RHEUMATOLOGIC DISORDERS IN WOMEN

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Although many may think of rheumatology as the study of arthritis, occurring predominantly in older patients, many autoimmune and connective tissue diseases are actually diseases of young and middle-aged women. This article reviews common rheumatic diseases that most frequently occur in women, including fibromyalgia, rheumatoid arthritis (RA), Sjögren’s syndrome, systemic lupus erythematosus (SLE), and the antiphospholipid antibody syndrome (APLS). In this group of patients, many women are of childbearing potential, and special considerations for pregnancy can and often do arise; these are discussed as well. In addition, rheumatic conditions that more frequently affect older women, such as osteoarthritis (OA), polymyalgia rheumatica (PMR), and temporal arthritis, are discussed. Osteoporosis, which has been recognized as a significant women’s health issue, is reviewed.

RHEUMATOID ARTHRITIS

RA is probably the most common cause of chronic inflammatory arthritis, affecting approximately 1% to 2% of the general population. Approximately 75% of patients are women. Although the peak incidence is said to be during age 20 through 40, studies have shown that the incidence increases steadily with age.16 The precise cause of RA is still unknown; however, immunologic, cellular, and molecular studies have uncovered important new evidence regarding the immunopathology of
the disease. It is now thought that activation of T cells by means of dendritic cells may not require antigen. Therefore, there may not be only one antigenic trigger for this disease. Evidence has also shown that chronic immune stimulation results in altered synovial cell phenotype, causing a transformed-like state capable of invading articular cartilage and adjacent structures. Individuals possessing specific alleles localized to the third hypervariable region of the β chain of the HLA-DR molecule have a higher relative risk of developing RA.

The classic clinical signs of RA are a symmetric polyarthritis involving the small joints of the hands and feet. Eventually, nearly every joint in the body may become involved with the exception of the distal interphalangeal joints of the hands and the thoracic and lumbar spine, which are notable for their lack of involvement. In contrast, the upper segments of the cervical spine are frequently involved. Joint stiffness after inactivity is a hallmark of chronic inflammatory arthritis and is most notable on awakening in the morning and after sitting for long periods of time; the latter is known as the gel phenomenon. On physical examination, the joints are boggy because of underlying synovitis. Larger joints often have evidence of effusion. Rarely, joints may be so acutely inflamed that they are erythematous and hot. Characteristic hand deformities may readily suggest the diagnosis of RA, including ulnar deviation and swan neck and boutonniere deformities of the digits. Approximately 80% to 85% of patients with RA have detectable rheumatoid factor in their blood. Conversely, approximately 15% to 20% of RA patients never display rheumatoid factor positivity despite classic signs of the disease.

RA may also result in extra-articular and extrasynovial disease manifestations. Extrasynovial features result from the extension of joint pathology to adjacent structures. Important clinical examples of extrasynovial disease include ruptured popliteal cyst, ruptured extensor tendons of the hand, entrapment neuropathies, and rheumatoid nodules. A ruptured or dissected popliteal cyst often presents with painful swelling of the calf. This syndrome may mimic thrombophlebitis. With time, especially if the patient is ambulatory, the swelling progresses distally and results in foot and ankle edema. If the dissected synovial fluid is hemorrhagic, an ecchymotic crescent may develop around the lateral malleolus. Although arthrography was once widely used to document the presence of popliteal cyst dissection into the calf, diagnostic ultrasound is currently the procedure of choice. Treatment includes elevation, rest, and nonsteroidal anti-inflammatory drug (NSAID) or local corticosteroid injection to reduce inflammation. Rupture of the extensor tendons of the hand may present dramatically with the development of flail digits because of unopposed flexor tendon action and inability of the patient to extend the involved digits. Usually the fourth and fifth digits are affected because those extensor tendons may be chronically frayed by passage over an eroded ulnar styloid encased by inflamed pannus. Surgical correction by tendon transfer is recommended on a semielective basis. The most common entrapment neuropathies in RA
Table 1. EXTRA-ARTICULAR MANIFESTATIONS OF RHEUMATOID ARTHRITIS

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<tr>
<th>Ocular</th>
<th>Pulmonary</th>
<th>Immunologic</th>
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<tr>
<td>Episcleritis</td>
<td>Pleuritis</td>
<td>Felty’s syndrome†</td>
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<tr>
<td>Scleritis</td>
<td>Interstitial fibrosis</td>
<td>Glandular</td>
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<td>Cardiac</td>
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<td>Pericarditis</td>
<td>Caplan’s syndrome*</td>
<td>Vascular</td>
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<td>Valvulitis</td>
<td>Bronchiolitis obliterans</td>
<td>Rheumatoid vasculitis</td>
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<td>Nodules</td>
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*Multiple pulmonary nodules in patients with pneumoconiosis and rheumatoid arthritis.
†Severe deforming rheumatoid arthritis, neutropenia, and splenomegaly.

include carpal tunnel syndrome, ulnar entrapment, and tarsal tunnel syndrome. Some degree of objective assessment of severity may be provided by electrodiagnostic studies. Splinting and local corticosteroid injection may be helpful. If motor weakness occurs, surgical release is usually required. Rheumatoid nodules usually develop at extensor surfaces of joints and at pressure points, such as the Achilles area, the occiput (in supine patients), and the sacral area (in wheelchair-bound patients). The most common site is at the olecranon process of the elbow. Nodules appear to be more common in seropositive patients and may predict disease severity.41

RA is a systemic disease and thus may involve multiple organ systems. Constitutional symptoms are frequent, and patients may experience low-grade fever, fatigue, and mild weight loss. Table 1 lists the extra-articular manifestations of RA.

Special consideration should be given to several issues when the RA patient requires presurgical clearance. Assessment for the presence of cervical spine disease must be done before the performance of intubation for general anesthesia to avoid severe brain stem or cord injury secondary to atlantoaxial subluxation. Patients on long-term corticosteroids should receive stress-dose steroids during the procedure. NSAIDs should be held approximately 7 days before surgery to permit platelet function to recover. It is reasonable to hold methotrexate during the immediate preoperative and postoperative period. It has been suggested that methotrexate may have an adverse effect on the outcome of total joint arthroplasty; however, this is still under investigation.6

