of granulomatous reactions [11], and can improve the ability of alveolar macrophages to inhibit the growth of mycobacteria [12–15].

Recent studies suggest that extrarenal production of 1,25(OH)₂D₃ occurs in the majority of patients with tuberculosis [2, 3], but no information is available comparing the production of vitamin D metabolites and the clinical presentation of these patients. Similarly, although few patients with tuberculosis have obvious abnormalities in calcium metabolism, the degree to which extrarenal 1,25(OH)₂D₃ production correlates with more subtle abnormalities in calcium homeostasis has not been evaluated. The purpose of this study was, therefore, to identify and quantify the metabolites of 25(OH)D₃ produced by fresh cells recovered by bronchoalveolar lavage (BAL) from patients with tuberculosis and control subjects, and to correlate the production of these metabolites with the clinical characteristics of the tuberculosis patients, including both the existence of abnormalities in calcium metabolism and the type of inflammatory lesions present.
Methods

Study populations

Patients with pulmonary tuberculosis. Pulmonary tuberculosis was studied prior to receiving any antituberculous therapy. Of the 14 patients (10 men and 4 women) who had a mean±SD age of 34±7 yrs, eight were of black ethnic origin, and six were Caucasians. None of them was human immunodeficiency virus (HIV) positive. Five of the subjects were smokers (24±12 cigarettes·day⁻¹). Tuberculin skin tests were strongly positive in all patients. Chest X-ray showed localized infiltrates with or without cavitation in 10 patients, and hilar adenopathy but without parenchymal infiltrates in the remaining four. Patients were studied prior to receiving any antituberculous therapy.

Control subjects. Three normal volunteers and two patients undergoing bronchoscopic evaluation for non-parenchymal pulmonary disorders served as controls. These individuals (2 men and 3 women) had an average age of 28±8 yrs. Two were cigarette smokers (3–20 cigarettes·day⁻¹).

Evaluation of calcium metabolism

Serum and urinary calcium concentrations were determined by atomic absorption photometry (Model 303, Perkin-Elmer, Norwalk, CT, USA), and serum calcium concentrations were corrected for proteinemia, as described by Alsever and Gotlin [16]. Serum and urinary phosphate were determined by a colorimetric method (Technicon, Rax T). Cyclic adenosine monophosphate (cAMP) was measured using a commercial radiocompetition assay (Amersham, Les Ulis, France). Immuno-reactive parathyroid hormone (PTH) was measured by an immunoradiometric assay using an antiserum directed against both 1–34 and 39–84 peptides (Incstar Corp., Stillwater, MN, USA). Plasma 25(OH)D₃ and 1,25(OH)₂D₃ were measured as described previously [1].

Calcium absorption tests were performed as described previously [17]. Briefly, after 3 days, during which the patient had a diet containing less than 400 mg of calcium·day⁻¹, blood and urine samples were drawn at 9,30 a.m. The patient was then given a standard breakfast and absorbed 1,500 mg of calcium. Calcium absorption tests were strongly positive in all patients. Cyclic adenosine monophosphate were determined by atomic absorption photometry (Model 303, Perkin-Elmer, Norwalk, CT, USA), and serum calcium concentrations were corrected for proteinemia, as described by Alsever and Gotlin [16]. Serum and urinary phosphate were determined by a colorimetric method (Technicon, Rax T). Cyclic adenosine monophosphate (cAMP) was measured using a commercial radiocompetition assay (Amersham, Les Ulis, France). Immuno-reactive parathyroid hormone (PTH) was measured by an immunoradiometric assay using an antiserum directed against both 1–34 and 39–84 peptides (Incstar Corp., Stillwater, MN, USA). Plasma 25(OH)D₃ and 1,25(OH)₂D₃ were measured as described previously [1].

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Normal ranges for the results of calcium metabolism evaluation were obtained from a group of 27 healthy volunteers. They were 20 men and 7 women, with a mean age of 42±10 yrs.

