Autocrine control of vitamin D metabolism in synovial cells from arthritic patients

Susan J Smith, Michael E Hayes, Peter L Selby, E Barbara Mawer

Abstract

Objective—This study was designed to investigate whether 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃), produced by activated synovial fluid macrophages, promotes its own catabolism by upregulating vitamin D-24-hydroxylase (24-OHase) in synovial fibroblasts through a vitamin D receptor (VDR) mediated mechanism.

Methods—Synovial macrophages and fibroblasts were derived from patients with rheumatoid arthritis. Expression of VDR and 24-OHase mRNAs was determined using in situ hybridisation. Vitamin D hydroxylase activity was determined by incubating cells with [¹²⁵I]-25-(OH)D₃, or [¹²⁵I]-1,25-(OH)₂D₃, and metabolite synthesis quantified using high performance liquid chromatography.

Results—1,25-(OH)₂D₃ increased expression of mRNA for both VDR and 24-OHase in fibroblasts by approximately threefold over 24 hours. 1,25-(OH)₂D₃ increased fibroblast 24-OHase activity, yielding 24-hydroxylated, and more polar, metabolites. In co-culture, fibroblasts were able to catabolise macrophage derived 1,25-(OH)₂D₃.

Conclusions—1,25-(OH)₂D₃ is produced by macrophages in vitro at biologically relevant concentrations and can increase its own catabolism by synovial fibroblasts; this effect is probably mediated via upregulation of both synovial fibroblast VDR and 24-OHase.


The active metabolite of vitamin D₃, 1α,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃), has immunoregulatory, pro-differentiating, and anti-proliferative properties that have been shown to inhibit the progression of a number of autoimmune diseases, including experimental autoimmune encephalomyelitis and autoimmune diabetes. A recent paper by Cantorna et al has shown that 1,25-(OH)₂D₃ can both prevent the development and halt the progression of arthritis in murine models of the human disease. Oral 1,25-(OH)₂D₃ treatment has also been shown to improve human psoriatic arthritis, and its analogue 1α-hydroxyvitamin D₃ inhibits type II collagen induced arthritis in rats.

Exogenous administration of 1,25-(OH)₂D₃ may be a useful therapeutic approach for arthritis, however substrate dependent endogenous production of 1,25-(OH)₂D₃ can occur within the arthritic joint in vivo. The source of the extra-renal 1,25-(OH)₂D₃ is likely to be the synovial macrophage, as we have demonstrated in vitro that macrophages isolated from the synovial fluids of patients with inflammatory arthritis express vitamin-D-1α-hydroxylase (1-OHase) activity, which can be regulated by locally encountered factors such as cytokines, for example, interferon gamma (IFNγ), bacterial lipopolysaccharide, and eicosanoids.

Another vitamin D hydroxylase enzyme, namely the 24-hydroxylase (24-OHase), is responsible for the catabolism of 1,25-(OH)₂D₃, and is expressed by synovial fibroblasts. 1,25-(OH)₂D₃ and its receptor (VDR) bind to the vitamin D response elements (VDREs) of target genes to control their transcription and, as the promoter region of the human 24-OHase gene contains VDREs, it appears that the activity of the synovial fibroblast 24-OHase might be under the control of the local concentration of macrophage derived 1,25-(OH)₂D₃.

In this study we wanted to investigate how induction of synovial fibroblast 24-OHase by 1,25-(OH)₂D₃ may, in turn, regulate the local concentration of 1,25-(OH)₂D₃ in the synovial joint. To this end, we could be done via several mechanisms. Firstly, it may promote catabolism of existing 1,25-(OH)₂D₃ to 1,24,25-trihydroxyvitamin D₃ (1,25-(OH)₂D₃), 24,25-(OH)₂D₃, and its analogue 1α,25-(OH)₂D₃. Secondly, the 24-OHase may lessen the pool of precursor 25-(OH)₂D₃ available to macrophages for 1-hydroxylation (which is known to be substrate dependent), by diverting 25-(OH)₂D₃ into the synthesis of 24,25-dihydroxyvitamin D₃ (24,25-(OH)₂D₃). An increase in 24,25-(OH)₂D₃ concentration may itself provide a third mechanism to reduce entry of freshly synthesised 1,25-(OH)₂D₃ into the system; we have demonstrated that 24,25-(OH)₂D₃ can be converted to 1,24,25-(OH)₃D₃ by synovial fluid macrophages (unpublished data), and will therefore compete with 25-(OH)₂D₃ as a substrate for 1-hydroxylation.
synovial fibroblast 24-OHase by 1,25-(OH)\(_2\)D\(_3\) in vitro, at both the molecular and functional level, and to determine whether this effect is mediated via VDR. Expression of synovial fibroblast VDR and 24-OHase mRNAs was determined using in situ hybridisation. The effects of exposure to 1,25-(OH)\(_2\)D\(_3\) on the metabolism of [\(\text{3H}\)]-25-(OH)\(_2\)D\(_3\) and [\(\text{3H}\)]-1,25-(OH)\(_2\)D\(_3\) by synovial fibroblasts, and the effects of fibroblasts on the metabolism of 1,25-(OH)\(_2\)D\(_3\), produced by macrophages when the two cell types were co-cultured, were also investigated using a hydroxylase assay.