RHEUMATOID ARTHRITIS AND PREGNANCY

The relationship between RA and pregnancy has long intrigued clinicians and immunologists. Although SLE may flare during pregnancy, RA has been observed to improve or even go into remission during pregnancy. Many investigators have studied the immune and inflammatory response during pregnancy in an attempt to identify mechanisms that might lead to new therapeutic approaches for RA. Investigators have found several interesting humoral and cellular immu-
nologic alterations, including increased levels of a serum $\alpha_2$ globulin (also known as pregnancy zone protein), synthesis of fetal suppressive factors, and alteration of the T-cell cytokine profile. Postpartum the T-cell cytokine profile switches to a TH1 profile featuring interferon $\gamma$, and interleukin-2 (IL-2). Some of the most potentially important observations with respect to pregnancy and the immunopathogenesis of RA concern the relationship of the maternal-fetal human leukocyte antigen (HLA) status and RA activity. As mentioned previously, RA is associated with certain HLA class II haplotypes (HLA-DR4). Fetal major histocompatibility complex (MHC) proteins appear to gain access to the maternal immune system because pregnant women develop antibodies to paternal HLA antigens. Nelson and colleagues studied the association between maternal-fetal HLA compatibility and frequency of remission of RA and found that HLA mismatching at DR and DQ loci correlated with improvement in the mother's RA. These data suggest that introduction of foreign HLA antigens influenced the autoimmune response; similar mechanisms may play a role in affording protection from the development of RA.

Nulliparous women generally are found to have a twofold increase in the relative risk for the subsequent development of RA. Women with RA have been found to have smaller families than unaffected women. Although fertility is generally not impaired in RA, fecundity—the probability of successful conception—is reduced in women with RA. Clinically, 50% to 75% of women with RA experience some type of improvement in their arthritis during pregnancy. Improvement appears to progress throughout gestation, and many patients achieve complete remission and are able to stop all medication by the last trimester. Labor and delivery are usually uneventful in women with RA, and there appears to be no adverse effect of maternal disease on the outcome of the fetus, including spontaneous abortion, prematurity, and low birth weight. Occasionally, severe hip disease may prevent normal vaginal delivery; however, patients with mild hip disease or those who have undergone successful hip replacement may be candidates for a vaginal delivery. Patients who have cervical spine disease and who require cesarean section under general anesthesia are at risk from complications of atlantoaxial subluxation (see earlier). These women may require cervical bracing in the operating room to prevent cervical spine hyperextension. If intubation is required, seated nasotracheal intubation is often preferred.

For patients whose disease does not remit during pregnancy or for those not entering a complete remission, some form of antirheumatic therapy is required. The use of antirheumatic drugs in pregnancy has been reviewed by Ostensen. The following statements summarize medication use in the pregnant RA patient:

- NSAIDs have not been shown to be teratogenic; therefore prophylactic discontinuation of NSAIDs before pregnancy is not usually necessary.
• NSAIDs do, however, have an effect on fetal renal function and constrict the ductus arteriosus; these effects usually are transient.
• Most studies show a lack of adverse effects on mother and fetus; however, because of the increased risk of neonatal bleeding, including brain hemorrhage, NSAID should be stopped 6 weeks before delivery.
• Although animal studies demonstrate an association between prednisone administration and minor congenital abnormalities, such as cleft palate, extensive clinical experience in humans has not demonstrated an increased risk for fetal malformations.
• Corticosteroids are generally considered among the safest and most widely used agents during pregnancy. Administration of stress-dose steroids is advised during labor and delivery for patients on long-term steroids.
• When one or just a few joints are involved, administration of intraarticular corticosteroid is the preferred management approach.
• In deciding whether to continue or begin disease-modifying agents during pregnancy, the benefit to the mother must be weighed against the potential risk to the fetus.
• No evidence of fetal malformation has been reported with gold or hydroxychloroquine therapy; however, clinical experience is limited.
• Extensive experience exists with regard to sulfasalazine because of its use in inflammatory bowel disease. No evidence of fetal malformation has been uncovered. It is suggested that sulfasalazine may be used during pregnancy.
• Azathioprine is not teratogenic in humans. Fairly extensive experience with azathioprine in pregnancy exists from reports of renal transplant centers. No congenital malformations have been reported.
• Cytotoxic drugs are teratogenic. Methotrexate, cyclophosphamide, and chlorambucil should be withheld 3 months before conception.

SJÖGREN'S SYNDROME

Approximately 20% of RA patients have secondary Sjögren’s syndrome. An equal number of individuals without any other connective tissue disorder have primary Sjögren’s syndrome. Approximately 1% of the population is estimated to have this disease, and at that, it may be underdiagnosed. Underdiagnosis has been attributed to lack of awareness of this disorder and a tendency to diagnose mild or atypical SLE in the face of multiple autoantibodies. The cardinal symptoms of Sjögren’s syndrome are xerostomia and xerophthalmia. Although many common conditions, such as anxiety, aging, and medication use, can cause dry mouth, the patient with Sjögren’s syndrome has persistent severe dryness that often interferes with eating and speaking. Talal has popularized the cracker sign, where Sjögren’s patients cannot chew or swallow a
saltine cracker without exogenous liquid. Eventually the persistent severe dry mouth results in chronic oral candidiasis with oral fissuring and cracking along with rampant dental decay. Xerophthalmia is usually perceived not as dryness but as a persistent foreign body sensation. Typically, patients complain of a gritty or sandy feeling in their eyes. Careful slit-lamp examination with vital dye staining may reveal corneal abrasion. If the dry eye is not compulsively cared for, severe keratoconjunctivitis, scarring, and visual loss may occur. Salivary gland swelling is often but not invariably present.

As mentioned earlier, approximately 50% of Sjögren’s patients have RA or, less commonly another connective tissue disorder. Fifty percent have primary Sjögren’s with no evidence of a concomitant connective tissue disease. It is becoming increasingly recognized, however, that Sjögren’s syndrome is in and of itself a multisystem disorder. The major extraglandular manifestations are listed in Table 2. Although listed as extraglandular manifestations of Sjögren’s syndrome, primary biliary cirrhosis and the CREST syndrome (calcinosis, Raynaud’s, esophageal dysmotility, sclerodactyly, telangiectasia) are independent autoimmune disorders that have a high frequency of association with Sjögren’s syndrome. The issue of central nervous system involvement in Sjögren’s has been controversial. Alexander¹ has published series of patients in whom the incidence of central nervous system disease was fairly high and included manifestations such as dementia and multiple sclerosis-like symptoms. Other authors believe that true central nervous system involvement in Sjögren’s is quite rare and that some published cases may represent overlap with SLE, concurrent autoimmune neurologic disorders, or psychiatric disease. Central nervous system involvement in Sjögren’s exists but is, in the authors’ experience, quite rare; this entity requires further documentation and classification. Of major concern to internists caring for Sjögren’s patients is the excess risk of developing