Bronchoalveolar lavage

Informed consent was obtained from all patients and control subjects. BAL was performed using 4 or 5 aliquots (50 ml each) of sterile saline [18]. A radiologically abnormal lung segment was lavaged when present, and the right middle lobe or lingula when the radiograph was normal.

Culture of lavage fluid was systematically performed and always remained negative for bacteria. Total and differential cell counts and the evaluation of the expression of CD4 and CD8 surface antigens on T-lymphocytes were performed as described previously [18]. The viability of cells recovered by lavage and stained with acridine orange and ethidium bromide was: controls 86±2%; and tuberculosis patients, 81±14%. The number and types of cells recovered by lavage from patients and control subjects are summarized in table 1.

Metabolism of 25(OH)D₃ by cells in vitro

Techniques used to quantify and characterize the production of vitamin D metabolites by lavage cells have been described previously [1, 3]. Briefly, lavage cells were washed twice using Dulbecco’s modified Eagle medium (Boerhinger Mannheim GmbH, Penzberg, Germany) and 1×10⁶ cells were incubated for 150 min in the presence of [³H]25(OH)D₃ (final concentration either 2.5×10⁻⁹ M or 1×10⁻⁶ M), and vitamin D metabolites were extracted and purified by sequential passage on a high performance liquid chromatography (HPLC) system using two different solvent systems (n-hexane: isopropanol and methylene chloride:isopropanol). The rate of conversion of [³H]25(OH)D₃ into [³H]1,25 (OH)₂D₃ and [³H](3E)- or (5Z)-19-nor-10-oxo-25(OH)D₃ was determined by calculating the percentage of total radioactivity with an appropriate elution profile after purification by HPLC. Results are expressed as fmole·10⁴ cells per 150 min, based on the assumption that the specific activity of the product was the same as that of the substrate. All incubations and the subsequent purification of metabolites were performed in duplicate, and each value reported in the study represents the mean of duplicate determinations.
The interassay coefficient of variation of duplicate determinations was: 1,25(OH)_2D_3 25±4%; (5Z)-19-nor-10-oxo-25(OH)D_3, 16±6%; and (5Z)-19-nor-10-oxo-25(OH)D_3, 17±5%. The intra-assay coefficient of variation of two determinations of the same sample was 5±3%; 3±2%; and 4±2% for the three metabolites evaluated, respectively. Methods used for determining the specific activity of metabolites, their UV spectra, and their capacity to bind 1,25(OH)_2D_3 receptors have been described previously [1, 3].

Statistical methods

Results are expressed as mean±SD. Comparison of the production of metabolites between two groups was performed by the Kruskal-Wallis one-way analysis of ranks procedure. Correlations between the production of 25(OH)D_3 metabolites and other metric variables were evaluated by linear regression. In each case, a p<0.05 was considered significant.

Results

Characterization of 25(OH)D_3 metabolites synthesized by cells in vitro

Cells recovered by BAL from normals and patients with tuberculosis were able to metabolize 25(OH)D_3 into more polar metabolites. When extracts containing metabolites of [3H]25(OH)D_3 were separated by HPLC using the n-hexane:isopropanol solvent system, two predominant peaks of radioactivity were observed, which eluted after the [3H]25(OH)D_3 substrate. A first peak (region "1" in fig. 1a) eluted slightly ahead of synthetic 1,25(OH)_2D_3, and was composed almost entirely of (5Z)-19-nor-10-oxo-25(OH)D_3 (see below). A second peak coeluted with unlabelled synthetic 1,25(OH)_2D_3 (region “2” in fig. 1a).

When the metabolites coeluting with synthetic 1,25(OH)_2D_3 (region “2” in fig. 1a) were pooled, concentrated and rechromatographed, using the methylene chloride:isopropanol solvent system, four peaks of radioactivity could be resolved (fig. 1b): a small peak eluting immediately after the solvent front (elution volume 0.30 relative to synthetic 1,25(OH)_2D_3), which was not further analysed; two closely adjacent peaks (elution volumes 0.54 and 0.69, respectively, relative to synthetic 1,25(OH)_2D_3) corresponding to the (5Z)- and (5E)-isomers of 19-nor-10-oxo-25(OH)D_3 (referred to hereafter as 5Z and 5E) (see below); and, in some samples, a sharp well-defined peak which coeluted with synthetic 1,25(OH)_2D_3.

