Involvement of bone in rheumatoid disease was first described by Barwell in 1865 [1] and since then has been assessed by pathological [2], biochemical [3–7] and radiological techniques, most recently using single and dual photon absorptiometry and dual energy X-ray absorptiometry [8–18]. There is accelerated bone loss, both locally to affected joints [19], and generally [11] with reduced bone mass [8, 10, 12–18, 20] and an increased risk of fracture [21, 22]. Impaired mobility is associated with an increased risk of falling [23], and stress fractures related to osteoporosis and angular joint deformities also occur [24]. Localized bone loss around the inflamed joint is a characteristic feature of rheumatoid arthritis and related to disease activity [19] but whether generalized osteoporosis is associated with all cases of rheumatoid arthritis or just some related to sex, menopausal status, disease duration, disease activity, disease severity and functional class, or steroid therapy is unresolved. There have been numerous attempts to look at these variables to establish which patients with rheumatoid arthritis are at risk of osteoporosis but the methods used have varied and results conflict. There are similar difficulties with the data on corticoestrogens and osteoporosis [25].

The ends of the spectrum are clear. Early rheumatoid arthritis without major functional impairment is associated with osteoporosis adjacent to the joint but not with generalized osteoporosis [9]. Longstanding and destructive disabling disease is associated with low bone mass [10]. A wide variety of factors could cause this increased bone loss. Many patients with longstanding disease are post-menopausal women with impaired mobility, calcium malabsorption [26], vitamin D deficiency [27] and reduced androgens and oestrione [28]. Low dose steroids are used frequently [29] and there is renewed interest in their possible long-term benefits in rheumatoid disease [30]. Whether this has an adverse effect on bone is unclear as there are discordant results. They may not affect the axial skeleton [13, 16] but in this issue it is well demonstrated in a case-controlled study that men and post-menopausal women have a reduced appendicular bone mass with low dose steroid therapy, always below 10 mg prednisolone [18]. Fractures were also more common. Increased risk of fracture is not only associated with corticosteroid therapy but has been found in all patients with rheumatoid arthritis [21, 22], particularly if functionally dependent with a low body mass index [22], that is those with more severe disease. Disease severity, duration and activity appear to be important factors in determining bone loss [10, 14, 20]. The greatest loss is with initial impairment of function [10]. The cells and mediators involved in the inflammatory process such as the mast cell and its products, monocytes and interleukin-1 may be responsible for increased bone resorption [31]. This raises the question as to whether controlling rheumatoid disease will reduce bone loss not only locally at the joint but generally. In this issue Kalla et al. have demonstrated a reduction in metacarpal bone loss in patients following treatment with a variety of second-line agents [32]. This correlated with improvement in some measures of disease activity and function. This effect on bone mass might not only be by their effect on the inflammatory process but alternatively by improving functional class and the muscle stimulation to bone formation. Reduced physical activity in rheumatoid arthritis is associated with axial bone loss [14]. Functional strain is important in the control of bone remodelling, microarchitecture and fracture resistance [33] and formal exercise programmes will reduce bone loss in women [34]. A simple semiautomated method of assessing bone mass was used but the increasing availability of highly accurate and reproducible assessment by photon and X-ray absorptiometry of total and regional bone mineral content [35–37] may provide an alternative method of assessing response to second-line therapy, giving a composite measurement of control of inflammation and of functional improvement.

Changes in bone turnover can also be assessed by biochemical markers, and this allows the mechanism of bone loss to be investigated, be it increased absorption, decreased formation or both. Results have been, however, variable. Osteocalcin or bone gamma-carboxyglutamic acid-containing protein (BGP) is synthesized by osteoblasts and is a sensitive marker of bone formation [38]. Levels have been found to be increased [3], normal [4, 5] or reduced [6] in rheumatoid arthritis, possibly representing the variety of influences on bone metabolism in this disease. More interesting are the pyridinium cross-links. Pyridinoline is the predominant cross-link of cartilage and deoxypyridinoline is primarily located in the collagenous matrix of bone. Both are increased in rheumatoid arthritis, but urinary pyridinoline is related to disease activity [7], perhaps representing articular damage, whereas urinary deoxypyridinoline reflects the generalized increased in bone turnover and loss. These may provide complementary measures of therapeutic efficacy in rheumatoid arthritis and osteoporosis.

