Chapter 12
Osteoporosis in Rheumatologic Conditions and Inflammatory Disorders

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The concept of inflammation-induced bone loss among patients with rheumatic diseases has gained increasing attention in the medical community in recent years. Osteoporosis may begin with inflammation, but joint pain, relative immobilization, with increasing loss of function, and glucocorticoid therapy also contribute substantially to evolving bone loss. A number of rheumatologic conditions including systemic sclerosis are considered noninflammatory, yet individuals with this condition and others of a similar nature are also at increased risk of osteoporosis. In this chapter, the pathogenesis, diagnosis, and epidemiology of inflammatory and noninflammatory-induced osteoporosis will be discussed with respect to several rheumatologic disorders: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS). Management approaches, both pharmacologic and nonpharmacologic, will be considered.

Rheumatoid Arthritis (RA)

Etiology and Pathogenesis

The hallmark of rheumatoid arthritis is chronic joint inflammation, which can lead to erosive destruction of joints. Locally, this destruction occurs along the subchondral bone at the margins of joints and at the boundary between articular cartilage and bone. However, bone loss can also be more generalized throughout the skeleton, a process that leads to clinically significant osteoporosis. The severity of disease activity, as indicated by inflammatory markers, is an independent risk factor for development of osteoporosis.

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Predictive Factors and Models

In a landmark study to determine which patients with RA should be tested for osteoporosis, Haugenberg and colleagues [1] proposed five criteria—age, weight, inflammation, immobility, and ever-use of corticosteroids.

More recently, Hauser et al. developed a clinical prediction model to assess the most influential factors in osteoporosis development in RA subjects [2]. Termed the osteoporosis prediction in RA tool (OPRA), it enables clinicians to use a point allocation according to the two factors with the strongest predictive qualities for osteoporosis development. While the authors of this report evaluated erythrocyte sedimentation rate (ESR), Larsen score, and years since menopause (in females), only older age and lower BMI were found to be independent predictive measures [2].

Epidemiology of Osteoporosis in RA

In the United States, an estimated 1.5 million individuals are affected by rheumatoid arthritis, a condition involving chronic joint inflammation with potential consequences of joint erosions and destruction. Women are two to three times more likely to develop RA than men, with the most common onset of the condition between ages 30 and 60. Although osteoporosis is among the more common extra-articular manifestations of RA, epidemiologic studies have been highly variable. Older investigations may overestimate prevalence because many of these were conducted at large rheumatology clinics that served the most severely impaired RA patients. In 2000, a study examining 925 women with RA, most of whom were postmenopausal, found that frequency of osteoporosis as measured by DXA was 28.8 % at the lumbar spine and 36.2 % at the femoral neck [3, 4]. Despite the large sample size of this study, the prevalence estimates are likely elevated, due to the selection of patients from 21 rheumatology centers who were referred to a specialist for advanced management of RA. Among the more recent literature, efforts have been made to give more accurate estimates of osteoporosis with RA. Population-based studies are more representative of actual disease prevalence. A study of 394 patients drawn from a county registry of RA patients in Oslo, Norway, found that the overall prevalence of osteoporosis was increased by a factor of two, compared with an age-matched population of non-RA subjects living in the same region [5]. Using the standard definition of osteoporosis as determined by DXA, the prevalence of osteoporosis for the population as a whole was 16.8 % in the lumbar spine (L2-4) and 14.7 % for both the femoral neck and the total hip, among all subjects in the population, but a stepwise increase occurred in each succeeding decade, with the 60–70 year old group having the highest percentage of osteoporosis at each of the three locations and the greatest percentage of BMD reduction at individual bone sites. Predictors of low BMD were older age, glucocorticoid use, and physical disability.

Since the report of Haugenberg and colleagues in 2000 [5], earlier and more aggressive treatment with stronger, disease-modifying antirheumatic drugs (DMARDs) has been initiated. This change in the approach to patient care may reduce osteoporosis or delay its onset. Other, more recent investigations have also been undertaken. In the trial by Hauser et al. [2] nearly all patients had received DMARDs and over half were also on oral or intramuscular glucocorticoids or had taken them in the past. The researchers found that 29.9 % of RA patients had osteoporosis compared with 17.4 % age and gender-matched non-RA patients. Female gender, age, years since menopause, erythrocyte sedimentation rate (ESR), and body mass index (BMI) were the strongest risk factors for osteoporosis development.

Many of the larger studies dealt predominantly or solely with women, but some, centering on men with RA, indicated a prevalence of osteoporosis from 10 % to 29 %. Most of the studies were small and focused on different age groups, accounting for this varied prevalence [6–9]. They found a higher prevalence of osteoporosis in their study group of 50 men, but the age of subjects was 67. Femoral osteoporosis was seen in 29 % of the subjects, while lumbar spine osteoporosis was observed in 19 %. Interestingly, reduced BMD was independent of testosterone levels, distinguishing these findings from those seen in men with senile osteoporosis unrelated to rheumatic disorders [6].

Fractures in RA Patients

A number of investigations have explored the circumstances leading specifically to fractures, with and without osteoporosis, in the RA population. A large investigation of 110 patients, prospectively followed for 8.4 years, revealed that years of prednisone use, high disability index, older age, and limited physical activity, as well as prior diagnosis of osteoporosis, were predictive of incidence for fracture. Regarding vertebral fractures specifically, evidence of vertebral deformity on imaging, corticosteroid use greater than one year, and diagnosis of low BMD at the hip could predict fractures in lumbar spine. Both fear of falling and history of prior falls were significant associations with fractures primarily in the hip. Kaz Kaz and colleagues [10] showed that tender joints and prior level of disability were predictive for falls, but they did not specifically investigate if falls directly translated to fractures. Women who were unable to do stand-ups and demonstrated inability or limited ability to perform heel–toe walking also carried higher ESRs, worse outcomes on the Health Assessment Questionnaire (one of the first patient-reported outcomes) [11], and a greater number of tender joints.

Another investigation [12] examining correlates of falls and fear of falling found similar results but focused more directly on pain control. In this study by Jamison et al., increased pain intensity, in addition to a greater number of comorbid medical conditions and lower functional walking status, was seen in RA patients with fear of falling but were less prevalent in healthy control subjects. Amin and colleagues [13]

have shown that in contrast to prior investigations, fracture rates were considerably higher in younger RA patients relative to older ones (odds ratio 4.3 for subjects under age 50 yet 1.7 among those age 51 or older). Reasons for this finding may be a greater level of activity and participation in higher fall risk actions in younger individuals.

