Skeletal blood flow in Paget’s disease of bone and its response to calcitonin therapy

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Summary

1. Blood flow to the skeleton was measured by the \(^{18}\text{F}\) clearance method of Wootton, Reeve & Veall (1976) in 24 patients with untreated Paget’s disease. In every patient but one, resting skeletal blood flow was increased. There was a significant positive correlation between skeletal blood flow and serum alkaline phosphatase and between skeletal blood flow and urinary total hydroxyproline excretion.

2. Fourteen patients were re-studied after they had received short-term (7 days or less) or long-term (7 weeks or more) calcitonin. Skeletal blood flow, alkaline phosphatase and urinary hydroxyproline excretion fell towards normal in every case. There was some evidence from the short-term studies that calcitonin produced a more rapid fall in skeletal blood flow than in alkaline phosphatase.

3. Glomerular filtration rate appeared to increase transiently in response to calcitonin.

Key words: blood flow, calcitonin, \(^{18}\text{F}\)fluoride, Paget’s disease of bone, glomerular filtration rate.

Introduction

In 1877 Paget described a form of ‘chronic inflammation of bones’, subsequently known as Paget’s disease or osteitis deformans, and suggested that the characteristic bone lesions were hyperaemic (Paget, 1877). Edholm, Howarth & McMichael (1945) attempted to quantify this phenomenon both indirectly, by measuring cardiac output, and directly, using venous occlusion plethysmography to measure blood flow to diseased bone. Later, however, they came to regard plethysmography as unsatisfactory for quantitative measurements owing to immeasurable venous drainage via the medulla (Edholm & Howarth, 1953). No other quantitative measurements of bone blood flow in Paget’s disease have been reported, although arteriography (Storsteen & Janes, 1954) and radionuclide-uptake studies (Fletcher, Butler, Henry, Solaric-George & Donati, 1973) have provided indirect evidence of the increased bone blood flow.

It is well known that skin temperature is increased over affected bone in Paget’s disease (Klippel & Weil, 1908) and this, it has been supposed, merely reflects the increased bone blood flow. However, it has recently been suggested that there is only a modest increase in blood flow to bone and that most of the observed increase in blood flow to an affected extremity is the result of cutaneous vasodilatation (Heistad, Abboud, Schmid, Mark & Wilson, 1975). The development of an ethically and technically satisfactory method for the measurement of blood flow to bone in man (Wootton, Reeve & Veall, 1976) has enabled us to make direct measurements of bone blood flow in Paget’s disease and to confirm that it is blood flow to bone which is raised. We have also been able to study the effects of treatment with calcitonin.
All calcitonins were administered by intramuscular injection, except in patient SF, who received an intravenous infusion: S, salmon calcitonin; P, porcine calcitonin; sH, synthetic human calcitonin. EHDP, disodium ethane-1-hydroxy-1,1-diphosphonate.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Calcitonin administered between measurements (MRC units)</th>
<th>Pre-</th>
<th>Post-</th>
<th>Pre-</th>
<th>Post-</th>
<th>Pre-</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Alkaline phosphate* (KA units/100 ml)</td>
<td>Glomerular filtration rate (ml/min)</td>
<td>Skeletal blood flow† (% of blood vol./min.)</td>
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<td>72</td>
<td>7 x 100 (S) daily</td>
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<td>93</td>
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<td>M</td>
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<tr>
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<td>86</td>
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<td>66</td>
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<td>150</td>
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<td>Short-term calcitonin</td>
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<td>Long-term calcitonin</td>
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<td>BL</td>
<td>M</td>
<td>66</td>
<td>7 x 160 (P) daily; 28 x 20 mg of EHDP/kg daily</td>
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<td>9-7</td>
<td>80</td>
<td>85</td>
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<td>100</td>
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<td>RR</td>
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<td>16-8</td>
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<td>83</td>
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<td>56-7</td>
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<td>11-7</td>
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<td>125</td>
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<td>110</td>
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<td>GA</td>
<td>F</td>
<td>75</td>
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<tr>
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<td>79</td>
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<td>23-6</td>
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<td>FH</td>
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<td>73</td>
<td>56 x 100 (S) daily</td>
<td>18-6</td>
<td>11-9</td>
<td>73</td>
<td>85</td>
<td>7-1</td>
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</table>