Rheumatoid arthritis does predispose to increased risk of fracture with loss of bone mass in many patients but is this risk recognized by clinicians? What proportion of women are counselled at menopause and offered preventative treatment with hormone replacement therapy to maintain their bone mass? How effective is HRT in preventing bone loss in rheumatoid arthritis? How many patients on corticosteroids are recognized as being at risk and offered prophylactic therapy? These questions now need to be addressed. Certainly there is sufficient evidence that we should be aware of and try to reduce this increased risk as a fracture is clearly a catastrophe in an already disabled patient.

A. D. WOOLF

*Royal Cornwall Hospital, Truro*
REFERENCES


OSTEOPOROSIS IN RHEUMATOID ARTHRITIS—THE LABORATORY PERSPECTIVE

In rheumatoid arthritis (RA) osteopenia develops early in the course of the disease particularly in the juxta-articular regions as shown by radiological changes and by a quantitative reduction in metacarpal and distal forearm bone density [1,2]. Later, generalized osteopenia develops, as shown by reduced bone density of the lumbar spine, femoral neck and total skeleton [3,4]. It is widely believed that there is an increased occurrence of osteoporotic fractures in patients with long-standing RA, although evidence for this is not strong [5].

In addition to decreased bone density, there is an increased rate of bone loss in RA [4]. This means that the overall rate of bone resorption must have exceeded that of bone formation and this could occur in association with either an overall increase or decrease in bone turnover. Although the study of bone remodelling in RA may be difficult, most of the evidence points towards an increase in bone turnover. Thus, the 24-h retention of labelled bisphosphonate is increased [6], but this could represent increased local blood flow around affected joints. Bone histomorphometry of juxta-articular bone shows increased remodelling as assessed by increased osteoid surface and increased osteoclastic bone resorption [7]; bone from the iliac crest also shows an increase in surface extent of osteoid, consistent with a generalized increase in bone remodelling [8].

The use of biochemical markers to assess bone formation in RA may be misleading. Serum alkaline phosphatase, for instance, may be elevated as a result of drugs used in RA, and may not reflect changes in bone metabolism unless the bone isoenzyme is measured separately. Osteocalcin, a bone-specific protein produced by osteoblasts, appears to be a promising serum marker of bone formation in other situations, but studies in RA patients have produced conflicting results [9,10]. Perhaps this may be explained by the findings of Fairney et al. [11] which suggests the existence of low levels of fully carboxylated, and higher than expected levels of incompletely carboxylated osteocalcin in the synovial fluid of patients with severe RA. Moreover, glucocorticoids may selectively suppress osteocalcin synthesis independently of changes in the synthesis of other bone matrix constituents.

Traditional markers of bone resorption may also mislead. For instance, hydroxyproline may reflect collagen turnover in tissues other than bone and is also derived partly from degradation of complement (C1q), and this may be increased in active inflammatory conditions. The pyridinium crosslinks released during the breakdown of mature collagen show promise as specific and specific markers of bone resorption. They have several advantages over hydroxyproline in that they are not metabolized, they are not absorbed from the diet, and they are more tissue-specific. They may therefore be more accurate markers of collagen breakdown. The urinary excretion of the bone-specific crosslink, deoxypyridinoline, was increased in active RA, consistent with an increased rate of bone resorption [12].

The pathogenesis of this high remodelling osteopenia has not been determined. It could result from a combination of factors including the effect of disuse on the skeleton and the interactions among mediators of inflammation, including hormones and cytokines, on bone cells [13,14]. Many cytokines and other agents derived from macrophages, T-cells and from connective tissue cells have been shown to have effects on bone metabolism in various experimental systems. For instance, prostaglandin E, transforming growth factor a, interleukin-1 and tumour necrosis factors all stimulate bone resorption in vitro and several such mediators and cytokines have been identified in synovial fluids from patients with RA [15,16].

There have been conflicting results about the effect of RA on calcium homoeostasis. The majority of workers have reported normal levels of serum calcium (corrected for albumin) and phosphate, together with normal serum vitamin D and parathyroid hormone levels. Van Soesbergen et al. reported low serum 25-hydroxyvitamin D but this may have resulted from low D-binding protein levels [8].

To date, most studies have shown a tendency to greater bone loss in corticosteroid treated patients, although this is often not statistically significant. This tendency is greater in the early stages of treatment and in regions of predominantly trabecular bone and is greater with increasing steroid dose [3,4]. In this issue, Butler et al. [17] report decreased distal radius bone mineral content in men and post-menopausal women treated with low-dose steroids.

What can be done to prevent bone loss or even increase bone mass? One might predict that non-ste-