**Methods**

**SOURCE OF SYNOVIAL CELLS**

Synovial fibroblasts (designated F733), derived from an explant culture from a patient with rheumatoid arthritis, were kindly supplied by Dr David Taylor. Cells were routinely grown in Dulbecco’s modified Eagle’s medium (DMEM) containing 1 × 10\(^{-3}\) M sodium pyruvate (Gibco), 2 × 10\(^{-3}\) M L-glutamine, 50 IU/ml penicillin, 50 µg/ml streptomycin, and 10% v/v fetal bovine serum (Imperial) and passaged every 1–2 weeks using 0.25% trypsin, 0.02% EDTA in phosphate buffered saline (Imperial). Cells were used at passage 10 in these experiments.

A primary culture of synovial fluid macrophages was established from the synovial fluid of a patient with rheumatoid arthritis using the method of Hayes et al.\(^{12}\) Briefly, the synovial fluid sample was diluted in RPMI-1640 culture medium containing 2% v/v fetal bovine serum, 4 × 10\(^{-3}\) M L-glutamine, 10 IU/ml penicillin, and 10 µg/ml streptomycin. From experience, we have found that incubating the sample in 2% v/v fetal bovine serum, rather than 10% v/v fetal bovine serum, encourages the culture of macrophages, but not fibroblasts, thus allowing fibroblast free cultures of macrophages to be established. Any macrophage culture contaminated by fibroblasts can be readily identified, because fibroblasts proliferate in culture and can be seen as colonies.

The sample was incubated at 37\(^\circ\)C in a humidified atmosphere of air with 5% carbon dioxide for 2–3 days; after this time macrophages had adhered to the culture plate surface and non-adherent cells were washed away. All cells from the sample stained positive for non- and non-adherent cells were washed away. All phages had adhered to the culture plate surface and 10% v/v EDTA in phosphate buffered saline (Imperial). Cells were used at passage 10 in these experiments.

**DETERMINATION OF mRNA EXPRESSION USING IN SITU HYBRIDISATION**

F733 cells were pre-treated for five or 24 hours with 5 × 10\(^{-8}\) M 1,25-(OH)\(_2\)D\(_3\) (Hoffman La Roche) or vehicle (0.125% v/v ethanol) in glass chamber slides (Lab-Tek) and fixed in 10% v/v formaldehyde. Expression of VDR and 24-OHase mRNA was determined using in situ hybridisation with [\(\text{35S}\)] labelled riboprobes.

The 2.1 kb human VDR cDNA probe was kindly supplied by Drs J Omdahl and B May, cloned into the Pst I site of Bluescript KS+. The in situ hybridisation technique used in this study has previously been described by Mee et al.\(^{17}\) Controls were sense riboprobe and RNase A treated cells (Sigma; 1 mg/ml in water for one hour at 37\(^\circ\)C) to ensure that probe binding to cells was RNA specific. Probe hybridisation was detected by dipping slides in photographic emulsion (Ilford K3) diluted 1:1 with distilled water and developed after seven days at 4\(^\circ\)C. The radiation produces silver grains within the emulsion that can be visualised as “black dots” and, as the path length of [\(\text{35S}\)] is 15–20 µm, the positions of the black dots localise the areas of probe binding.

Cells were counterstained using eosin and Harris haematoxylin and examined using light field microscopy. Probe hybridisation was quantified with a QuantiMix 600 image analyser linked to a Leica DM microscope (Leica UK Ltd),\(^{13}\) allowing the percentage cell area covered by silver grains to be calculated, corrected for background levels of probe binding.