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<tr>
<th>Extraglandular Manifestations of Sjögren's Syndrome</th>
<th>Neurologic</th>
<th>Pulmonary</th>
<th>Hematologic</th>
<th>Vascular</th>
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<tbody>
<tr>
<td>Rheumatic Neurologic</td>
<td>Peripheral neuropathy</td>
<td>Interstitial fibrosis</td>
<td>Anemia</td>
<td>Vasculitis</td>
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<tr>
<td>Arthritis</td>
<td>Cranial neuropathy</td>
<td>Tracheobronchitis</td>
<td>Leukopenia</td>
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<tr>
<td>Myositis</td>
<td>Central nervous system disease</td>
<td>Pseudolymphoma</td>
<td>Paraproteinemia</td>
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<td>CREST overlap</td>
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<td>Lymphoma</td>
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<td>Cutaneous</td>
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<tr>
<td>Dry skin</td>
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<td>Hyperglobulinemic purpura</td>
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<td>Gastrointestinal</td>
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<td>Achalasia</td>
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<td>Hematologic</td>
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<td>Atrophic gastritis</td>
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<td>Anemia</td>
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<tr>
<td>Pancreatitis</td>
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<td>Leukopenia</td>
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<tr>
<td>Autoimmune hepatitis</td>
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<td>Paraproteinemia</td>
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<td>Primary biliary cirrhosis</td>
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<td>Lymphoma</td>
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<td>Renal</td>
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<td>Renal tubular acidosis</td>
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Rheumatic Neurologic
Arthritis
Myositis
CREST overlap
Cutaneous
Dry skin
Hyperglobulinemic purpura
Gastrointestinal
Achalasia
Atrophic gastritis
Pancreatitis
Autoimmune hepatitis
Primary biliary cirrhosis
Renal
Renal tubular acidosis

Table 2. EXTRAGLANDULAR MANIFESTATIONS OF SJÖGREN'S SYNDROME
lymphoma, which has been estimated at 44-fold. Patients at highest risk have long-standing disease and significant salivary swelling and adenopathy. Additional predictive signs are the development of hepatosplenomegaly, leukopenia, and pulmonary and renal lymphocytic infiltrates; loss of specific autoantibodies (ANA, RF, SS-A/B); and emergence of monoclonal proteins. The finding of Swenson's antibodies in patients planning conception raises concern for the development of neonatal lupus in the infant (see SLE and pregnancy later). Although first recognized in mothers with SLE, any woman with circulating anti-SS-A/B is at risk for having a fetus with neonatal lupus erythematosus. This would include those with Sjögren's syndrome or even asymptomatic women.

The diagnosis of Sjögren's syndrome is made on clinical grounds and usually requires the documentation of keratoconjunctivitis sicca (dry eye and abnormal corneal staining on slit-lamp examination) and salivary dysfunction. Many authors believe that a minor salivary gland biopsy is the most specific and preferred method of documenting salivary involvement. A consensus on an appropriate set of diagnostic criteria has not yet been reached, although approximately a half-dozen criteria sets have been proposed internationally.

Treatment of uncomplicated Sjögren's syndrome relies basically on moisture replacement using artificial tears and saliva. Frequent ophthalmologic and dental examinations are necessary to avoid complications. Extraglandular disease, especially pulmonary and renal, and vasculitis may require treatment with systemic corticosteroid.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

SLE is a multisystem disease characterized by the presence of multiple autoantibodies. It is much more common in women with a female-to-male ratio of approximately 9:1. It is also more common in African-Americans and Asians than in whites or Hispanics. The exact cause of SLE remains unknown but is believed to be related to a combination of genetic, environmental, and hormonal factors. Abnormalities in the *fas* gene resulting in defects in the apoptotic pathway have been identified in murine and human SLE. This may explain persistence of autoreactive T cells in SLE.

The major manifestations of SLE are summarized in Table 3. Arthritis is the most frequent manifestation of SLE, occurring in approximately

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<th>Table 3. CLINICAL FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS</th>
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<td>Arthritis</td>
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<tr>
<td>Rash</td>
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<td>Malar rash</td>
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<td>Photosensitivity</td>
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<td>Discoid lesions</td>
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<td>Oral ulcers</td>
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76% to 88% of cases.18 The pattern of joint involvement in SLE often resembles that of RA; it is a symmetric inflammatory arthritis that involves multiple joints, including the small joints of the hands (metacarpophalangeals and proximal interphalangeals), wrists, ankles, feet, and knees. In fact, in patients in whom the clinical picture is dominated by arthritis, SLE is most often confused with RA. A careful history and physical examination, however, may reveal other suggestions of SLE and should lead the examiner to obtain the appropriate serologies (see later).

Patients with SLE frequently exhibit a variety of rashes, most commonly a malar rash, photosensitivity, or discoid lesions. The classic malar or butterfly rash of SLE occurs on the cheeks and across the bridge of the nose but typically spares the nasolabial folds. This rash tends to come and go without scarring and often varies with disease activity. Discoid lesions are rounded, slightly scaling lesions occurring on the face, extremities, scalp, and ears that are characterized by atrophy and follicular plugging and tend to leave scars.

Oral, and occasionally nasal, ulcerations are seen in patients with SLE; these are typically painless, and the patient may be unaware of their presence. Thus, careful examination for these lesions should be carried out in all patients suspected of having SLE. SLE also commonly affects serosal surfaces, and patients may have pleuritis, pericarditis, or abdominal serositis.

Although not specific enough for SLE to be included in the diagnostic criteria, Raynaud’s phenomenon and alopecia are common manifestations of the disease. Patients also commonly have constitutional symptoms, such as fever, fatigue, and weight loss, and may have lymphadenopathy or hepatosplenomegaly.

The presence or absence of major organ involvement is a major determinant of course and prognosis in SLE; major organ involvement most commonly takes the form of hematologic, renal, or central nervous system involvement. Patients with hematologic involvement may have leukopenia (especially lymphopenia), hemolytic anemia, or thrombocytopenia.