* Laboratory reference range: 4.0-12.0 KA units/100 ml.
† Normal value: 4.0-6.0% of blood volume/min.
Method

Subjects

Pretreatment studies were made in a group of 24 patients with Paget's disease of bone, all subjects having first given informed consent in a manner approved by the Hospital Ethical Committee. Fourteen patients were re-studied during calcitonin therapy; five patients had received calcitonin for 7 days or less ('short-term') and nine for 7 weeks or more ('long-term'). Table 1 summarizes the clinical information.

Calcitonin

Four patients in each group received daily intramuscular injections of salmon calcitonin. One patient was given an intravenous infusion of synthetic human calcitonin and the rest received porcine calcitonin by intramuscular injection. Of these five patients, all in the long-term group, two were later changed to salmon calcitonin, and one received disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) for a short period. Table 1 contains full details of these therapies.

Skeletal blood flow

Resting skeletal blood flow was measured by the $^{18}$F clearance technique, which necessitates a single intravenous injection of tracer doses of $^{18}$F and $^{31}$Cr-labelled EDTA followed by serial venous blood sampling and collection of urine for 2 h. From the radioactivity data, the unidirectional skeletal clearance of $^{18}$F can be deduced; full details have been published previously (Wootton et al., 1976).

Biochemical methods

Serum alkaline phosphatase activity was measured by the standard method used with the Vickers M 300 analyser. Isoenzymes of alkaline phosphatase were measured by a simplified heat-inactivation procedure (Moss & Whitby, 1975). Urinary total hydroxyproline concentration was measured by a colorimetric technique (Seymour & Jackson, 1974). Glomerular filtration rate, measured during the determination of skeletal blood flow, was calculated from the plasma clearance of $^{51}$Cr-labelled EDTA by the method of Chantler, Garnett, Parsons & Veall (1969).

Results

Resting skeletal blood flow in the patients with untreated Paget's disease of bone ranged from 4.4 to 18.9% of blood volume/min, in contrast to the range 4.4–5.9% of blood volume/min measured in a group of eight normal subjects studied previously.

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![Fig. 1. Serum alkaline phosphatase and resting skeletal blood flow in 24 patients with untreated Paget's disease of bone. The hatched area is the normal range. The line of regression shown is: $y = 6.018x + 5.78$ ($r = 0.77$, $P < 0.001$; logarithmic transformation).](image-url)
(Wootton et al., 1976). In comparison with these subjects, resting skeletal blood flow was increased in 23 of the 24 patients. In the remaining patient, skeletal blood flow was normal, but the disease was almost inactive: the alkaline phosphatase was barely raised [12·5 King–Armstrong (KA) units/100 ml; laboratory reference range 4·0–12·0 KA units/100 ml], there was no radiological evidence of Paget's disease and a $^{99m}$Tc-pyrophosphate bone scan showed limited involvement of the right side of the pelvis only. In the group as a whole, the extent of the disease (as judged by alkaline phosphatase activity) and the increase in skeletal blood flow were positively correlated ($r = 0·77$, $n = 24$, $P < 0·001$) (Fig. 1), as were urinary total hydroxyproline excretion and skeletal blood flow ($r = 0·74$, $n = 19$, $P < 0·001$) (Fig. 2). (These correlation coefficients were calculated after logarithmic trans-
Skeletal blood flow in Paget's disease of bone

Fig. 4. Changes in alkaline phosphatase and skeletal blood flow in two groups of patients with Paget's disease receiving calcitonin: 'short-term' treatment was for 7 days or less; 'long-term' treatment was for 7 weeks or more (Table I). Bars represent the mean change in each group. Calcitonins administered: ●, salmon; ■, porcine or porcine followed by salmon; □, porcine followed by disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP); ○, synthetic human.