**DETERMINATION OF VITAMIN D HYDROXYLASE ACTIVITY**

**Effect of 1,25-(OH)\(_2\)D\(_3\) on synovial fibroblast vitamin D hydroxylase activity**

To study the effects of 1,25-(OH)\(_2\)D\(_3\) on F733 vitamin D hydroxylase activity, cells were pre-treated with 1,25-(OH)\(_2\)D\(_3\) (10\(^{-7}\) to 10\(^{-11}\) M), or vehicle (ethanol, 0.25% v/v), in DMEM containing 6.25 µg/ml insulin, 6.25 µg/ml transferrin, 6.25 ng/ml selenous acid, 1.25 mg/ml bovine serum albumin (BSA), 5.35 µg/ml linoleic acid (ITS); Becton Dickinson), 2 × 10\(^{-3}\) M L-glutamine, 50 IU/ml penicillin, and 50 µg/ml streptomycin. Cells were incubated for 24 hours in a humidified atmosphere of 95% air, 5% carbon dioxide, then washed and left for three hours in ITS+ supplemented DMEM; this allowed time for any pre-treatment 1,25-(OH)\(_2\)D\(_3\) to be metabolised by cells before incubation with substrate. Enzyme activity was then determined by incubating cells for 1.5 hours in fresh DMEM containing either 25-(OH)\(_2\)D\(_3\) or 1,25-(OH)\(_2\)D\(_3\) (358 pg/ml and 43.5 pg/ml respectively), supplemented with 5 × 10\(^{-8}\) dpm tritiated substrate (25-hydroxy [26,(27)-methyl-\(\text{3H}\)] cholecalciferol ([\(\text{3H}\)]-25-(OH)\(_2\)D\(_3\)), specific activity about 15.0 Ci/µmol or 1α,25-dihydroxy [26,27-methyl-\(\text{3H}\)] cholecalciferol ([\(\text{3H}\)]-1,25-(OH)\(_2\)D\(_3\)), specific activity about 173 Ci/µmol; Amersham) 0.5% v/v BSA (Orthodiagnostic Systems Ltd) and 2 × 10\(^{-3}\) M L-glutamine, using the hydroxylase assay described previously by Hayes et al.\(^{12}\) A blank incubation (no cells) was also included in the assay. Metabolites were extracted using chloroform: methanol; 3:2 v/v and quantified using high performance liquid chromatography (HPLC) and liquid scintillation counting.

Briefly, the chloroform layer was extracted and analysed on a manual injection normal phase HPLC system developed with a mobile phase of n-hexane/isopropanol/methanol, 115:3:5 (v/v) and a Zorbax-Sil column (4.6 mm × 25 cm). Eluant fractions were collected, the radioactivity measured, and the
known specific activity of substrate used to calculate the rate of synthesis of vitamin D$_3$ metabolites in each sample. An aliquot of the upper aqueous phase of the extraction mixture was also counted as a measure of more polar metabolites.

**Synovial macrophages and fibroblasts in co-culture**

A co-culture system was established to determine whether synovial macrophage derived 1,25-(OH)$_2$D$_3$ could be directly 24-hydroxylated by F733 in vitro to form 1,24,25-(OH)$_3$D$_3$. F733 were grown in sterile 12 mm diameter polystyrene well inserts (Costar), which could fit into the wells of a 12 well tissue culture dish (Corning) in which the macrophages were cultured. The inserts had a 3.0 µm porous membrane that allowed the culture medium to move freely between the chambers. Adequate synthesis of 1,25-(OH)$_2$D$_3$ by macrophages was ensured by pre-treatment for 24 hours with $5 \times 10^{-9}$ M interferon gamma (IFN$_\gamma$; Advanced Protein Products Ltd). After