Treatment of Osteoporosis in RA

Pharmacologic Intervention

Based on the dose and duration of glucocorticoids used for treatment of RA, patients may experience a negative calcium balance and, in turn, vitamin D levels below serum levels of 30 ng/ml—the desired level for bone protection of skeletal stores [14]. Given the minimal cost, the low risk of vitamin D toxicity, and potential benefit in reduction of fracture risk, a 2000 Cochrane review concluded that all patients requiring glucocorticoids should be started on calcium and vitamin D supplementation [15]. An individual's dietary calcium intake should be evaluated to determine the optimal dose. Serum vitamin D 25OH levels are the best measure of vitamin D physiologic status. A minimum desirable level would be 30 ng/ml, but aiming for 40–60 ng/ml is ideal in patients taking steroids. Increases in serum levels to this extent are best accomplished with supplemental oral vitamin D ranging from 1,000 to 2,000 IU in most cases, although selected individuals with levels under 30 ng/ml will require higher doses [16]. In addition, evidence suggests that active vitamin D analogs may be more effective in fracture reduction in patients receiving high-dose glucocorticoids, regardless of the medical condition for which they are prescribed [17].

Anti-TNF therapeutic agents have shown promise in arresting the synthesis of antiresorptive factors responsible for bone loss in several rheumatic conditions, including RA. Their effectiveness has been demonstrated over short-term prospective studies [18] as well as longer-term evaluations of up to two years [19]. More recently, Korczowska and colleagues found that infliximab is active as early as two weeks into treatment [20]. By examining levels of a number of inflammatory cytokines including TNF-α, IL-6, IL-17, and IL-23, as well as markers of bone formation (osteocalcin) and two markers of bone resorption (deoxypyridinoline and N-telopeptide), they determined that all cytokines and metabolic indexes evidenced reduced levels at follow-up times of two weeks, 14 weeks, six months, and one year. Adalimumab, another anti-TNF-α agent, has also demonstrated the ability to preserve but not increase BMD in the lumbar spine and femoral neck. This group investigated 50 patients with RA followed prospectively over a year for changes in BMD. While no increase was seen in the overall study sample, an association was found between the decrease in serum CRP at 16 weeks and an increase in BMD in the femoral neck at one year [21].

To date, bisphosphonates have been the primary mode of treatment for glucocorticoid-induced osteoporosis. Alendronate, risedronate, and zoledronic

acid have all received FDA approval for treatment of glucocorticoid-induced osteoporosis (GIO), but osteoporosis due to RA is not caused solely by steroids. Medications that address a variety of physiologic abnormalities in rheumatoid patients are best suited to this population. Studies on both alendronate and risedronate indicate that they reduce future fracture risk [22, 23]. Eastell et al. showed that risedronate prevented further bone loss in patients with RA who were taking glucocorticoids [24] and Lems et al. reported that alendronate had a protective effect on markers of bone loss as well as BMD in RA patients taking chronic low-dose steroids [25]. Ebina and colleagues [26] investigated the effect of switching from weekly or daily risedronate or alendronate to a once monthly oral regimen of minodronate, an agent thought to have superior effects in inhibiting farnesyl diphosphate synthase, an enzyme that which induces an apoptosis of osteoclasts and thereby compromises their antiresorptive properties of bone. This agent is approved for use in Japan but currently not in the United States. The additional benefit gleaned from the study was that compliance with a monthly agent was potentially superior to that with a daily or weekly pill.

Limited data exists on the effect of once annual zoledronic acid (ZA) for the treatment of osteoporosis in RA. While ZA has been approved for the prevention and treatment of GIO, its use is just now gaining acceptance in the RA population. One major clinical trial demonstrated that ZA was superior to risedronate in increasing lumbar spine BMD over a prospective time of one year [27]. Subjects involved in the treatment evaluation arm had all received at least three months of glucocorticoids. A summary of therapies to date is given in Table 1 [19–21, 27–30].

To date, no studies on PTH (also called teriparatide, brand name Forteo) have been conducted with a specific focus on osteoporosis treatment for RA patients. In two reports [28, 29], Saag et al. illustrated the benefit of PTH in patients with GIO by demonstrating that it was superior to alendronate in terms of changes in BMD and in prevention of morphometric vertebral fractures. In a recent commentary by Gennari and Bilezekian [31] the idea that teriparatide may be a superior treatment for RA-associated osteoporosis has emerged, based on its direct action on osteoblasts and osteocytes (Fig. 1) [31].

Nonpharmacologic Intervention

Due to increased inflammation, restricted movement, and tight, painful joints, patients with RA have 30–75 % the muscle strength of able-bodied, similarly aged adults and one-half the endurance of age-matched adults. Reduced muscle strength in combination with the above factors leads to an overall lower level of physical activity and fitness [32]. Lack of fitness and an increased sedentary lifestyle contribute to the 50–60 % increased incidence of cardiovascular-related mortality observed in individuals with RA [33]. Exercise can help reduce these rates if a physical training program is appropriately tailored to increase muscle strength in a way that will prevent further joint trauma and educate patients about safe forms of exercise in cardiovascular disease. A 2009 Cochrane review examined eight clinical trials [34]

Table 1 Medication study outcomes

Drug	Recommendations	Notes/references
Zoledronic acid	A single 5 mg IV infusion	One major clinical trial demonstrated that ZA was superior to risedronate in increasing lumbar spine BMD over a prospective time of one year [27]
PTH teriparatide	20 mcg injection subq/day into thigh or abdominal wall	Demonstrated benefits of PTH in patients with GIO; indicated PTH was superior to alendronate in terms of changes in BMD and prevention of morphometric vertebral fractures [28, 29]
Calcium	1,000–1,500 mg/day	Caution in patients with renal disease or history of kidney stones [30]
Vitamin D (in setting of glucocorticoids)	1,000–1,500 IU/day	Give amount necessary to maintain serum vitamin D25OH at 30 ng/ml or higher [30]
Anti-TNF		
Infliximab	3 mg/kg IV infusion at baseline, two weeks, six weeks, then every eight weeks	Increases BMD [20]; improves bone metabolism and BMD in patients with RA and AS [19]
Adalimumab	40 mg subq per 14 days	Maintains but does not increase BMD in lumbar spine and femoral neck [21]