Evidence supporting the conclusion that the metabolite which coeluted with 1,25(OH)_2D_3 in two successive HPLC chromatographic steps was 1,25(OH)_2D_3 has been published previously [1, 3]. Additional findings supported the idea that the metabolites, the chromatographic properties of which were similar to 5Z and 5E, were, in...
fact, these metabolites. Firstly, the putative 5Z, isolated using the n-hexane:isopropanol solvent system, eluted mostly as a single peak at the position expected for 5Z when rechromatographed using the methylene chloride:isopropanol solvent system. In addition, a minor fraction eluted at the position expected for 5E, as would be expected from the isomerization of 5Z into 5E [19, 20]. Similarly, when the putative 5E, purified by sequential chromatography using the two solvent systems, was rechromatographed using the methylene chloride:isopropanol solvent system, some radioactivity which initially had an elution volume relative to 1,25(OH)2D3 of 0.69, now had an elution volume of 0.54. This phenomenon would be expected for the isomerization of 5E into 5Z [19, 20]. Furthermore, when cells were cultured in the presence of 10−6 M 25(OH)D3 and these metabolites were purified by HPLC, the products had a UV spectrum similar to that of synthetic 5Z and 5E, and did not compete with the binding of synthetic [3H]1,25(OH)2D3 in the receptor binding assay [19, 20].

Metabolism of [3H]25(OH)D3 by lavage cells

When fresh lavage cells from patients with tuberculosis were incubated in the presence of 2.5×10−9 M [3H]25(OH)D3, detectable amounts of [3H] 5Z and 5E were produced in all cases (fig. 2b and c). [3H]1,25(OH)2D3 was also produced by lavage from all tuberculosis patients tested (fig. 2a). In contrast, lavage cells from controls did not produce detectable amounts of 1,25(OH)2D3. Interestingly, lavage cells from two patients produced considerably more 1,25(OH)2D3 than the remaining 12 patients (fig. 2a); these two patients had overt hypercalcaemia and elevated plasma 1,25(OH)2D levels (see below). The amount of 1,25(OH)2D3 produced by lavage cells was 10–100 fold smaller than the amount of 19-nor-10-oxo-25(OH)D3 produced by these cells. No correlation was observed between 1,25(OH)2D3 production by lavage cells and that of 5Z- or 5E-isomers. Lavage cells from controls also produced considerable amounts of 5Z and 5E. The production of 5Z, but not of 5E, by lavage cells from controls was slightly lower than that of lavage cells from patients with tuberculosis (p<0.05).

Relationship between the conversion of 25(OH)D3 into 1,25(OH)2D3 by lavage cells and the characteristics of the patients

Calcium and phosphorus metabolism. Two patients had hypercalcaemia and increased post-load urinary calcium excretion, associated with elevated plasma levels of 1,25(OH)2D3, normal serum concentrations of phosphorus (table 2, patients No. 1 and 2) and low serum PTH concentrations (data not shown). Five other patients had normocalcaemia but increased post-load urinary calcium excretion (patients Nos. 4 and 9–12); two of these had elevated 1,25(OH)2D plasma levels, whereas three had a normal value. The remaining seven patients had normal calcium metabolism and plasma 1,25(OH)2D levels (patients Nos 3, 5–8, 13, 14). Although, plasma 1,25(OH)2D levels were normal (n=10) or elevated (n=4), plasma 25(OH)D concentrations were at or below the lower limit of normal (tuberculosis patients 3.9±2.0 ng·ml−1; controls 16±7 ng·ml−1; p<0.01). Finally, serum PTH concentrations (50.4±23.6 pg·ml−1; normal range <80 pg·ml−1), nephrogenic cAMP (1.5±0.4 nmoles·dl−1 glomerular filtrate; normal range <3 nmoles·dl−1), and tubular reabsorption of phosphate (93±3%; normal range >82%) were normal in all patients.

