MATTERS ARISING

Bone mineral density and bone turnover in spinal osteoarthritis

The study by Peel and colleagues of bone mineral density and bone turnover in spinal osteoarthritis confirms the finding of our own and other recent studies that bone density in osteoarthritis is increased not because of osteophytes, but as a result of low bone turnover, as demonstrated using d-pyridinolinium crosslinks as markers for bone resorption.

In line with the latter findings of low bone turnover, our observations indicate that osteos at the iliac crest survive longer in patients with osteoarthritis, diagnosed by hand radiography. We found a significantly greater degree of mineralisation, as shown by gradient density bone fractionation and backscatter electron microscopy.

In addition, we have been able to show that the mechanism of this high bone density in osteoarthritis is attributable not only to a low turnover, but also to a high content of growth factors (insulin-like growth factors 1 and 2, and transforming growth factor β).1

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LETTERS TO THE EDITOR

Effect of isradipine on endothelin-1 plasma concentrations in patients with Raynaud’s phenomenon

Raynaud’s phenomenon is a common microcirculatory disorder the pathogenesis of which remains obscure.1 Significantly increased concentrations of plasma endothelin-1 (ET-1), suggesting a possible pathogenic role of this peptide, have been reported in a majority of patients with Raynaud’s phenomenon.2 Among different agents used to treat the condition, generally with disappointing results,1 calcium antagonists seem to be the most useful.2 We have investigated the effects of a new calcium antagonist (isradipine) on vasopastic episodes and plasma concentrations of ET-1 in patients with primary (type I) and suspected secondary (type II) Raynaud’s phenomenon, using a double blind, placebo controlled, and randomised parallel group trial.

The study was approved by the local ethics committee. In accordance with Kallemberg et al.,3 patients were classified as having type I Raynaud’s phenomenon in the absence of other clinico-serological manifestations, and type II when Raynaud’s phenomenon was associated with one or more symptoms of connective tissue disease not fulfilling the American Rheumatism Association criteria for a definite diagnosis. After giving their informed consent, 33 consecutive outpatients (table) with active Raynaud’s phenomenon (14 with type I; 19 with type II), diagnosed according to Allen and Brown,4 were recruited to the study during the winter. The mean duration of their Raynaud’s phenomenon was 6.7 (SD 5) years (range 2–19). Subjects with a history of cardiomyopathy, renal, hepatic, or metabolic disorders, traumatic factors, or those treated with anti-inflammatory drugs were excluded from the trial; patients receiving vasoconstrictor treatment underwent a two week washout period. Initially, each patient underwent careful physical examination, chest radiography, electrocardiography, and routine blood chemistry investigations. In addition, auto-antibodies (antinuclear antibody) were sought and nailfold capillary microscopy was performed according to techniques described previously.5 (table).

Clinicoepidemiological, serological, and capilaroscopic characteristics of 33 patients with Raynaud’s phenomenon

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (year)</th>
<th>Duration of Raynaud’s phenomenon (year)</th>
<th>Associated clinical features (%)</th>
<th>Auto-antibodies (%)</th>
<th>Nailfold capillary microscopy</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Capillary tortuosity (%)</td>
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<td></td>
<td></td>
<td></td>
<td>Capillary loss (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enlarged capillaries (%)</td>
</tr>
<tr>
<td>Type I</td>
<td>n = 14</td>
<td>36 (15)</td>
<td>6·7 (5·9)</td>
<td>44*</td>
<td>0</td>
</tr>
<tr>
<td>Type II</td>
<td>n = 19</td>
<td>50 (15)</td>
<td>6·7 (3·9)</td>
<td>90**</td>
<td>85</td>
</tr>
</tbody>
</table>

Values are number, or mean (SD), as relevant.

1. Transient mild arthralgias, achromolysis and osseous disomplastic in three, sclerodactyly in seven, or autoimmune tyroephasy in two subjects. *Antinuclear antibody in 15 patients; antinuclear extractable nuclear antigen antibody in four (two ribonucleoprotein) and four (SS-A); antinucleosome antibody in five; anti-smooth muscle antibody in one. $A scleroderma-like pattern was present in two patients.

Subsequently, patients were allocated randomly to receive, at 08:00, isradipine 5 mg/day (18 patients; eight with type I Raynaud’s phenomenon) or placebo (15 patients; six with type I Raynaud’s phenomenon) for a three week period. Patients treated with placebo were comparable to those in the group treated with isradipine as regards baseline clinicocerological values. Each patient received an instruction booklet and a clinical diary for daily recording of episodes of Raynaud’s phenomenon, variations in blood pressure, and possible side effects.

Statistical analysis was carried out by means of Student’s t and Wilcoxon’s tests.

At the beginning and the end of the trial, the plasma concentration of ET-1 was measured using a radioimmunoassay kit (Endothelin 1-2 RIA, Biomedica Gesellschaft mbH, Wien, Austria; normal values: mean 0.49 pg/ml (2SD 0.20)) with some modifications. Four of the 33 patients enrolled, one receiving isradipine and three receiving placebo, withdrew after a few days of treatment because of low compliance. In isradipine treated patients only, there was a significant reduction in the number of acute attacks from a mean of 2.6 (SD 1.8, SEM 0.4)/day to 1.5 (0.9–0.2)/day (p < 0.005), in discomfort score (on a scale of 0–10) from 7.4 (2.0–6.0) to 5.2 (2.0–5.0) (p < 0.0005), and in hand disability score (on a scale of 0–3) from 1.8 (1.0–0.8) to 1.3 (0.9–0.2) (p < 0.005). This clinical improvement was mirrored by a significant reduction in plasma concentrations of ET-1 from 1.60 (0.94, 0.25) pg/ml to 1.12 (0.67, 0.18) pg/ml (p < 0.025) (figure) during isradipine treatment. Patients receiving placebo did not show significant variations in any clinical parameter or in ET-1 concentrations. In the isradipine treated group, no differences were demonstrated between patients with type I and type II Raynaud’s phenomenon. In addition, no significant variations in blood pressure were observed. The study demonstrates a clinical and biochemical effect of isradipine in the treatment of Raynaud’s phenomenon, which is mirrored in changes in plasma ET-1 concentrations.
Survival after aortic dissection in giant cell arteritis

Acute aortic dissection in giant cell arteritis is rare and usually fatal. It is associated with hypertension and is commoner in females.