---

**Figure 1** Photomicrographs showing hybridisation of $[^{35}S]$ labelled riboprobe for 24-OHase and VDR mRNAs in F733 synovial fibroblasts. F733 cells were pre-treated with $5 \times 10^{-8}$ M 1,25-(OH)$_2$D$_3$ or vehicle (0.125% v/v ethanol), fixed, then hybridised overnight with $[^{35}S]$ labelled riboprobe for 24-OHase or VDR mRNA. (A) Twenty-four hour vehicle treated cells, 24-OHase probe; (B) 24 hour 1,25-(OH)$_2$D$_3$ treated cells, 24-OHase probe; (C) RNase A treated control slide, 24-OHase probe; (D) 24 hour vehicle treated cells, VDR probe; (E) 24 hour 1,25-(OH)$_2$D$_3$ treated cells, VDR probe; (F) RNase A treated control slide, VDR probe. Bar = 50 µm, cells counterstained with eosin and Harris haematoxylin (Sigma).
M 1,25-(OH)₂D₃. The position of an unidentified product, which was more polar than 2D₃ (peak B), and 1,25-(OH)₂D₃ (peak C). As no radioactive tracer was available, the expected position of a tritiated 1,24,25-(OH)₃D₃ peak was calculated using an ultraviolet trace of unlabelled markers in conjunction with the radioactive trace above. The solid trace in figure 2 (A) shows the typical metabolism of substrate [³H]-25-(OH)D₃ (peak A), 24,25-(OH)₂D₃ (peak B), and 1,25-(OH)₂D₃ (peak C). As no radioactive tracer was available, the expected position of a tritiated 1,24,25-(OH)₃D₃ peak was calculated using an ultraviolet trace of unlabelled markers in conjunction with the radioactive trace above.

Radioactivity (dpm/fraction) in marker

Retention time (min)

Radioactivity (dpm/fraction) in fibroblast sample

Radioactivity (dpm/fraction) in fibroblast sample

Results

REGULATION OF 24-OHASE AND VDR mRNAs BY 1,25-(OH)₂D₃ IN F733 SYNOVIAL FIBROBLASTS

Pre-treatment with 1,25-(OH)₂D₃ for either five or 24 hours increased probe binding to F733, indicating an increase in 24-OHase mRNA. At both time points some cells had very high activity while others had very low activity, possibly because of differences in the state of cell differentiation or cell cycle, or both. The extent of hybridisation was quantified and expressed as the % cell area covered by silver grains. There was a significant increase in probe binding (p < 0.01) from 2.3 (0.5)% (mean (SEM)) in cells treated with vehicle for five hours to 6.2 (1.0)% in cells treated with 1,25-(OH)₂D₃ for five hours (results not shown). There was a similar increase in probe binding (p < 0.05) from 1.7 (0.3)% in cells treated with vehicle for 24 hours (fig 1(A)) to 5.1 (2.2)% in cells treated with 1,25-(OH)₂D₃ for 24 hours (fig 1(B)). Both RNase A treated control slides (fig 1(C)) and sense riboprobe control slides showed only background levels of silver grains.

VDR mRNA (fig 1 (D–F))

There was an increase in probe binding to F733 cells after 24 hours of 5 × 10⁻¹⁰ M 1,25-(OH)₂D₃ treatment, but not after five hours. Percentage silver grain density for five hour vehicle, five hour 1,25-(OH)₂D₃ treated cells, and 24 hour vehicle were 1.4 (0.2)%, 1.5 (0.3)%, and 1.5 (0.2)% respectively. Binding after 24 hour 1,25-(OH)₂D₃ pre-treatment (4.5 (0.5); fig 1(E)) was significantly increased compared with the 24 hour vehicle (fig 1(D)) p < 0.01 and five hour treatment values (p < 0.01). Again, both RNase A treated control slides (fig 1(F)) and sense riboprobe control slides showed only background levels of silver grains.

Expression of Vitamin D Hydroxylase Activity (From Hydroxylase Assays)

Metabolism of [³H]-25-(OH)D₃ by synovial fibroblasts pre-treated with 1,25-(OH)₂D₃

The HPLC trace in fig 2 (A) shows the typical metabolism of [³H]-25-(OH)D₃ (peak A) to [³H]-24,25-(OH)₂D₃ (peak B) and an unidentified metabolite (peak D) by F733 cells pre-treated for 24 hours with 10⁻¹⁰ M 1,25-(OH)₂D₃. Fig 3 (A) shows that synthesis of [³H]-24,25-(OH)₂D₃ was increased in a dose dependent manner by increasing pre-treatment concentrations of 1,25-(OH)₂D₃, with a mean pre-treatment, macrophages were washed once with basal medium, then incubated alone or in combination with F733 for a further 24 hours with [³H]-25-(OH)D₃ (12.5 ng/ml) using the hydroxylase assay described above.