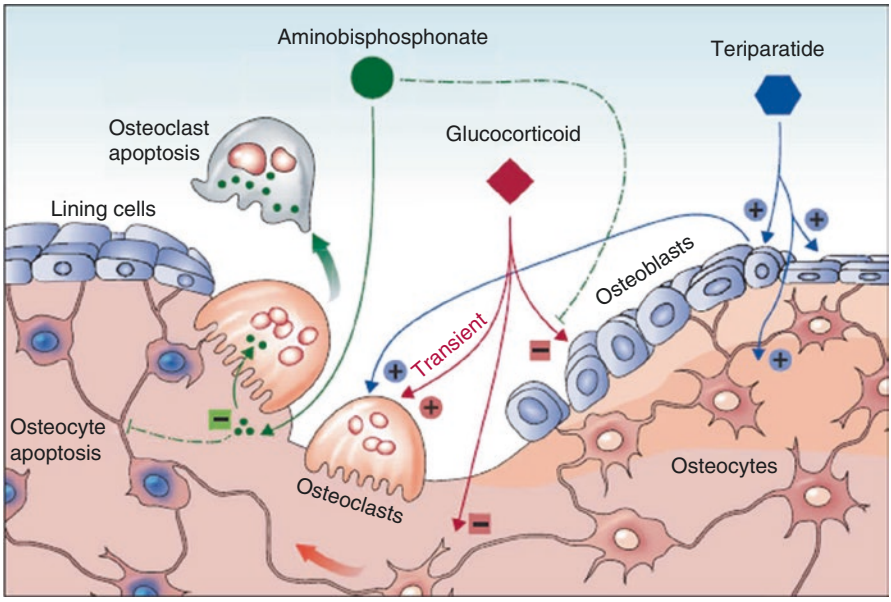

Fig. 1 Effects of glucocorticoids, bisphosphonates, and teriparatide on bone cells. *Dashed lines* indicate potential effects of bisphosphonates (*Source*: Gennari and Bilezekian [31]. Reprinted with permission)

Table 2 Criteria for functional status classification in rheumatoid arthritis

Class I	Full functional ability to perform activities of daily living, including self-care, vocational, and avocational
Class II	Limited functional ability to perform avocational activities. Relatively normal ability to perform typical vocational and self-care activities
Class III	Limited functional ability to perform both vocational and avocational activities. Relatively normal ability to perform typical self-care activities
Class IV	Limited functional ability to perform vocational, avocational, and typical self-care activities

Source: Hochberg et al. [35]

related to exercise in patients with RA and concluded that both overall fitness and more specific strength training are required to improve functional outcome. Moreover, if dynamic activity is carried out properly, no increased disease activity or pain should ensue.

The preceding recommendations are largely based on the less involved patients with RA. The American College of Rheumatology has published guidelines on the four levels of functional capacity of patients with RA as given in Table 2 and the majority of studies to date have focused on patients at the less severe Class I or II level of the disease [35].

In a study conducted by de Jong et al., subjects who underwent a 75 min, twice weekly exercise session involving bike training, circuit training, volleyball, basketball, or other ball sports, experienced increased physical well-being and functional status [36]. The majority of subjects saw no radiologic progression of joint appearance, but a subset of those with baseline severe radiologic damage did see a progression of disease. In general, aerobic and resistance exercise conditioning has been shown to improve functional capacity, muscle strength [32, 37], and cardiovascular conditioning, particularly in terms of blood pressure and lipid profiles [38]. However, caution is required in subjects with Class III or IV RA since patients with more severe disease at baseline remain at high risk of disease exacerbation and increased joint damage [36].

Systemic Lupus Erythematosus (SLE)

Etiology and Pathogenesis

Systemic lupus erythematosus (SLE) is a chronic autoimmune condition involving inflammation in multiple body parts including the skin, joints, heart, lung, blood, kidney, and brain. The increased antibody production that precipitates the chronic inflammation leads to pain as well as adverse effects on the joints, with both problems contributing to generalized immobility of patients with SLE. Survival and morbidity rates have improved drastically over recent years, and evidence is emerging that long-term health conditions, including osteoporosis, are receiving

appropriate attention in management of persons with lupus. The etiology of bone loss in SLE represents the combined effects of traditional risk factors of osteoporosis (advanced age, postmenopausal status in women, low body weight, dietary deficiencies) as well as those inherent in rheumatoid conditions, including inflammation, metabolic factors, hormonal factors, serologic titers, and adverse effects of medication [39].

Chronic systemic inflammation leads to increased levels of tumor necrosis factor (TNF). It also increases oxidized low-density lipoproteins (oLDLs), which, in turn, induce elevated production of receptor activator of nuclear factor-kB ligand (RANKL) and further increase levels of TNF. Because both RANKL and TNF activate osteoclasts, increased bone resorption occurs. At the same time, oLDLs decrease bone formation by reducing osteoblast maturation. The combined effects result in lower BMD [39]. Additional evidence of decreased osteoblast activity stems from observations of decreased osteocalcin titers, indicating low bone formation, as supported by a study of premenopausal women with untreated SLE [40].

Hormonal factors have been shown to predispose SLE patients to bone loss as is the case in other populations. Specifically SLE patients experience more frequent episodes of months of amenorrhea, earlier (premature) menopause, and hyperprolactinemia. Males may experience low plasma androgen levels. Decreased vitamin D levels are another contributor to low BMD. Patients with SLE are consistently counseled to avoid sunlight, and others may be prescribed drugs such as hydroxychloroquine that directly blocks conversion of inactive to active forms of vitamin D [39, 41]. In addition, foods rich in vitamin D may add to GI distress given the prevalence of GI inflammation in SLE.

Serologically, the presence of anti-Ro antibodies is associated with a lower femoral BMD. This finding may be due to serologic adverse effects or it may be an indirect consequence of avoidance of sunlight. According to Mok et al. [42], anti-Ro antibodies are more commonly present in Chinese relative to Caucasian patients, perhaps because Chinese practice guidelines advise against sun exposure in SLE patients with anti-Ro antibodies. Ordinarily, a substantial percentage of vitamin D is absorbed from sunlight in certain seasons. Thus lack of exposure to sun may contribute to vitamin D deficiency as one factor in osteoporosis development. The presence of anti-Smith antibodies (a highly specific marker of SLE) and the absence of anti-Ro antibodies were found to correlate with improved femoral neck BMD [42].