We describe two patients who were diagnosed in life and who survived on medical treatment alone for a prolonged period: one for two years; the other still alive at three years. A third patient who required aortic grafting has survived 14 years. A literature review revealed 43 other cases, with only three survivors on medical care alone.

Case reports

PATIENT 1
A 68 year old white male presented with acute chest pain on exertion radiating to the back, accompanied by dyspnoea and sweating. He had noted weight loss of more than 7 kg over the previous months. A history of back and neck ache was ascribed to spondylosis, and shoulder pain to a rotator cuff lesion. His pulse was 60 beats/min regular, and his blood pressure was 150/70 mm Hg. An ejection murmur was noted at the left sternal edge. Examination was otherwise unremarkable.

The patient developed intermittent pyrexia over the next three weeks, and experienced frequent left sided stabbing chest pain. The leucocyte count increased from normal to 14.3 with a neutrophilia. The erythrocyte sedimentation rate (ESR) peaked at 94 mm/1st h and C reactive protein (CRP) at 260 mg/l. Blood and urine cultures were negative, and autoantibody screen was normal. The electrocardiogram (ECG) showed left ventricular hypertrophy, confirmed by trans-thoracic echocardiogram, which showed no other abnormality. Chest radiograph showed minor atelectasis at both lung bases. Indium labelled leucocyte scan showed some mediastinal uptake. Computed tomography (CT) of the thorax, without intravenous contrast medium (because of asthma), showed a normal mediastinum but a small rim of pleural fluid on the left.

At follow up, the patient complained of right thigh claudication. Radiofemoral delay was noted. CT of the abdomen showed internal displacement of calcified atheroma in the aorta, suggesting aortic dissection. Magnetic resonance imaging (MRI) confirmed this as distal to the origin of the left subclavian artery, extending to the aortic bifurcation. Eight weeks after discharge, he developed headaches, aching thighs and jaw claudication with temporal artery tenderness. Prednisilone 30 mg daily was begun with rapid improvement. Clinical improvement correlated with his ESR decreasing to normal and with gradual resolution of the radiofemoral delay.

PATIENT 2
A 68 year old white women presented with five days of worsening anterior pleuritic chest pain radiating to the left, sweats, nausea, and an increased temperature. She had a history of osteoarthritis, euthyroid Graves’ ophthalmopathy, Raynaud’s phenomenon, and long-standing hypertension. Temporal arteritis had been diagnosed on biopsy eight years previously, following a characteristic illness accompanied by an ESR of 121 mm/1st h. Prednisilone for three years had achieved remission.

On admission, the patient was pyrexial at 37°C. The heart rate was 110 beat/min with no radiofemoral delay, and the blood pressure was 140/90 mm Hg equal in both arms. There was dullness to percussion at both lung bases and bronchial breathing at the left base. ESR was 86 mm/1st h, and the leucocyte count 11.4 with a neutrophilia. ECG showed left ventricular hypertrophy. Chest radiograph showed bilateral small pleural effusions and a markedly widened mediastinum. CT of the thorax and abdomen revealed a dilated thoracic aorta with a dissection in the descending portion. Transoesophageal echocardiography (TOE) initially suggested dissection commencing at the aortic root; however, repeat CT, arch aortography and MRI confirmed type B dissection. The patient was treated with a β blocker to maintain normal blood pressure, and prednisolone at a dose of 20 mg. The pain resolved and she was discharged, remaining well and normotensive for two years. Mediastinal widening then began to accelerate, MRI imaging confirming a grossly dilated dissecting descending aorta and dilatation of the ascending aorta (figure). She died soon afterwards.

pressure or hypertensive episodes were recorded during the trial. Among the side effects, mild flushing (35%) and headache (25%) were the most frequent in isradipine recipients.

This study has demonstrated the favourable effects of isradipine on patients with Raynaud’s phenomenon; moreover, it is the first to demonstrate a significant reduction in plasma concentrations of ET-1 during calcium antagonist treatment. The most usual manifestations of Raynaud’s phenomenon are pain and numbness in the fingers, which in some subjects can be complicated by skin ulcers requiring prompt intervention. In the present study, isradipine was able to reduce the frequency, severity, and disabling nature of acute attacks of Raynaud’s phenomenon; this result agrees with previous experience of the use of calcium antagonists in patients with Raynaud’s phenomenon, and reflects an appropriate selection of patients to receive the treatment. In addition, the clinicoclinical manifestations and changes in capillaroscopic findings in this series of patients, including those with type I and type II Raynaud’s phenomenon, were relatively homogeneous.

The clinical improvement of our patients with Raynaud’s phenomenon in response to isradipine was reflected in a reduction in plasma concentrations of ET-1. Although the pathophysiological function of ET-1 remains unknown, a number of vascular disorders are characterised by increased concentrations of this vasoactive peptide. How isradipine may influence the titres of ET-1 is difficult to explain but, because ET-1 is released in response to ischaemic stimuli, we hypothesise that isradipine is able to induce a change in ET-1 concentrations indirectly, by improving tissue perfusion. The findings of this preliminary investigation merit further investigation in larger series of patients with Raynaud’s phenomenon.

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