Renal disease generally presents with proteinuria or an abnormal urinary sediment and, later, a rising creatinine. Patients with lupus nephritis may also have hypertension and pedal edema. Lupus nephritis has been classified by the World Health Organization into five classes or types of nephritis, with class IV (diffuse proliferative glomerulonephritis) having the worst prognosis and requiring aggressive intervention with immunosuppressive therapy (see later). Persistently high titers of anti-dsDNA antibody and low levels of C3 or C4 have been associated with a higher risk of developing significant renal disease. Renal biopsy is helpful in selected patients to identify the type and activity of the lesion in lupus nephritis.4

Neuropsychiatric lupus can be one of the most difficult and challenging diagnostic dilemmas. In recent years, much attention has been focused on finding new modalities for evaluating patients with neuropsychiatric disease in SLE. The neurologic manifestations of SLE are
protean. Although the classic central nervous system manifestations of SLE are seizures and psychosis, patients also commonly have headache, depression, or subtle mood or personality changes related to their lupus. It is essential to rule out infection in all patients with SLE and central nervous system disease, particularly in patients on corticosteroids or other immunosuppressive therapies. Many of the medications used to treat SLE may have neuropsychiatric side effects, including corticosteroids, NSAIDs, hydroxychloroquine, and azathioprine. Secondary fibromyalgia (see later) is common in SLE and may complicate the clinical picture further, especially in patients with nonfocal complaints. Patients with SLE may also have aseptic meningitis (especially related to NSAID use), pseudotumor cerebri, or involvement of cranial or peripheral nerves. Focal neurologic events, including transient ischemic attack, cerebrovascular accident, transverse myelitis, or embolic disease, should raise a suspicion of an associated antiphospholipid syndrome (see later). Multiple laboratory and neuroimaging studies have been used to evaluate patients for neuropsychiatric lupus, although there is no single test that can confirm this diagnosis. Lumbar puncture may be helpful both to look for evidence of neurologic involvement of SLE and to rule out infection. Patients with SLE and central nervous system involvement may have elevated cerebrospinal fluid protein, lymphocytic pleocytosis, oligoclonal bands, or an increased cerebrospinal fluid IgG index. In recent years, cerebrospinal fluid antineuronal and serum antiribosomal-P antibodies have been associated with neuropsychiatric lupus, particularly diffuse (nonfocal) disease. Magnetic resonance imaging may be helpful in some cases but is nonspecific; in addition, a normal magnetic resonance imaging scan of the brain does not rule out central nervous system lupus. Single-photon emission computed tomography scans have also been used to evaluate patients for neuropsychiatric lupus and have been reported to have a high sensitivity (90%) but a low specificity (33%).

The diagnosis of SLE should never be made on the basis of a positive laboratory test alone. In the context of the appropriate signs and symptoms, however, the antinuclear antibody (ANA) is a useful screening test. The ANA is greater than 95% sensitive for SLE, and thus its absence should make one reconsider the diagnosis. The major limitation of the ANA is its lack of specificity. A variety of conditions other than SLE may be associated with a positive ANA, including other rheumatic diseases (other connective tissue diseases, RA), organ-specific autoimmunity (e.g., thyroiditis), chronic liver disease, chronic infections, aging, malignancy, and certain medications (see later). More specific serologic tests for SLE include anti–double-stranded DNA and anti-Smith antibodies. These are much less sensitive, however, being present in only approximately 50% and 30% of patients with SLE. In some patients, it may be useful to follow serially the titer of anti-dsDNA antibody and levels of complement (C3 and C4) because these may vary with disease activity. Patients with SLE may also have a variety of other autoantibodies, including anti-RNP, antihistone, and SSA antibodies.
Anti-RNP antibodies, when present alone, are associated with mixed connective tissue disease but may also be seen as part of the constellation of autoantibodies found in patients with SLE. Anti-histone antibodies are generally associated with drug-induced lupus (see later) but may also be seen in a significant number of patients with native SLE. SSA antibodies (anti-Ro antibodies, Sjögren’s antibodies) have been shown to have a variety of clinical associations and may be seen in patients with SLE, with or without secondary Sjögren’s syndrome. SSA antibodies have been associated with cutaneous lupus (especially subacute cutaneous lupus), have been associated with risk of neonatal lupus in SSA-positive mothers (see later), and have been described in ANA-negative lupus. More recently, the presence of SSA antibodies in patients with SLE has also been associated with hypergammaglobulinemic purpura and interstitial pneumonitis. A biologic false-positive test for syphilis (positive VDRL with a negative FTA) may also be seen in patients with SLE, especially in those with an associated APLS (see later). Laboratory findings in SLE are summarized in Table 4.

Treatment of SLE begins with reassurance and education of the patient. Patients should be advised that not all patients with SLE have severe, life-threatening disease; many patients have relatively mild disease without major organ involvement that can be treated fairly easily. Patients with SLE should be counseled to wear a potent sunscreen on a regular basis and to avoid excessive sun exposure. Patients who have arthritis as their major manifestation can often be treated with NSAIDs. In patients with refractory arthritis or in those with serositis (pleuritis, pericarditis) or cutaneous disease, antimalarial agents, such as hydroxychloroquine, may be helpful. Topical corticosteroid preparations are often used in patients with cutaneous disease, either alone or as an adjunct to treatment with antimalarials. Systemic corticosteroids are used in two ways in SLE: (1) Low-dose steroids (<10 to 15 mg/day) may be used for manifestations such as arthritis or mild pleuroperticarditis, and (2) high-dose steroids (1 mg/kg/day) for major organ involvement or vasculitis. Patients with major organ involvement often need

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<th>Table 4. LABORATORY FEATURES OF SYSTEMIC LUPUS ERYTHEMATOSUS</th>
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<tr>
<td>Hematologic</td>
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<td>Leukopenia (lymphopenia)</td>
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<td>Hemolytic anemia</td>
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<td>Thrombocytopenia</td>
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<td>Renal</td>
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<td>Proteinuria</td>
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<td>Hematuria</td>
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<td>Active urinary sediment (casts)</td>
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<td>Increased serum creatinine</td>
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*Disease specific.
additional immunosuppressive therapy, most commonly with azathioprine or cyclophosphamide. It is important to identify patients who have class IV lupus nephritis (diffuse proliferative glomerulonephritis) because intravenous cyclophosphamide (Cytoxan) in addition to high-dose steroids is generally considered to be the treatment regimen of choice for this lesion. Azathioprine and cyclophosphamide are potent immunosuppressive agents with significant potential side effects, including bone marrow suppression, increased risk of infection, and increased risk of subsequent malignancy. One special concern with the use of cyclophosphamide is the risk of ovarian failure and infertility, especially because SLE most commonly occurs in women of childbearing age. Ovarian failure is also of particular concern for women with SLE who are on long-term corticosteroid therapy because of the increased risk of osteoporosis. Although the overall incidence of ovarian failure with the use of cyclophosphamide for lupus nephritis is approximately 50%, data suggest that the incidence may be lower in younger patients.26, 48

SYSTEMIC LUPUS ERYTHEMATOSUS AND PREGNANCY

It has been reported that SLE may flare during pregnancy or in the postpartum period, although studies have questioned this long-standing belief.37 In addition, women with SLE have an increased risk of having premature delivery, low-birth-weight infants, and spontaneous abortion.37 Despite these potential problems, many women with SLE have successful pregnancies. Careful planning is essential, however, for optimal outcome in SLE pregnancies. First, the timing of pregnancy is critical in women with SLE; ideally, patients should have quiescent disease. Especially important is the lack of active renal disease during pregnancy. Patients who do have active disease during pregnancy should be treated; active SLE during pregnancy is generally treated with corticosteroids. Azathioprine, however, has been used during pregnancy in selected patients in whom the risk of active disease or steroid complications outweighs the risk of the medication. (For discussion on the use of specific agents during pregnancy, see RA and pregnancy, earlier).