In terms of medications that contribute to osteoporosis in SLE, Jardinet et al. reported a loss of lumbar spine bone in premenopausal SLE patients given corticosteroid therapy over a prolonged period of time [43, 44] but exactly how long is uncertain. Studies are divided as to whether corticosteroids confer an overall positive effect on BMD by reducing inflammation and enabling patients to be more active while allowing inflammatory markers to remain at lower levels. In their review of 16 articles focusing on the effect of corticosteroid use on osteoporosis in SLE, Garcia-Carrasco et al. [41] reported that seven studies found no association, but nine others demonstrated an adverse effect of steroids. In general, prolonged use

Table 3 Summary of studies of BMD in SLE patients

Source	Design	No. of patients	BMD lumbar region	BMD hip
Bultink et al. (2005) [48]	Transversal	107	39 % osteopenia and 4 % osteoporosis in any location	74 % osteopenia, 3 % osteoporosis
Mok et al. (2005) [42]	Cross-sectional	34	33 % osteopenia, 42 % osteoporosis	74 % osteopenia, 3 % osteoporosis
Becker et al. (2001) [45]	Cross-sectional	67	11 % osteopenia, 6 % osteoporosis	13 % osteopenia, 3 % osteoporosis
Lakshminarayanan et al. 2001 [47]	Cross-sectional	92	32 % osteopenia, 15 % osteoporosis	35 % osteopenia, 12 % osteoporosis
Sinigaglia et al. (2000) [3]	Cross-sectional	84	23 % osteoporosis in any location	
Pons et al. (1995) [49]	Cross-sectional and longitudinal	43	18 % osteoporosis in patients with corticosteroids	
Formiga et al. (1995) [55]	Cross-sectional	74	12.1 % osteoporosis in any location	

of higher doses of steroids appears to have a deleterious effect on BMD in either hip, lumbar spine, or both [41], whereas pulsed steroids given for short-term exacerbations or complications have a decreased long-term effect [41, 44].

In addition to corticosteroids, cyclophosphamide, typically used to address life-threatening organ involvement, is associated with premature menopause and osteoporosis. Cyclosporine reduces new bone formation by activating osteoclasts and suppressing osteoblasts. High-dose methotrexate, also associated with bone loss and fractures, is occasionally given to patients with advanced SLE [46]. In contrast to other agents used to treat SLE symptoms, use of hydroxychloroquine is noted to have a positive effect on BMD at the spine [42, 47] as well as the hip [47]. Table 3 [3, 42, 45, 47–50] summarizes risks of low BMD in lumbar spine and separately in the hip, based on the results of individual investigations.

Fractures in SLE Patients

The prevalence of fractures in SLE patients ranges from 6 % to 26 %, with symptomatic fractures occurring in only 6–12.5 % of these patients [51]. Despite this elevated occurrence, only a few high-quality studies on fracture prevalence, prevention, and treatment, as described below, have been conducted Ramsey-Goldman [51] and coauthors determined that fracture risk was related to duration of treatment with glucocorticoids, whereas Zonana-Nacach et al. [52] examined the cumulative exposure to corticosteroids in terms of overall dose, finding that for every 36.5 g of corticosteroid consumed, the risk of fracture nearly doubled.

Subsequently, Lee et al. [46], along with Ramsey-Goldman and colleagues [51], considered the frequency of fractures in a cohort study of 304 women with established SLE who were followed for six years. Overall 12.3 % experienced fractures and among those BMD *Z*-scores at the hip but not at the spine were significantly lower in the group of SLE patients with fractures compared to those without fractures. Borba et al. [53] investigated the presence of vertebral fractures in a cross-sectional study of 70 patients having established SLE and 22 controls. Although the mean age of subjects was only age 32, fracture deformity in image screening was found in 21 % of subjects with SLE but in none of the aged-matched healthy controls.

Focusing on risk factors for vertebral fractures, Mendoza-Pinto and colleagues [54] studied 210 subjects with a mean age 48 in which osteopenia was present in 50.3 % of subjects with vertebral body fracture and osteoporosis in 17.4 %. At least one vertebral fracture was detected in 26.1 %. Patients with vertebral fractures had a higher mean age (50 ± 14 vs. 41 ± 13.2 years, $p = 0.001$), higher disease damage (57.1 % vs. 34.4 %, $p = 0.001$), lower BMD at the total hip (0.902 ± 0.160 vs. 982 ± 0.137 g/cm^2, $p = 0.002$), and postmenopausal status (61.9 % vs. 45.3 %, $p = 0.048$). Stepwise logistic regression analysis revealed that only age ($p = 0.001$) and low BMD at the total hip ($p = 0.007$) remained as significant factors for the presence of vertebral fracture [54]. A summary of risk factors for fractures is given in Table 4 [51, 55].

Evidence suggests that fractures in SLE are not necessarily a function of low BMD. A study of Dutch patients found that 20 % of subjects had vertebral fracture, defined as greater than 20 % reduction of vertebral body height—a criterion developed by Genant et al. [56]. Using this measure, the threshold for identifying a fracture by radiographs is lower than that in other studies, potentially accounting for the higher fracture occurrence. Nevertheless, it should be noted that of the 107 participants, 73 % of those with fractures by the Genant et al. semiquantitative identification tool had height reductions of 20–25 % in at least one vertebra, 23 % of subjects had 25–40 % vertebral body height reduction, and 4 % had vertebral body height reduction greater than 40 %. Yet among the entire sample, only 4 % of subjects had a DXA scan with *T*-scores below 2.5, the threshold for meeting the definition of osteoporosis. In this investigation, males had a higher fracture rate than did females. Moreover, findings reported that 11 % of subjects had a prior nonvertebral fracture. This study also identified a number of conditions commonly seen among rehabilitation patients that further increase risk of fractures (Table 4).

Treatment

Initial Measures

Prior to considering pharmacologic treatment, the traditional first steps are optimizing overall nutrition, limiting alcohol, and eliminating smoking, if applicable. Beyond these measures, optimizing calcium and vitamin D stores is advised [57].