Discussion

Blood flow to the skeleton in normal man at rest amounts to some 300 ml/min, which represents slightly less than 5% of the cardiac output. In a group of normal subjects, inter-individual variance was least when their skeletal blood flows were expressed in units of % of blood volume/min, in which the mean normal flow is 5.1 (SD = 0.51, n = 8) (Wootton et al., 1976). In comparison with this group, all patients with Paget's disease had much increased skeletal blood flow before treatment, except one in whom biochemically the disease was barely active. Although the mean age of the Paget's group is rather higher than that of the normal subjects, we have no evidence to suggest that the observed increase in bone blood flow is an age effect. Moreover, the severity of the disease, as judged either by the serum alkaline phosphatase activity or by the urinary hydroxyproline excretion, is positively associated with the increase in skeletal blood flow. In fact, it is possible to predict skeletal blood flow from alkaline phosphatase alone in this group of patients; the uncertainty on the prediction, 22.5%, is of the same order as that associated with the use of other indices of skeletal blood flow such as radiocalcium kinetic measurements (Wootton, Reeve & Veall, 1977).

Paget's disease of bone is a condition in which bone turnover at the affected sites is substantially increased. The close correlation that we have observed between skeletal blood flow and two indices of skeletal turnover emphasizes how closely linked are the metabolism of the skeleton and its blood supply.

It is evident from our observations that total blood flow to the skeleton in Paget's disease of bone may be increased several times above normal, depending on the severity of the condition, implying that blood flow to the diseased bone is increased many-fold. Heistad et al. (1975), using a plethysmographic technique similar to that of Edholm et al. (1945), together with adrenaline iontophoresis, concluded that the major part of the increased blood flow to the affected limb in Paget's disease supplied the skin rather than the bone. Unfortunately, they neglected to take into account the evidence provided more than 20 years previously (Edholm & Howarth, 1953) that plethysmography is not a satisfactory technique for
the quantitative measurement of bone blood flow. It is therefore likely that the increased limb soft-tissue blood flow they observed is associated with increased blood flow to the bone lesions of Paget’s disease, which they were unable to measure.

After treatment with calcitonin, the biochemical indices of Paget’s disease fall and bone-healing progresses, although some patients may prove refractory (Haddad & Caldwell, 1972). From the work reported here, it is clear that skeletal blood flow also falls during treatment and would presumably return to normal if treatment restored the biochemical indices to normal. Our results also suggest that a relatively greater change in skeletal blood flow than in alkaline phosphatase occurs during the early phase of treatment (Fig. 4), so that the vascular response may precede the biochemical response. Since a raised intramedullary pressure is known to be closely associated with pain in the proximal femur, and can be rapidly relieved by pressure reduction (Arnoldi, Lemperg & Lindholm, 1971), a plausible hypothesis for the commonly observed action of calcitonin in relieving bone pain would be through a lowering of intramedullary pressure secondary to the reduction of bone blood flow.

The observation that calcitonin increases glomerular filtration rate in the short term but not in the long term is interesting, in view of the earlier observations of Bijvoet, van der Sluys Veer, de Vries & van Koppen (1971). They described the natriuresis which followed continuous infusion of the hormone. After 48 h, during which there was a considerable loss of extracellular fluid into the urine, a new steady state was achieved and they suggested that there was decreased fractional reabsorption of sodium by the proximal tubule. Clearly an increased glomerular filtration rate, by increasing the flow of filtrate through the proximal tubule of the kidney, could contribute to decreased sodium reabsorption. The possible relationship between plasma calcitonin concentration and glomerular filtration rate requires further investigation.

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References