Women with SLE who are contemplating pregnancy should be screened for SSA and SSB antibodies (Sjögren’s antibodies) because of the associated risk of congenital heart block and neonatal lupus. Even in mothers who possess these antibodies, however, the risk of congenital heart block is less than 10%. SSA and SSB antibodies can cross the placenta and cause the neonatal lupus syndrome in the fetus.8 This syndrome is characterized by rash, hepatitis, pericarditis, and, most importantly, congenital heart block. Congenital heart block is manifested by slowing of the fetal heart rate during the second or third trimester. Pregnant women with SSA or SSB antibodies should be monitored with nonstress tests and fetal echocardiograms beginning in the 16th week.46 Intrauterine treatment with dexamethasone and plasmapheresis has
been used with some success. Screening for associated APLS (see later) should also be performed because of an increased risk of spontaneous abortions, especially second-trimester and third-trimester miscarriages.

HORMONAL FACTORS AND SYSTEMIC LUPUS ERYTHEMATOSUS

Women with SLE may have irregularities of the menstrual cycle, either secondary to their underlying disease or related to the use of medications such as corticosteroids or cyclophosphamide (see previously). In addition, a number of women with SLE report mild flares in their disease around the time of their menses each month, mainly consisting of increased joint pain, rashes, or pleuropericarditis.

Although once considered to be relatively contraindicated in SLE, the use of estrogens in women with lupus is currently controversial. Oral contraceptives containing low-dose estrogens have been used in selected patients with relatively quiescent disease. In postmenopausal women with SLE, estrogen replacement therapy is more commonly considered for treatment or prevention of osteoporosis, especially in those who have required long-term corticosteroid therapy. In one retrospective study of 60 women with SLE, no exacerbation of disease activity was reported with the use of estrogen replacement therapy. In a study of nurses treated with estrogen replacement therapy, however, an increased incidence of SLE was reported. The one setting in which most authors would agree that estrogens are contraindicated in SLE is in the presence of an associated APLS because of the risk of thrombosis. Thus, the decision to give women with SLE estrogen-containing compounds should be individualized.

Androgenic hormones are being evaluated for therapeutic use in SLE. Preliminary results using dehydroepiandrosterone (DHEA) appear promising, and additional studies are in progress.

DRUG-INDUCED LUPUS

Patients taking certain medications may develop a clinical syndrome indistinguishable from native SLE which can be associated with a positive ANA. Drug-induced lupus is generally characterized by fever, arthralgia or arthritis, and serositis (pleuritis, pericarditis). Patients usually have an elevated erythrocyte sedimentation rate and a positive ANA, generally with a homogeneous pattern. In addition, the majority of patients have antihistone antibodies. Approximately one third of patients with native SLE, however, may also have antihistone antibodies. One feature that may be helpful in distinguishing drug-induced lupus from native SLE is that renal or central nervous system involvement is extremely rare in drug-induced lupus. In addition, as opposed to native SLE, drug-induced lupus has an equal sex predominance and is uncom-
mon in African-Americans. The medications most commonly implicated in drug-induced lupus include procainamide, hydralazine, methyldopa, chlorpromazine, isoniazid, and anticonvulsants.

**ANTIPHOSPHOLIPID ANTIBODY SYNDROME**

APLS may occur as a primary syndrome or coexist with connective tissue diseases, most commonly SLE. Historically, several names have been used to describe the same syndrome, including the *lupus anticoagulant* and the *anticardiolipin antibody syndrome*. The lupus anticoagulant is a misnomer for two reasons. First, as mentioned, patients with this syndrome do not necessarily have lupus. Second, although an anticoagulant effect is seen in vitro (prolongation of the partial thromboplastin time [PTT]), the syndrome is paradoxically characterized by thrombosis in vivo. Patients with APLS may have recurrent arterial or venous thrombotic events, including transient ischemic attack, stroke, myocardial infarction, deep venous thrombosis, and pulmonary embolism. In addition to thromboses, women with APLS may have recurrent spontaneous abortions, especially in the second and third trimesters. Thrombocytopenia, migraine headaches, and livedo reticularis are frequently seen in patients with APLS. Patients may less commonly have sterile endocarditis (Libman-Sacks endocarditis) or chorea.

Several different laboratory tests can be used to evaluate patients suspected of having APLS. Because any one or any combination of tests may be positive in an individual patient, a combination of tests is generally required for an adequate evaluation. The activated PTT and other phospholipid-dependent tests of coagulation may be prolonged. In patients with a circulating lupus anticoagulant, the addition of normal plasma does not correct the PTT. An assay for the presence of a circulating anticoagulant, such as the dilute Russel viper venom time (dRVVT), and specific anticardiolipin antibodies should be measured. A biologic false-positive test for syphilis may also be seen (i.e., a positive Venereal Disease Research Laboratory with a negative fluorescent treponemal antibody). More recently, assays for B2 glycoprotein I, a cofactor for antiphospholipid antibodies, have become available and may be useful in evaluating selected patients for suspected APLS. For instance, anticardiolipin antibodies have been reported to occur in the setting of infection, but these patients generally do not have thrombotic events and generally do not have antibodies to B2 glycoprotein I. Patients with primary APLS may also have a positive ANA, and this does not necessarily indicate that the patient has underlying SLE.

Treatment of APLS depends on the specific manifestations and clinical setting and should be individualized for each patient. For example, patients who are incidentally found to have a circulating anticoagulant or anticardiolipin antibodies who have not had recurrent thrombotic events or spontaneous abortions do not require treatment. Conversely, patients who have had major thrombotic events and have laboratory
evidence of APLS generally require lifelong anticoagulation, usually with warfarin (Coumadin).

In pregnancy, treatment of APLS should also be individualized, depending on the woman’s prior obstetric and medical history. Women who have not had thromboses or prior pregnancy loss may be observed or treated with one baby aspirin per day. Women who have had multiple spontaneous abortions or significant thrombotic events are generally treated with a combination of subcutaneous heparin and aspirin during pregnancy. In the past, a combination of corticosteroids and aspirin has also been used, but this approach has been largely abandoned because of increased maternal morbidity. In general, the use of corticosteroids in APLS is reserved for associated thrombocytopenia or associated SLE activity. Several cases of steroid-responsive valvulitis (mitral regurgitation) have been reported in patients with APLS. Lastly, preliminary reports of the use of intravenous immunoglobulin during pregnancy in women with APLS who have failed aspirin and subcutaneous heparin appear to be promising, and controlled trials are currently underway.