Table 4 Risk factors for fractures in SLE

Risk factor	Frequency or relative risk based on chosen study outcome	Notes
Age at diagnosis	RR not calculated	Older age is more likely to cause fracture
Cumulative glucocorticoid exposure	RR 1.17–1.3	Prolonged use is worse
Use of oral contraceptives	RR not calculated	Lower use associated with higher fracture risk
Timing of menopause	RR not calculated	Early menopause more likely to be associated with fracture
Dementia	RR 1.67	
Seizures	RR 2.01	
History of one or more cerebrovascular events	RR 1.49	
Prior osteoporotic low velocity fracture	RR 4.26	
Use of oral diabetic agents	RR 1.39	
Concurrent malignancy	RR 1.23	

Sources: Adapted from Ramsey-Goldman et al. [51], Bultink et al. [55]
RR Relative Risk

Calcitriol has been found to reduce bone loss in subjects with SLE who were on corticosteroids. Lambrinoudaki and colleagues found improvement of BMD at the lumbar spine in premenopausal women with SLE who took 0.5 mcg calcitriol daily for two years, compared with controls [58]. Conversely in a study of hypogonadal amenorrheic women, hormone replacement therapy but not calcitriol led to improvements in BMD of the lumbar spine. No increase in BMD in either the hip or radius was noted.

Estrogens and Androgens

No specific studies on selective estrogen receptor modulators exist, but recent interest has emerged in exploring the use of dehydroepiandrosterone (DHEA) for treatment of disease activity and osteoporosis due to SLE [57]. Along with its metabolite dehydroepiandrosterone sulfate (DHEAS), DHEA is the most abundant circulating adrenal steroid in humans [59]. Normal human levels of DHEA are 1–50 nM, but levels of DHEA, DHEAS, and androgens decline in states of chronic inflammation including RA and SLE and are reduced even further by steroids [60]. In a number of clinical trials described in the review by Sawalha and Kovats [59], the average daily use of corticosteroids was significantly reduced in the months following initiation of a daily dose of DHEA, but studies differed on the effectiveness of trial doses of DHEA in improving the Systemic Lupus Erythematosus Activity Index.

In terms of whether DHEA and DHEAS exert direct effects on bone, studies demonstrate conflicting results. In a small study of 19 SLE patients [61], the nine subjects who received DHEA showed no change in BMD at six months, whereas the ten placebo subjects experienced significant reduction in BMD. The subjects in this study all had advanced forms of active, systemic lupus affecting multiple organ systems. A second study of 37 subjects by Formiga et al. [62] found a positive correlation between DHEAS levels and BMD in the lumbar spine and femoral neck. The same study demonstrated a negative correlation in DHEAS and serum PTH, which may explain the potential role that DHEA may play in protecting bone. However, other studies have shown less of a benefit from DHEA, particularly one investigation looking at subjects with quiescent SLE [63]. Researchers are now attempting to determine (1) which groups of SLE patients may benefit from DHEA and (2) at what stage of the disease, in terms of duration and severity, are DHEA and its metabolite DHEAS most likely to make a significant difference in function and bone health [59].

Bisphosphonates

Although a number of investigations have examined the benefits of bisphosphonates on BMD in subjects receiving corticosteroids for rheumatoid conditions, no single study focuses solely on those with SLE. However, patients with SLE represent 5–15 % of subjects in several investigations. The majority of these analyses did not separate groups of patients but instead, often combined men, premenopausal, and postmenopausal women, and in doing so, complicated the ability to draw conclusions. Overall, positive effects on BMD were seen in most subsets of patients [22, 27, 64]. However, no conclusions could be drawn regarding the effectiveness of bisphosphonates for fracture prevention due to the absence of fractures in both the control and treatment groups, reported in the prevention studies on GIO. To date, no dedicated studies on the value of PTH, growth hormone, or insulin-like growth factor have been undertaken in SLE patients or in patients with GIO that include a notable percentage of participants with SLE. However, interest in exploring the potential for agents that work on the osteoblast continues to grow.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is an inflammatory, arthritic condition involving the axial skeleton and traditionally affecting males, often starting before age 40 [65]. Inflammation is both erosive leading to osteopenia and proliferative, with abnormal bony overgrowth and bridging syndesmophytes that fuse the vertebrae to create the appearance of a “bamboo spine.” [65]. The result is rigid kyphotic posture as well as mid back and shoulder pain, limiting spinal flexibility and functional mobility. The structural changes may also affect the ribs and can compromise breathing

mechanics. Patients may be subject to atelectasis and pneumonia, and, in severe cases, the architectural changes actually predispose the spine to spinal cord injury [66]. Perhaps even more frustrating for patients is that AS is often diagnosed late, in its advanced stages. The most effective treatment agents, TNF-α blockers, have limited impact if given late but are fairly successful if administered early in the disease process [65]. Although AS only affects 0.5 % of the US population, it results in work disability, eventual withdrawal from the workforce, substantial health costs, and a reduced quality of life [67].

The causes of AS are a mix of genetic and environmental factors, influenced by both autoimmune and autoinflammatory factors. Genetic evidence points to specific immune pathways, namely, interleukins 17 and 23 upregulation, activation of nuclear factor kappa B, and genes controlling CD8 and CD4 T-cell subsets. Autoreactive T cells and autoantibodies denote an autoimmune process, while autoinflammatory processes are characterized by mutations in single immunomodulatory genes and accelerated cytokine production [65]. In terms of environmental factors that contribute to the disease or accelerate an already established case, certain microbes can trigger a disease flare. Internal and external mechanical stress can promote inflammation throughout the body, particularly in the axial spine and fibrocartilaginous enthuses and enhance production of interleukin IL-23R$^+$ T cells. In addition animal studies suggest that weight-bearing and biomechanical stress contribute to the inflammatory component of AS [68].

Diagnosis of Osteoporosis in AS

Although osteoporosis is common in AS, it is often diagnosed late due to visual confounding by syndesmophytes and ankyloses. Consequently, BMD measurements may be artificially high and the extent of osteopenia or osteoporosis may not be appreciated [69].

Because spinal hyperostosis in AS is often positioned around the zygapophyseal joints, the vertebral endplates of disks, and the annulus fibrosus, with relative sparing of the lateral sides, lateral DXA scans may be more useful than anteroposterior (AP) views in terms of evaluating possible osteoporosis. Moreover lateral scanning permits exclusive examination of the vertebral body, comprised of 80 % trabecular bone [70]. In Klingberg et al.'s [70] study of 87 AS women and 117 men using both lateral and AP lumbar BMDs, the lateral view revealed significantly more cases of osteoporosis in men with AS than did the AP view. At the same time, the AP view revealed high rates of osteoporosis in women, whereas the lateral view did not, indicating that certain modalities of imaging are better suited to males versus females in making an early diagnosis. In a number of senses, both the lateral and AP view may be needed since the combination will allow a three-dimensional volumetric BMD which is a superior measure to a two-dimensional area BMD.