There was a correlation between post-load urinary calcium excretion and both 1,25(OH)2D plasma levels...
(r=0.84; p=0.0001) (fig. 3a) and 1,25(OH)₂D₃ production by lavage cells (r=0.59; p=0.035). Furthermore, a correlation was also found between 1,25(OH)₂D plasma levels and 1,25(OH)₂D₃ production by lavage cells (r=0.67; p=0.008) (fig. 3b). The quantity of 1,25(OH)₂D₃ produced by lavage cells from hypercalcaemic patients was 20 fold higher than that of non-hypercalcaemic patients (240±10 vs 10.1±8.7 fmol; p=0.03).

Clinical features. 1,25(OH)₂D plasma level and 1,25(OH)₂D₃ production by lavage cells were correlated with the proportion of lymphocytes present (r=0.46; p=0.03; and r=0.87; p=0.0001, respectively) (fig. 3c). No other correlations between 1,25(OH)₂D₃ production by lavage cells and the proportion of other inflammatory cells (macrophages, neutrophils, eosinophils and mastocytes) and/or CD4 and CD8 lymphocyte subsets were found. Both patients with hypercalcaemia and very high 1,25(OH)₂D₃ production had extensive cavitary disease and a high proportion of lymphocytes recovered by lavage (>40%). Other patients whose lavage cells produced more modest amounts of 1,25(OH)₂D₃ had disease of similar form and severity and equivalent numbers of lymphocytes were recovered by lavage (fig. 3c).

Of the other clinical variables evaluated, two were identified which were associated with an increased production of 1,25(OH)₂D₃ by fresh lavage cells. Firstly, lavage cells from black patients with tuberculosis produced more 1,25(OH)₂D₃ than did those from Caucasian patients (p=0.03). Secondly, cells from patients with hilar adenopathy but no parenchymal abnormality produced more 1,25(OH)₂D₃ than did patients with other forms of tuberculosis (p=0.05). These two clinical variables were not, however, independent. Indeed, 4 out of 8 black patients presented with hilar adenopathy only, whereas this presentation was not seen in the six

Table 2. Calcium and phosphorus metabolism in patients with tuberculosis

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Plasma 1,25(OH)₂D pg·ml⁻¹</th>
<th>Plasma 25(OH)D ng·ml⁻¹</th>
<th>Serum calcium mmol·l⁻¹</th>
<th>Serum phosphate mmol·l⁻¹</th>
<th>Urinary calcium (mmol·mmol⁻¹ creatinine)</th>
<th>1,25(OH)₂D₃ production (lavage cells)*</th>
</tr>
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<tr>
<td>1</td>
<td>110</td>
<td>4</td>
<td>3.50</td>
<td>1.30</td>
<td>0.20</td>
<td>230</td>
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<tr>
<td>2</td>
<td>108</td>
<td>6</td>
<td>2.95</td>
<td>1.05</td>
<td>0.17</td>
<td>1.80</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>5</td>
<td>2.32</td>
<td>1.30</td>
<td>0.10</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>106</td>
<td>4</td>
<td>2.43</td>
<td>1.39</td>
<td>0.43</td>
<td>2.74</td>
</tr>
<tr>
<td>5</td>
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<td>1</td>
<td>2.52</td>
<td>1.19</td>
<td>0.23</td>
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</tr>
<tr>
<td>6</td>
<td>46</td>
<td>5</td>
<td>2.40</td>
<td>0.91</td>
<td>0.18</td>
<td>0.70</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>7</td>
<td>2.37</td>
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<td>0.28</td>
<td>0.62</td>
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<tr>
<td>8</td>
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<td>0.98</td>
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</tr>
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<td>67</td>
<td>6</td>
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<td>1.45</td>
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</tr>
<tr>
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<td>0.83</td>
<td>0.24</td>
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<tr>
<td>11</td>
<td>35</td>
<td>6</td>
<td>2.35</td>
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<tr>
<td>12</td>
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<td>2</td>
<td>2.30</td>
<td>1.09</td>
<td>0.22</td>
<td>1.29</td>
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<tr>
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Normal range (20–60) (6–30) (2.10–2.55) (0.89–1.21) (<0.30) (<0.77)