FIBROMYALGIA

Fibromyalgia is an extremely common soft tissue pain syndrome that occurs much more frequently in women than in men; it has been reported that 80% to 90% of patients with fibromyalgia are women. Increased awareness of fibromyalgia, both by primary care physicians and by the general public, is likely leading to increased recognition and diagnosis of this disorder. There is no single test or combination of tests that can make a diagnosis of fibromyalgia; the diagnosis remains a clinical one and can be made in the presence of characteristic findings and only after careful exclusion of other disorders.

The syndrome of fibromyalgia is characterized by diffuse aches and pains; the typical fibromyalgia patient often has difficulty localizing her chief complaint. Although the exact cause of fibromyalgia remains unknown, patients generally have an underlying sleep disorder. Most patients describe overwhelming daytime fatigue. It is now thought that many patients who have been given the diagnosis of chronic fatigue syndrome have fibromyalgia. Many fibromyalgia patients may be unaware of their sleep disturbance or fail to mention it because they do not think it is relevant to their complaints of generalized pain. Thus, it is important to try to elicit a history of sleep disturbance in any patient suspected of having fibromyalgia. When asked, patients usually admit to difficulty falling asleep or, more commonly, waking up several times throughout the night. They also describe nonrestorative sleep, in which they do not feel refreshed in the morning despite what may appear to be a good night’s sleep. In addition, patients with fibromyalgia often have symptoms of irritable bowel syndrome. Complaints of morning stiffness, paresthesia, and Raynaud’s-like phenomenon may raise the possibility of an underlying connective tissue disease, although with
careful history taking fibromyalgia patients typically do not have true Raynaud's (triphasic color change of the digits). Similarly, although patients with fibromyalgia often believe that they have swelling of their hands or other joints, this is not confirmed on objective examination. Lastly, women with fibromyalgia may have symptoms of the female urethral syndrome, characterized by symptoms of cystitis in the absence of documentable infection.

On examination, patients with fibromyalgia have typical paired tender points. These exquisitely tender points are generally symmetric and are located at the occiput, trapezius, anterior chest wall, epicondyle, low back, trochanteric region of the hips, and medial aspect of the knees bilaterally. Other points, such as the center of the forehead and the lateral aspect of the knees, should be nontender and may be used as control points. Other than these tender points, the remainder of the musculoskeletal examination in fibromyalgia should be normal; there should be no evidence of synovitis, restricted range of motion, or muscular weakness.

Similarly, laboratory results should be normal in patients with fibromyalgia, including routine laboratory tests, erythrocyte sedimentation rate, and measurements of creatine phosphokinase and thyroid function. Up to 6% to 10% of the normal population may have a positive ANA, and a low positive ANA in the setting of diffuse musculoskeletal pain is often misdiagnosed as SLE or other connective tissue diseases. Many of these patients may turn out to have fibromyalgia; the correct diagnosis can be made only if the examiner is guided by the clinical picture.

Treatment of fibromyalgia is largely aimed at improvement of the underlying sleep disorder. Low-dose tricyclic antidepressants, such as amitriptyline 10 to 25 mg taken at bedtime, are generally considered to be the treatment of choice in fibromyalgia. Alternatively, muscle relaxants may also be used at bedtime to improve sleep. NSAIDs may also be helpful in selected cases. Lastly, an exercise program is a frequently overlooked but important part of the treatment regimen in patients with fibromyalgia.

OSTEOARTHRITIS

OA is the most common rheumatic disorder affecting adults in the United States. Over the past decade, knowledge concerning the biochemical and genetic mechanisms of OA development has dramatically increased. These data underscore the importance of viewing OA as a heterogeneous disorder with multiple genetic and metabolic causes and not simply as one entity. This approach has a major effect on the choice of therapy as discussed subsequently.

Some rheumatologists classify OA as being either primary or secondary. Primary OA implies an idiopathic cause. Secondary OA implies that the degenerative joint disease is a consequence of some other
Table 5. CAUSES OF SECONDARY OSTEOARTHRITIS

<table>
<thead>
<tr>
<th>Chronic joint disease</th>
<th>Metabolic disorder</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Hemoglobinopathy</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Spondyloarthropathy</td>
<td>Obesity</td>
<td>Posttraumatic</td>
</tr>
<tr>
<td>Crystalline arthropathy</td>
<td>Endocrinopathy</td>
<td></td>
</tr>
<tr>
<td>Infectious (septic) arthritis</td>
<td>Renal disorder</td>
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</tbody>
</table>

process affecting the joint. Most commonly, these include metabolic, traumatic, or other rheumatic conditions (Table 5). Even the entity of primary idiopathic OA, which was previously thought to be an inevitable and nonspecific degeneration of cartilage associated with aging, is being challenged by newer genetic and biochemical information. Studies of families with generalized OA occurring at an early age have identified specific genetic abnormalities most often in the COL2A1 gene, which encodes the α1 chain of type II collagen, the most abundant collagen isotype in articular cartilage. These patients develop Heberden’s and Bouchard’s nodes at an early age, often in their 20s. They also develop OA changes in the weight-bearing joints, such as the hips and knees. Clinically, women often presenting with prominent hand OA relate a history of that disorder in their mothers and grandmothers. Thus, it appears that a clinical subset of OA is familial and in some instances has a specific genetic basis. Another group of OA patients has been found to have congenital spondyloepiphyseal dysplasia. These patients develop precocious OA of the spine and the long bones secondary to disordered epiphyseal growth. Many of these individuals have also been found to have mutations in the COL2A1 gene. Inheritance patterns of spondyloepiphyseal dysplasia are variable and have been found to be autosomal dominant, autosomal recessive, and X-linked. It is apparent that OA is a genetically and clinically heterogeneous condition.

Erosive or inflammatory OA is a form of hand OA in which there appears to be active inflammation at the proximal interphalangeal and distal interphalangeal joints. Radiographs reveal typical but extensive OA changes with irregular erosion of cortical bone. It is speculated that deposition of crystals such as hydroxyapatite may be causative in the inflammatory response. Familial OA has been associated with hydroxyapatite deposition as well as calcium pyrophosphate deposition.