Statistics

Statistical analysis of results was carried out with Instat for MacIntosh (version 2.01), using analysis of variance (ANOVA) and Student’s t test. Non-normally distributed data were log transformed before analysis.

Figure 2. HPLC profile of synovial fluid fibroblast (A) [³H]-25-(OH)D₃ and (B) [³H]-1,25-(OH)₂D₃ metabolism. HPLC conditions are as described in Methods. The dotted traces show the positions of known tritiated forms of 25-(OH)D₃ (peak A), 24,25-(OH)₂D₃ (peak B), and 1,25-(OH)₂D₃ (peak C). As no radioactive tracer was available, the expected position of a tritiated 1,24,25-(OH)₃D₃ peak was calculated using an ultraviolet trace of unlabelled markers in conjunction with the radioactive trace above. The solid trace in figure 2 (A) on the left shows the metabolism of substrate [³H]-25-(OH)D₃, to its 24-hydroxylated form, [³H]-24,25-(OH)₂D₃, by synovial fluid fibroblasts pre-treated for 24 hours with 10⁻¹⁰ M 1,25-(OH)₂D₃. The position of an unidentified product, which was more polar than [³H]-25-(OH)D₃, is indicated by peak D. The solid trace in figure 2 (B) shows the metabolism of substrate [³H]-1,25-(OH)₂D₃ by synovial fluid fibroblasts pre-treated for 24 hours with 10⁻¹⁰ M 1,25-(OH)₂D₃. A metabolite with an elution time representing that of [³H]-1,24,25-(OH)₃D₃ is shown by peak E and the position of an unidentified product, which was more polar than [³H]-1,25-(OH)₂D₃, is indicated by peak F; dpm = disintegrations per minute.
of 73.8 (5.3) fmol/h/10^6 cells in controls (vehicle treated), and maximum activity of 463.1 (14.6) fmol/h/10^6 cells in 10^-8 M pre-treated cells (p < 0.01). The unidentified metabolite (peak D in figures 2(A), and 3(B)), which was more polar than 24,25-(OH)_{2}D_{3}, was also synthesised in a dose dependent manner, and was not present in blank (no cells) samples, indicating this is a metabolite and not an incubation artefact. This metabolite was not 25,26-dihydroxyvitamin D_{3}, which elutes between 24,25-(OH)_{2}D_{3} and 1,25-(OH)_{2}D_{3} in our solvent system.

An aliquot of the aqueous phase was added to scintillation cocktail and [3H] dpm measured. The unidentified radioactivity present in the aqueous phase (corrected from the blank (no cells) incubation) increased with 1,25-(OH)_{2}D_{3} pre-treatment concentration (fig 3 (C)). This radioactivity indicates the presence of more polar products than those found in the chloro-
Table 1: Metabolism of [3H]-25-(OH)D₃ by synovial fibroblasts and macrophages incubated separately and in co-culture

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Metabolite synthesis (pmol/incubation/24 h)</th>
<th>Aqueous phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24,25-(OH)D₃, 1,25-(OH)D₃, 1,24,25-(OH)₃D₃</td>
<td></td>
</tr>
<tr>
<td>Macrophages (untreated)</td>
<td>12.1 (4.6) nd 12.4 (0.3) 6.7 (0.0)</td>
<td>1.5 (0.1)</td>
</tr>
<tr>
<td>IFNγ pre-treated macrophages</td>
<td>nd 34.6 (3.0) nd 1.3 (0.5) 1.3 (0.3)</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td>F733 (untreated)</td>
<td>10.9 (0.8) nd nd</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td>Co-culture</td>
<td>7.1 (0.2) 12.4 (0.3) 6.7 (0.0)</td>
<td>5.4 (0.2)</td>
</tr>
</tbody>
</table>

Results are expressed as mean (SEM), n=3; nd=none detected. The co-culture incubation consisted of F733 (untreated) and IFNγ pre-treated macrophages.