*: results are expressed as fmol 1,25(OH)₂D₃ produced by 10⁶ fresh lavage cells incubated in the presence of 2.5×10⁻⁹ M 25(OH)D₃ for 150 min. ND: not determined; Pt: patient; 1,25(OH)₂D: 1,25 dihydroxyvitamin D; 25(OH)D: 25 hydroxyvitamin D.

![Fig. 3. Correlations between: a) post-load urinary calcium excretion and plasma 1,25 dihydroxyvitamin D (1,25(OH)₂D) level; b) plasma 1,25(OH)₂D level and 1,25 dihydroxyvitamin D₃ (1,25(OH)₂D₃) production by lavage cells; c) 1,25(OH)₂D₃ production by alveolar cells and the percentage of lymphocytes recovered in bronchoalveolar lavage. Note the log scale in (b) and (c).](image-url)
Caucasians evaluated (p=0.04). In addition, more lymphocytes were recovered by lavage from black patients than from Caucasians 42.5±24.5% (n=8) and 15.2±15.8% (n=6) of total lavage cells, respectively (p=0.01).

Relationship between 5Z- or 5E-isomer production by lavage cells and clinical characteristics. No correlations were observed between the production of 5E- and 5Z-isomers by lavage cells from patients with tuberculosis and the indices of calcium and phosphorus metabolism evaluated in this study, or the clinical features of the patients (data not shown).

Discussion

In this study we have characterized the metabolites of 25(OH)D, produced by immune and inflammatory cells, obtained by bronchoalveolar lavage, from patients with tuberculosis and controls, and compared the production of these metabolites with clinical characteristics of the patients. Our results suggest that: 1) spontaneous production of 1,25(OH)2D3 by these alveolar cells occurs commonly in tuberculosis, but represents a minor proportion of the total vitamin D metabolites produced; 2) increases in circulating 1,25(OH)D are likely to make a major contribution to the abnormalities of calcium metabolism observed in tuberculosis patients, but do not entirely explain these abnormalities; and 3) the production of 1,25(OH)2D3 by lavage cells is quite variable, and depends, in part, on the clinical characteristics of the tuberculosis patients.

25(OH)D3 metabolites produced by lavage cells

The major metabolites of 25(OH)D3 produced by fresh lavage cells both from controls and patients with tuberculosis had chromatographic and spectroscopic characteristics previously described for the (5Z)- and (5E)-isomers of 19-nor-10-oxo-25(OH)D3 [19–22]. Considerable overlap was observed in the production of these metabolites by cells from controls and patients, and only the production of the 5Z-isomer by lavage cells was slightly different when comparing the two study groups. The production of 19-nor-10-oxo-25(OH)D3 by a variety of epithelial and haematopoietic cells has been described previously [19, 21, 22]. However, the physiological role of this metabolite, particularly in the control of 1α,25(OH)D hydroxylase activity, if any, has not been established [19, 21, 22].

In contrast to controls, immune and inflammatory cells from tuberculosis patients were also capable of synthesizing 1,25(OH)2D3. The production of 1,25(OH)2D3 at sites of granulomatous reactions has previously been reported in sarcoidosis and tuberculosis [1–3, 23–25]. However, the characteristics of this production are quite different in these two diseases. In sarcoidosis, the 1,25(OH)2D3 production has been found in 7 day cultured alveolar macrophages obtained only from patients who had known calcium metabolism abnormalities [25]. It may also be observed after in vitro activation by various mediators, i.e. lipopolysaccharides and gamma-interferon, in macrophages from patients without such calcium metabolism abnormalities [23, 25]. By contrast, in tuberculosis, 1,25(OH)2D production has been found in fresh as well as in cultured alveolar cells; even if macrophages may also contribute sometimes to this production, lymphocytes are the predominant source of vitamin D metabolism in lung of tuberculosis patients [1, 3].