Emohare and coauthors [71] went a step further and tested computerized tomography (CT) attenuation models in lieu of DXA as a tool to assess osteoporosis and

fractures in AS patients. In a group of 17 patients, they diagnosed 82–88 % of subjects with osteoporosis based on the threshold sensitivity of the machine selected. Pickhardt et al. [72] has proposed the novel concept that data from abdominal CT images, which included the L1 vertebra but were obtained for other purposes, can be used to identify patients with osteoporosis without additional radiation exposure or expense: If the L1 vertebra was not fractured, an estimate of lumbar bone density can be made without having the patient undergo another scan.

Challenges exist not only in the diagnosis of osteoporosis but, also, at times in the identification of fractures. A number of cases illustrate the challenges that syndesmophytes and the spinous overgrowth create. In the cervical spine, new fractures may be missed in the immediate hours after an injury such as a fall. Pain may be present, but radiographs may not reveal a fracture until 24 hour later, and then, often only by MRI or CT [73]. In the case described by Fatemi et al., a nondisplaced fracture was missed by plain imaging and CT; not until 20 hour later, when the fracture had become displaced and the patient had returned to the hospital with new neurologic symptoms, was an MRI performed. Harrop et al. [74] have also described a case of a missed surgical fracture but only a high-definition multidetector CT revealed the deformity; standard CT, plain radiographs, and MRI all failed to diagnose the fracture. The question of whether MRIs should be done after any injury to the neck or lower spine in AS patients is raised in the literature. While the cost of an MRI is not insignificant, it bears no comparison to the potential cost to patients and society of a spinal cord injury arising from an undiagnosed fracture. Figures 2 and 3 demonstrate cervical spine fracture as well as extensive ankylosing spondylitis in thoracic and lumbar portions of this patient's spine. This question warrants further analysis in future investigations.

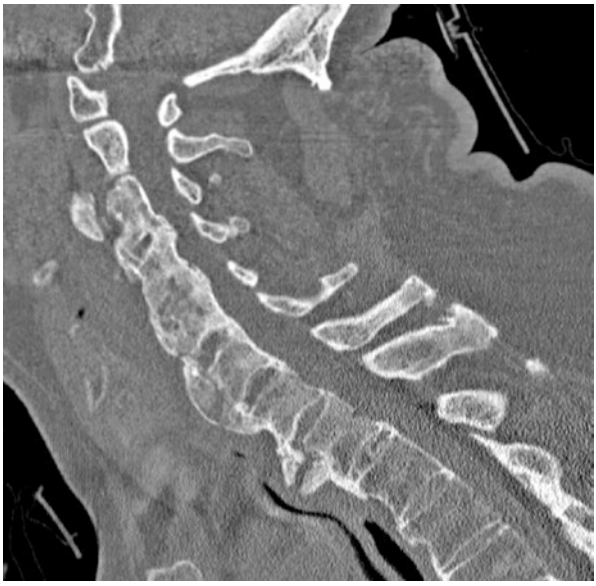

Fig. 2 CT scan of cervical spine demonstrating ankylosing spondylitis. In a 75-year-old male with longstanding disease. Image demonstrates an age-indeterminate fracture of C5 anterior osteophyte with upper thoracic ankylotic changes (*Source*: Thomas Jefferson University Department of Radiology, Philadelphia, PA. Used with permission)

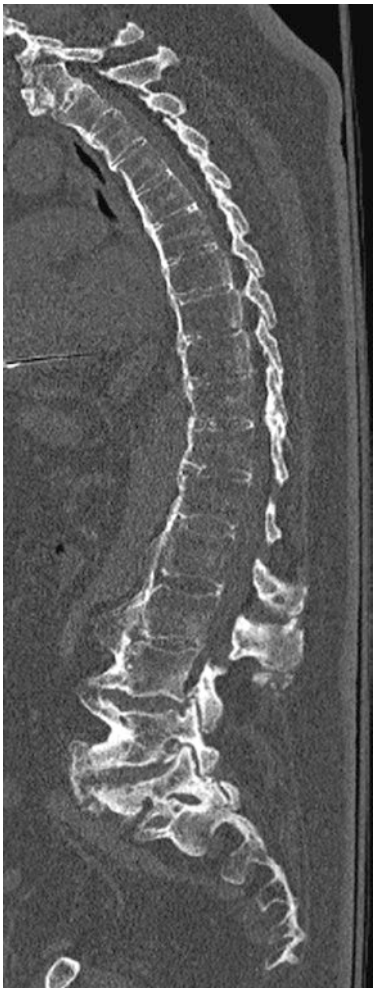

Fig. 3 CT of thoracolumbar spine in a patient with ankylosing spondylitis. Image illustrates the middle and lower thoracic as well as the lumbosacral spine demonstrating ankylosing spondylitis throughout multiple areas, along with superimposed multi-level degenerative changes (*Source*: Thomas Jefferson University Department of Radiology, Philadelphia, PA. Used with permission)

Etiology and Pathophysiology of Osteoporosis in AS

The study by Klingberg et al. [70] found that low BMD in AS patients was associated with female sex, older age, low body mass index, heredity for fractures, scores on the physical activity at home and work index [75], and the number of years since menopause. Additional factors relate to function and medications: disease duration, high Bath Ankylosing Spondylitis Metrology Index (BASMI), high modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), elevated inflammatory parameters (ESR, CRP), and low hemoglobin. Factors that influenced osteoporosis in AS, as well as others that were examined and not relevant to AS, are summarized in Table 5 [69, 70, 76–78].