There has been a shift in philosophy concerning the management of OA over the past few years. Reasons for this include an increased realization of the role for physical measures, such as strengthening exercise and walking, in the management of OA and controversy regarding the use of NSAIDs for OA. In 1991, Bradley and colleagues published a report concluding that for patients with chronic knee pain and radiographic evidence of OA, anti-inflammatory doses of ibuprofen (2400 mg/day) were not superior to analgesic doses of ibuprofen (1200 mg/day) or acetaminophen (4000 mg/day). This report suggested that the risk-to-benefit ratio of NSAID administration for OA, especially in
elderly patients, was high, and it led to a general reexamination of prescribing patterns for elderly OA patients. Accordingly, guidelines for the management of OA of the knee (Fig. 1) published in 1995 by a subcommittee of the American College of Rheumatology list acetaminophen as the first-line therapy for knee OA. For elderly patients requiring NSAID therapy, a thorough understanding of common and uncommon NSAID adverse effects is mandatory (Table 6). Nonacetylated salicylates and newer NSAIDs that appear to inhibit cyclooxygenase-2 selectively are considered to be safer. Patients at higher risk for gastrointestinal complications (very elderly, multiple medical problems, chronic anticoagulation, prior peptic ulcer disease) should receive prophylaxis with misoprostol. Approximately 25% of patients are unable to tolerate misoprostol because of lower gastrointestinal problems (cramping, diarrhea). Should those patients require NSAIDs, proton-pump inhibitors (omeprazole) and H₂ blockers appear to provide some degree of protection.

**POLYMYALGIA RHEUMATICA AND TEMPORAL ARTERITIS**

PMR is a common musculoskeletal disorder affecting older individuals. Generally, PMR does not occur in people under 55 years of age, although it may occur on rare occasions. PMR most frequently occurs in whites and is about twice as common in women as in men. PMR is characterized by pain and stiffness in the cervical spine, shoulder, and hip girdle regions. Patients characteristically have significant morning stiffness (>1 hour) and stiffness after sitting for prolonged periods of time (gelling). On physical examination, joint inflammation is uncommon, and weakness of the proximal muscles is distinctly absent. Laboratory findings include elevated erythrocyte sedimentation rate (often markedly elevated), an increased α₂ fraction on serum protein electrophoresis, anemia, and elevated liver function tests (especially alkaline phosphatase).

**Table 6. COMMON AND UNCOMMON SIDE EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS**

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Respiratory</th>
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<tbody>
<tr>
<td>Gastropathy</td>
<td>Exacerbation of bronchospasm</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>Headache</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>Confusion</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Depression</td>
</tr>
<tr>
<td>Cardiovascular-renal</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Reduced glomerular filtration rate</td>
<td>Hematologic</td>
</tr>
<tr>
<td>Blunted response to antihypertensives</td>
<td>Easy bruisingability</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Increased bleeding time</td>
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<tr>
<td></td>
<td>Platelet dysfunction</td>
</tr>
</tbody>
</table>
Nonpharmacologic management (education, weight loss, exercise)

Local corticosteroid injection

Acetaminophen (up to 1 g 4 times/d) for pain

Topical capsaicin cream

For inadequate response add low-dose ibuprofen or nonacetylated salicylate

For inadequate response, use full-dose NSAID (with misoprostol if indicated)

If response inadequate and surgery contraindicated, consider joint lavage or arthroscopic debridement

If response inadequate, consider total joint arthroplasty


Treatment with low-dose corticosteroids (prednisone 10 to 15 mg/day) produces a dramatic clinical response, so much so that if the patient does not respond to this regimen within 2 weeks, the diagnosis should be reconsidered.
All patients in whom the diagnosis of PMR is made should be counseled about the association with temporal arteritis and advised to report any symptoms of temporal arteritis immediately. Approximately 15% to 20% of patients with PMR have an associated temporal arteritis. Conversely, nearly 50% of patients with temporal arteritis have a prior or coexisting history of PMR. Patients with temporal arteritis may complain of headaches, visual disturbance (diplopia, amaurosis), scalp tenderness, jaw claudication, or throat pain. Occasionally, patients with temporal arteritis may present with fever of unknown origin. On examination, the temporal arteries may be tender or indurated, and a pulse discrepancy between the two sides may be appreciated. Laboratory findings are similar to those seen with PMR. Patients with suspected temporal arteritis should have a temporal artery biopsy to try to confirm the diagnosis. Caution should be used in interpreting biopsy results, however, because the inflammation in temporal arteritis may skip areas and the biopsy may be falsely negative. A negative biopsy result in patients in whom there is a high clinical suspicion of temporal arteritis should not dissuade the physician from treating the patient. In contrast to PMR, treatment of temporal arteritis requires high-dose corticosteroid (prednisone 1 to 2 mg/kg/day). Treatment of suspected temporal arteritis is considered to be a medical emergency and should not be delayed waiting for the biopsy result because inflammation involving the ophthalmic branch may lead to irreversible visual loss. Because PMR/temporal arteritis is generally a disease of the elderly, a population already at risk for osteoporosis, patients treated with corticosteroids should be evaluated and treated for osteoporosis (see later). Studies have looked at the use of methotrexate as a steroid-sparing agent in the long-term treatment of PMR/temporal arteritis.15

OSTEOPOROSIS

Osteoporosis can be defined as a systemic skeletal disorder characterized by low bone mass and structural deterioration of bone with resultant increases in bone fragility and fracture risk. Epidemiologic data combined with advances in the diagnosis and treatment of osteoporosis have focused a great deal of professional and public attention on this disorder. Approximately 1 in 10 people in the United States is affected by osteoporosis; 80% are women. It is estimated that women at age 50 have nearly a 40% lifetime fracture risk resulting in more than 1 million fractures yearly. Approximately 0.5 million of these fractures affect the spine, and 0.25 million affect the hip.11 The economic impact of hospitalization and rehabilitation has been estimated to exceed $10 billion yearly. It can readily be seen that medical consequences of these fractures can be equally costly in terms of morbidity and mortality. Fractures may necessitate prolonged hospitalization or surgery with attendant risks of thromboembolic disease and infection. Prevention of osteoporosis should be a priority for clinicians caring for women.
The causes of osteoporosis are multifactorial but relate to the fact that bone is a metabolically active tissue constantly undergoing remodeling. Osteoclastic resorption of bone is normally counterbalanced by formation of new bone. When bone formation does not keep pace with bone resorption, osteopenia and osteoporosis occur. Excess bone resorption occurs with aging, lack of physical activity, and deficiency of calcium and gonadal hormones, especially estrogen. Bone mass peaks during the third decade of life. In the following years, there is a gradual decline in bone mass. When women reach menopause, however, bone loss becomes accelerated. It appears that in the absence of gonadal hormone, bone mass is perceived to be inappropriately high, and rapid resorption ensues. Poor intake of dietary calcium and reduced exposure to sunlight, which often occur with aging, result in elevated levels of parahormone and enhanced bone resorption. Known genetic and lifestyle factors appear to be associated with an increased risk of osteoporosis:

- White or Asian ethnicity.
- Family history.
- Thin habitus.
- Smoking.
- Nutrition (low calcium intake, vegetarian diet, anorexia/bulimia).
- Physical inactivity.
- Alcoholism.
- Early menopause.
- Exercise-associated amenorrhea.