Discussion

We have demonstrated previously that 1,25-(OH)D₃ may be synthesised locally within the arthritic joint and have studied the regulation of synovial macrophage 1-Ohase activity in vitro. We have now extended these observations to show that, in vitro at least, fibroblasts of synovial origin can regulate the local 1,25-(OH)D₃ concentration at or near its site of synthesis. Moreover, this mechanism is regulated in a dose dependent fashion by 1,25-(OH)D₃ itself, acting in a paracrine mode, with a significant effect seen at near physiological concentrations (10⁻¹⁰ M). The stimulatory effects of 1,25-(OH)D₃ on synovial macrophage 24-OHase activity may be mediated via stimulation of both 24-OHase and VDR gene transcription, or by increasing mRNA stability, with increased mRNAs at five hours and 24 hours respectively. Initial upregulation of 24-OHase activity may be sufficient to catabolise raised local 1,25-(OH)D₃ levels, however if supraphysiological concentrations of 1,25-(OH)D₃ persist, an increase in VDR mRNA and protein may be required to increase the clearance rate.

We have previously studied the effect of 1,25-(OH)D₃ on 24-OHase activity and mRNA in a variety of rheumatoid synovial fibroblast cell lines, and on the same lines at different passage numbers, and always found a stimulatory effect on both 24-hydroxylase and mRNA levels—so much so, that fibroblast cell lines are used as reliable positive controls in house for the in situ hybridisation method. We have not studied fibroblasts from osteoarthritic synovium, however it would be interesting to see if there were differences in the expression of these molecules in the different disease states, particularly as we have previously shown a difference in endogenous 1,25-(OH)D₃ synthesis in rheumatoid and osteoarthritis.

Once the stimulatory effect of exogenous 1,25-(OH)D₃ on fibroblast 24-OHase had been established, we examined the metabolism of 25-(OH)D₃ by macrophages and fibroblasts in co-culture. We have now demonstrated that synovial fibroblasts can metabolise macrophage derived 1,25-(OH)D₃ to 1,24,25-(OH)₃D₃, and more polar metabolites in exactly the same way as exogenous 1,25-(OH)D₃, confirming the hypothesis that fibroblasts are able to regulate the concentration of locally synthesised 1,25-(OH)D₃ in vitro.

Our experiments also indicate that a relatively small number of macrophages (2.18 x 10⁵ cells per incubation) have the ability to make a large amount of 1,25-(OH)D₃. The concentration of substrate 25-(OH)D₃, used in the co-culture system was physiological (12.5 ng/ml or 3.125 x 10⁻⁸ M) and resulted in 1,25-(OH)D₃ concentrations of approximately 6 x 10⁻⁸ M and 1.7 x 10⁻⁸ M in control and IFNγ stimulated cultures respectively after 24 hours. As the normal serum concentration of 1,25-(OH)D₃ is in the order of 10⁻¹⁰ M to 10⁻¹¹ M (20–50 pg/ml; from Mawer et al.), it is theoretically possible that, unless regulated, high concentrations of 1,25-(OH)D₃ could be synthesised in the joint within a relatively short time period. The concentration of macrophage derived 1,25-(OH)D₃ was reduced to 6 x 10⁻⁸ M in the co-culture incubation (24 hour incubation of synovial fibroblasts and macrophages incubated separately and in co-culture).
bation with 2.18 × 10^7 macrophages and 1.1 × 10^6 fibroblasts), because of the catabolic effects of the fibroblast 24-OHase. This is one third of the concentration present in the IPNγ stimulated macrophages alone, although the regulatory effect of the fibroblasts may depend on the ratio of the different cell types and incubation time. Macrophages and fibroblasts are generally the predominant cell types in the rheumatoid lesion, but their relative proportion and distribution can be highly variable, even within the same specimen.20 21 We have measured the ratio of the di

The beneficial effects of 1,25-(OH)₂D₃ in a number of animal models of autoimmunity, including experimental autoimmune encephalitis and autoimmune diabetes,17,22 have led to the suggestion that 1,25-(OH)₂D₃, or one of its analogues, may be a valuable treatment approach to arthritis.4 It would be possible, rather than giving 1,25-(OH)₂D₃ or its analogues, systemically (as was the case for the animal experiments), to inject it locally into the joint, as for corticosteroid treatment, thus targeting the site of inflammation directly. Our findings on the ability of 1,25-(OH)₂D₃ to stimulate its own catabolism within the environment of the synovial joint would be of critical importance in regulating the local concentration of 1,25-(OH)₂D₃ in these circumstances.

Funding: this work was supported by the Arthritis and Rheumatism Council for Research.

Autocrine control of vitamin D metabolism in synovial cells from arthritic patients

Susan J Smith, Michael E Hayes, Peter L Selby and E Barbara Mawer

doi: 10.1136/ard.58.6.372