Table 5 Factors associated with osteoporosis in patients with AS

Source	*n*	Outcome of study
Franck et al. [69]	504	OPG levels are typically low, possibly contributing to the immune response and relative state of osteoclastogenesis seen in these patients
Klingberg et al. [70]	204	Low BMD was associated with female sex, older age, low body mass index, heredity for fractures, scores on the physical activity at home and work index, and number of years since menopause in the case of female patients
Gratacos et al. [76]	34	Only subjects with persistent active disease experienced significant bone loss early on; 5 % loss was seen in the lumbar spine and 3 % in the femoral neck over 19 months; of note, no significant bone loss was found in those with inactive disease; the group with active disease also showed elevated IL-6, but other factors including physical activity or medications for treatment impacted BMD
Maillefert et al. [77]	54	No significant change in lumbar BMD in the 34 subjects on average in the 2-year assessment but did observe a decline in femoral neck BMD of 1.6 %. The levels of ESR and CRP were only significantly elevated in the group with bone loss in the femoral neck
Cai et al. [78]	1001	Serum vitamin D levels and disease activity were tightly correlated (SMD = 0.71, $p < 0.001$), more so for the value of ESR than for CRP or BASDAI. Calcium and PTH levels were not related to disease activity

Among these factors, a number of researchers give greater weight to the degree of inflammation in fostering and advancing the extent of bone loss in AS. A prospective study of 34 patients with AS by Gratacos and colleagues [76] found that only subjects with persistent active disease experienced significant bone loss early in the disease course. Loss was seen in the lumbar spine (5 %) and in the femoral neck (3 %) over 19 months for those with active disease, whereas no significant bone loss was found in those with inactive disease. Moreover, the group with active disease had significantly higher levels of IL-6, but other factors including physical activity or medications for treatment impacted BMD.

A subsequent study by Maillefert et al. examined changes in bone density in patients with AS over a prospective 2-year period [77]. The questions posed were whether change in BMD in the lumbar spine and in the femoral neck were related to any of the three factors: physical impairment, persistent systemic inflammation as defined by ESR ≥28 mm/h, or mean C-Reactive Protein (CRP) ≥15 mm/l. The authors found no change in lumbar BMD in the 34 subjects on average in the 2-year assessment but did observe a decline in femoral neck BMD of 1.6 %. The levels of ESR and CRP were only significantly elevated in the group with bone loss in the femoral neck.

Biochemical markers of bone metabolism are altered in patients with AS. Franck and colleagues [69] examined how osteoprotegerin (OPG) levels might relate to inflammation and osteoporosis in AS patients. As a decoy protein receptor for the receptor activator of nuclear factor kappa B ligand (RANKL), OPG can bind to RANKL and, in doing so, prevent RANK-mediated nuclear factor kappa B activation, a step that is essential to transcription of immune-related genes and a regulator

of innate immunity [79]. The researchers found that OPG levels in AS patients are low, possibly contributing to their immune response. Another function of OPG is to reduce the production of osteoclasts by inhibiting their differentiation. This step is essential to preventing excess bone resorption; if OPG levels are low, a relative state of osteoclastogenesis ensues [80].

The role of vitamin D in osteoporosis prevention in AS patients remains uncertain. A study by Cai et al. in 2015 examined a series of eight case–control studies with a total of 533 AS patients and 478 matching controls [78]. They explored the correlation between ESR, CRP, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and levels of both serum calcium, PTH, and serum vitamin D25OH. Results found that serum vitamin D levels and disease activity were tightly correlated (standard mean difference (SMD) = −0.71, $p<0.001$), more so for the value of ESR than for CRP or BASDAI. Calcium and PTH levels were not related to disease activity. Additional studies on the role of vitamin D are indicated, but there is little harm in ensuring that patients have at least a serum vitamin D level of 30–35 mg/dl, which is the low end of the therapeutic range.

Epidemiology of Osteoporosis and AS

A number of studies have examined the prevalence of osteoporosis, measured under varying modalities, in patients with AS. The best recent estimate sets the overall prevalence of osteoporosis at 25 % and vertebral fractures at 10 %, noting that these figures are challenged by falsely elevated BMD and by lack of presentation by many patients, due to the absence of symptoms in advance of any fracture and often even following a vertebral fracture [81]. In general, osteoporosis is routinely underdiagnosed and undertreated due to diagnostic challenges, so prevalence estimates in early studies have been low, particularly in investigations that preceded recommendations to use CT or lateral DXA. In a review article by van der Weidjen et al. [82], seven investigations are considered with findings of low BMD in 51–54 % of subjects; however, a BMD level low enough to meet the WHO diagnosis of osteoporosis was only present in 13–16 % of patients. While this review focused on patients within 10 years of diagnosis, symptom onset of AS may precede its diagnosis and can be interpreted as neck or back pain. In many cases, AS is diagnosed late and screening for osteoporosis does not occur until it has reached more advanced stage [81].

In the report by Klingberg et al. [70] examining 204 patients with AS, 34 % of patients under age 50 had a BMD *Z*-score of <−1.0 at the hip and/or lumbar spine, and 4.9 % had BMD below the expected range for age, *Z*-score <2.0. However, for patients over 50, osteoporosis was far more prevalent: 43.6 % were osteopenic and 20.8 % met the definition of osteoporosis by World Health Organization standards. For both male and female patients combined, the spine was the most common location of osteopenia or osteoporosis, followed by the radius and then the femoral neck.

Ghozlani et al. examined the prevalence of both osteoporosis and vertebral fractures in persons with AS [83]. Osteoporosis was present in 25 % of their sample of 80 subjects, and 18.8 % had vertebral fractures. The group did not report rates of osteopenia. Relevant factors for low BMD were disease duration, elevated Bath Ankylosing Spondylitis Disease Activity Index, longer disease duration, and lower BMI. Wang et al. studied 504 subjects with more advanced AS than the other authors and found a much greater prevalence of osteoporosis in AS patients (9.7 % vs. 0 %) as well as osteopenia (57.5 % vs. 34.9 %), when compared with 106 age- and gender-matched controls [84]. At the lumbar spine, risk factors for bone loss were juvenile onset of disease, morning stiffness lasting more than 30 minutes, and elevated ESR, whereas at the femur, risk factors were male gender, older age, ankylosis of the hip and lack of regular AS treatment. Interestingly, the use of glucocorticoids did not correlate with bone loss in either the spine or hip.

Fractures in AS

The reported prevalence of vertebral fractures in AS patients ranges from 12 % to 32.4 %. One large investigation of 66,000 patients gave an estimate below 1 %, but this was based on patient questionnaires. Often patients may not realize they have a vertebral body collapse consistent with fracture unless pain or weakness results. Notably, 47 % of those completing questionnaires reported fractures that were significant enough to cause neurological damage [85]. The advantage of this study is that it was a population-based study and not drawn from a rheumatology clinic where cases tend to be more complex.