Osteoporosis is an asymptomatic disorder until fracture occurs. Therefore, most effort should be directed toward detection and prevention of osteoporosis. In the peripheral skeleton, minor trauma may lead to fracture. Colles’ fracture of the wrist and femoral neck fractures are common. As spinal osteoporosis progresses and multiple compression fractures occur over time, progressive deformity gives rise to symptoms. Exaggerated kyphosis leads to the classic dowager’s hump appearance. Chronic paraspinal muscle contraction leads to chronic backache. Abdominal protuberance and early satiety may occur. More severe and relatively more acute back pain occurs with spontaneous vertebral fracture. Pain usually resolves in 3 to 4 weeks. Endocrinopathies, drug therapy, inflammatory disorders, and malignancy may result in secondary osteoporosis (Table 7).

Prevention of osteoporosis begins with a knowledge of the patient’s background and lifestyle. This knowledge enables the clinician to identify patients who are at risk (see previous list). The availability of accurate, reproducible methods to measure bone mineral density (BMD) in patients identified to be at risk has been a major advance in selecting patients for preventive treatments. Dual-energy x-ray absorptiometry and advanced quantitative computed tomography provide rapid, accurate, and reproducible measurements of BMD of the spine, femur, and forearm. It has been well demonstrated that fracture risk can be predicted by low bone mass. Standard radiographs should be used to
evaluate suspected fractures; however, they have no place in diagnosing osteoporosis because it is estimated that at least a 30% reduction of bone mass must occur before osteopenia is evident on x-ray film. It is extremely important that bone density measurements be compared with those of normal young adults (T score) and not age-matched controls (Z score) because definitions of osteopenia ($T < -1$ standard deviation) and osteoporosis ($T < -2.5$ standard deviation) are related to the T score. Assays for molecules indicative of rates of bone turnover are becoming available for routine clinical use. These include molecules that measure bone resorption (urinary hydroxyproline) and bone formation (serum osteocalcin). These assays may distinguish between states of high and low bone turnover and predict rates of bone loss and response to therapy. The clinical utility of these markers is currently under development.

The best treatment for osteoporosis is prevention. Women who are past their peak bone density period should receive supplemental calcium unless there are medical contraindications. Menopausal women should be considered for hormone replacement therapy. Estrogen replacement is the most effective means of preventing osteoporosis in perimenopausal women. In addition, it ameliorates the symptoms of menopause, it has protective effects with regard to the prevention of coronary artery disease, and early studies demonstrate that it may modify symptoms of Alzheimer’s disease. The decision to start estrogen replacement therapy should be based on the woman’s menopausal symptoms, cardiovascular risk, osteoporosis risk (as determined by BMD measurement), and risk for breast and endometrial carcinoma as determined in conjunction with the woman’s gynecologist. When BMD measurements indicate the presence of osteoporosis, estrogen replacement therapy is then used as treatment for osteoporosis, although the efficacy of estrogen replacement therapy in patients with long-standing osteoporosis and multiple fractures is not clear. By inhibiting bone resorption, estrogen can increase bone mass at 2% to 4% per year and can reduce vertebral fracture rate.22

Patients should receive the equivalent of 6.25 mg of Premarin cycled

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### Table 7. SECONDARY CAUSES OF OSTEOPOROSIS

<table>
<thead>
<tr>
<th>Endocrinologic disorders</th>
<th>Drugs</th>
</tr>
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<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>Heparin</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Lithium</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Phosphate-binding antacids</td>
</tr>
<tr>
<td>Gastroenterologic disorders</td>
<td>Cholestyramine</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Malignancy</td>
</tr>
<tr>
<td>Hepatobiliary disease</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Inflammatory disorders</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Systemic mastocytosis</td>
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or in combination with progesterone. The role of progesterone in patients who have had hysterectomy has not been established. The availability of newer oral bisphosphonates and intranasal calcitonin has greatly enhanced the clinician's ability to manage osteoporosis in patients who cannot be treated with estrogen. The first bisphosphonate to be available clinically is etidronate (Didronel). Etidronate can stabilize and possibly increase bone mass and may reduce vertebral fracture rate. Etidronate must be given in a cyclical fashion usually at 400 mg/day for 2 weeks every 3 months; otherwise, poor bone mineralization may lead to the development of osteomalacia. Alendronate has been approved for the treatment of osteoporosis. Given at a dose of 10 mg daily, alendronate can increase BMD at a rate of 8% per year. Side effects of alendronate include esophagitis, so that patients must be instructed to take alendronate with 6 to 8 oz of water and not to lie down for 30 minutes after the dose. Coadministration of calcium preparations or foods containing calcium dramatically inhibits the absorption of bisphosphonates. Calcitonin nasal spray has also been approved by the Food and Drug Administration for the treatment of osteoporosis. Calcitonin is an antiresorptive drug that also appears to have analgesic properties so that it may be of particular benefit in the immediate postfracture period. Side effects of calcitonin that previously limited its use, such as flushing and nausea, are rarely seen with the intranasal preparation. Efficacy of osteoporosis therapy may be assessed by interval BMD measurements.

It is becoming increasingly apparent that corticosteroid-induced osteoporosis is an important health issue facing thousands of patients on long-term glucocorticoid therapy for a variety of inflammatory, autoimmune, and neoplastic disorders. The prevalence of vertebral fractures in asthmatics on long-term steroid therapy for at least 1 year is 11%. Because bone loss may occur relatively early in steroid therapy, prompt attention to preventing or treating osteoporosis should be given to all patients embarking on steroid therapy. The American College of Rheumatology published recommendations for the prevention and treatment of steroid-induced osteoporosis. Included in these recommendations is the suggestion that all patients receive calcium and vitamin D supplementation unless there are medical contraindications. Patients starting corticosteroids should also have bone density measurements. Those who are osteopenic or osteoporotic (T score ≤ −1) should receive hormone replacement therapy unless contraindicated. In those patients for whom hormone replacement therapy is contraindicated, a bisphosphonate or calcitonin should be prescribed.

References


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