1,25(OH)2D3 production and calcium metabolism

In this study, significant correlations were observed between serum calcium and post-load urinary calcium excretion and both the plasma levels of 1,25(OH)2D and spontaneous production of 1,25(OH)2D by lavage cells. Similar findings have been reported previously for patients with sarcoidosis [17, 25, 26]. These results are entirely consistent with the idea that 1,25(OH)2D3 produced by immune and inflammatory cells, acting in an endocrine fashion, contributes to the abnormalities of calcium metabolism observed in patients with tuberculosis.

Although "normal" 1,25(OH)2D plasma levels in hypercalciuria patients represent an inappropriate elevation of the circulating levels of this hormone, it should be emphasized that some of the findings in our study suggest that increased circulating levels of 1,25(OH)2D are probably not the only determinant of abnormal calcium metabolism in these patients. In particular, clearly abnormal post-load urinary calcium excretion was observed in seven patients, whereas plasma 1,25(OH)2D was elevated in only four of these individuals. In the remaining three patients, plasma 1,25(OH)2D levels were, in fact, near the middle of the normal range. In this context, patients with sarcoidosis and tuberculosis have previously been described in whom abnormalities in calcium metabolism did not correlate closely with plasma 1,25(OH)2D [1, 26, 27]. The local production of 1,25(OH)2D3 in tissues responding to this hormone (e.g., gut, bone or kidney) or the production of other mediators (tumour necrosis factor-α (TNF-α), prostaglandin E2 (PGE2), interleukin-1 (IL-1), etc.) by immune and inflammatory cells [28–30], which independently modify calcium metabolism [31], are two possible explanations for the dissociation between plasma 1,25(OH)2D3 levels and post-load calcium excretion observed in this and previous studies.

It is also noteworthy that lavage cells from all patients produced 1,25 (OH)2D3, whereas only a minority of patients had elevated plasma 1,25(OH)2D. Furthermore, although a significant correlation was observed between 1,25(OH)2D3 production by lavage cells and plasma 1,25(OH)2D, the correlation was not strong (r=0.67). The low plasma 25(OH)D concentrations observed in our patients could, in theory, reduce the 1,25(OH)2D3 production by these individuals in vivo (due to a lack of substrate), thereby explaining the weak correlation between in vivo and in vitro findings. Several findings argue
against this possibility. Firstly, no correlation was observed between plasma 25(OH)D levels and 1,25(OH)2D levels. Furthermore, no difference has been observed in prior studies comparing 25(OH)D levels in patients with granulomatous diseases who did and did not have elevated 1,25(OH)2D plasma levels and hypercalcaemia [17, 26]. The ability of 1,25(OH)2D production by immune and inflammatory cells to increase plasma 1,25(OH)2D probably depends on a number of factors, including: 1) the rate of 1,25(OH)2D synthesis by immune cells; 2) the extent to which extraenal 1,25(OH)2D production occurs in multiple sites, such as production by circulating cells [3]; 3) the magnitude of compensatory changes in renal 1,25(OH)2D production; and 4) the degree to which 1,25(OH)2D is retained at sites of immune reactions by cells expressing 1,25(OH)2D receptors [10]. In view of this complexity, it is not surprising that in vitro production of 1,25(OH)2D did not correlate closely with plasma 1,25(OH)2D levels.

1,25(OH)2D production in tuberculosis and clinical features

In this study, three factors were identified which were associated with increased production of 1,25(OH)2D by lavage cells, the proportion of T-lymphocytes among cells recovered by lavage, black ethnic origin, and presentation of tuberculosis as isolated adenopathy. The strong correlation found between 1,25(OH)2D production during tuberculosis normocalcaemia and elevated calcitriol in maintenance dialysis patients. Arch Intern Med 1986; 146: 1941–1945.

References