In the study by Ghozlani [83], fractures in lumbar vertebrae were seen in 18.8 % of patients, with the strongest risk factors being disease duration and mSASSS. This group only looked at vertebral fractures of grade 2 (reduction of 26–40 % loss of height) and grade 3 (reduction of >40 % loss of height). A summary of prior studies on prevalence of osteoporosis and vertebral fractures is given in Table 6 [70, 81–83, 85, 86].

Pharmacologic Treatment

Vitamins and Hormones

Although there are no formalized treatment guidelines for osteoporosis in AS endorsed by relevant European or North American organizations, AS screening for osteoporosis should occur in the first several years of diagnosis. The initial step in management consists of appropriate preventative measures, including review of dietary intake of calcium and vitamin D, screening baseline levels of serum calcium PTH and serum vitamin D25OH, and evaluation of endocrine abnormalities in

Table 6 Prevalence of osteoporosis and vertebral fractures in patients with ankylosing spondylitis

Source	*n*	Age	Sex (M/F)	AS disease duration, yrs	Modality	Results OP (%), VF (%)	Comments
Van der Weidjen et al. [82]	482	35	419/63	8	DXA (*T*-score)	OP 13–16 %	Systematic review
Klingberg et al. [70]	204	50	117/87	15	DXA (*T*-score)	OP 21 %	Based on lateral DXA scans, which showed low BMD in comparison to the AP projection
Ghozlani et al. [83]	80	39	67/13	11	DXA (*T*-score)	OP 25 %	Some vertebrae from the T4–L4 region were not adequately visualized
Vosse et al. [85]	59	57	44/13	25	Patient questionnaire	VF 0.4 %	Subjects completed questionnaires regarding CVFs

Sources: Adapted from Davey-Ranasinghe [81] and El Maghraoui A. [86]
AP anterioposterior, *DXA* dual-energy x-ray absorptiometry, *OP* osteoporosis, *VFs* vertebral fractures, *CVFs* clinically confirmed vertebral fractures

estrogen, testosterone, growth hormone, and thyroid function. However, there are no controlled trials of osteoporosis prevention or treatment with vitamin D, calcium, anabolic steroids, or other forms of hormone replacement.

Bisphosphonates

Two trials of pamidronate given to reduce inflammation rather than treat osteoporosis revealed a reduction in bone turnover markers [87, 88]. However no improvement in BMD was observed over the study evaluation period of 3–6 months. Both investigations took place 15–20 years ago and additional trials of alternative bisphosphonates may ultimately demonstrate greater potential.

Two published trials of zoledronic acid (ZA) for inflammation secondary to AS should be noted [89, 90]. In one investigation by Sargin and Senturk [89], ZA was well tolerated, and, after three months, reduced disease activity, less spine pain, and lower inflammatory markers (ESR and CRP) were found. The mechanism of bisphosphonates involves inhibition of osteoclastic activity and modulation of pro-inflammatory cytokines. Measures of bone turnover and bone density such as telopeptides, P1NP, or DXA scans were not examined. To date, no controlled studies of other bisphosphonates have been published that focus on improvement of BMD in AS patients.

TNF-α Inhibitors

As the reports of Gratacos [76] and Maillefert [77] have shown, disease duration and elevated ESR as well as CRP correlate with bone loss, and thus the role of TNF-α inhibitors may offer promise for treatment and further prevention of osteoporosis. Because TNF-α is a cytokine that increases bone resorption in states of estrogen deficiency and erosive arthritis affecting periarticular regions, blocking the action of TNF-α should theoretically result in a net gain of bone content.

Infliximab is a human neutralizing monoclonal antibody used successfully to decrease inflammation in rheumatoid conditions and spondyloarthropathies. Allali et al. [91] focused on 29 patients with various forms of spondyloarthropathy, most receiving 5 mg/kg at weeks 0, 2, and 6. Significant gains were seen in BMD of spine, total hip, and greater trochanter. Only four patients received corticosteroids during the study; notably, no increase in BMD was seen at any site in the four subjects. Values of ESR and CRP for the group as a whole demonstrated significant decreases between baseline and week number six and between baseline and final visit at approximately six months posttreatment.

A recent phase III clinical trial of 279 subjects taking infliximab for AS-related osteoporosis demonstrated a 2.5 % increase in spinal BMD and 0.5 % gain in hip BMD relative to control subjects who, in comparison, achieved BMD gains of 0.5 % in the spine and 0.2 % in the hip [92]. Subjects received either the study drug or placebo every two weeks. Early response to infliximab was seen in the form of elevated bone alkaline phosphatase (BAP) and/or increased osteocalcin, two alternative markers of bone formation. Subjects with high BAP early in the study and those with elevated osteocalcin levels just two weeks into the trial demonstrated significant gains in BMD at the end of the study, two years after the first dose of the drug.

Nonpharmacologic Treatment

Deficits in postural stability, coordination, proprioception, and balance are inherent in AS [73]. Pompeu et al. has described the consequences of altered posture with AS, specifically the combination of increased thoracolumbar kyphosis and hip flexion that displace the body's center of gravity anteriorly, resulting in horizontal gaze and a compensatory increase in knee flexion and ankle plantar flexion [93]. In a study of 12 AS subjects matched with 12 healthy age-equivalent controls, those with AS demonstrated significant reductions in range of motion for hip and knee extension, markedly decreased heel strike and plantar flexion in the initial contact phase of gait, and notable deficits in dynamic and static balance [94]. Physical therapists should focus on correction of these deficits as early as possible to maximize remaining function.

Impairments in proprioception and vestibular function have been reported in patients with AS. How much of a role nonsteroidal anti-inflammatory agents (NSAIDs) may play in this observation is unclear. This class of drugs has been

known to cause ototoxicity, and, given the high use in populations with rheumatic diseases, the effect of NSAIDs on balance and proprioception is potentially detrimental [73]. Spinal enthesopathy may intensify deficits further.

When vision (via kyphosis) is impaired along with sensation and proprioception, the risk of falls is increased significantly. This concern, combined with motor weakness, endurance deficits, and adverse medication effects, only increases the need for structured physical therapy to educate patients on protective fall techniques and anticipatory safety measures. No studies on AS patients have focused on an exercise program specific to osteoporosis, but the risk of spinal fractures is substantial at all phases of disease. Many therapy centers incorporate structured home exercise programs to meet functional deficits and offer long-term guidance for safe mobility in the home and community.

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