Osteoarthritis in Older Adults

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OBJECTIVE: This review highlights the clinical and pathophysiologic features of osteoarthritis (OA) of the peripheral joints and discusses the current and future management options for this common but potentially disabling disease. This article also addresses the contribution of osteoarthritis to falls and functional impairment in older people.


CONCLUSIONS: Osteoarthritis is the most prevalent articular disease in older adults. Disease markers that will detect early disease and allow early intervention with pharmacologic agents that modify, if not halt, disease progression are much needed, but they are presently unavailable. Current management should include safe and adequate pain relief using systemic and local therapies and should also include medical and rehabilitative interventions to prevent, or at least compensate for, functional deficits. Although OA can result in impaired mobility and lower extremity function, its contribution as a cause of recurrent falls or impaired self-care, relative to other comorbid conditions, remains ill-defined. Further analysis of the determinants of disability, loss of mobility and falls in older patients with OA is needed. J Am Geriatr Soc 46:216–223, 1998.

Arthritis and other rheumatic conditions are among the most prevalent chronic health problems in the United States. Osteoarthritis (OA) is the most prevalent articular disease among adults 65 years and older. This chronic degenerative arthropathy frequently leads to compromised function and loss of independence. This review will highlight the major clinical features of OA in the peripheral joints, current and future management, and the impact of this disease on older persons.

EPIDEMIOLOGY

Osteoarthritis is the most common articular disease of older adults. Reported incidence and prevalence rates of OA in specific joints vary widely, however, because of differences in the contributing risk factors and the case definition of OA (Table 1). OA may be defined by radiographic abnormal-

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Table 1. Estimates of Radiographic and Symptomatic OA by Location

<table>
<thead>
<tr>
<th>Location</th>
<th>Prevalence of Radiographic OA</th>
<th>Prevalence of Symptomatic OA</th>
<th>Incidence of Radiographic OA</th>
<th>Incidence of Symptomatic OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td>63–84% (\geq 55) yrs(^{3,11})</td>
<td>2–4% community based(^6)</td>
<td>30–71% clinic based(^7)</td>
<td>100(^8)</td>
</tr>
<tr>
<td>Knee</td>
<td>6–14% (\geq 55) yrs(^{12})</td>
<td>10–30% (65–79) yrs(^7,9,10)</td>
<td>2%/YEAR(^{10})</td>
<td>240(^{6,10})</td>
</tr>
<tr>
<td>Hip</td>
<td>3–6% (\geq 55) yrs(^{16})</td>
<td>1%(^4,7)</td>
<td>3–4% (\geq 55) yrs(^4)</td>
<td>88(^8)</td>
</tr>
</tbody>
</table>

disability than more sedentary individuals.\(^{23}\) Clarification of this issue, which impacts on treatment recommendations, is essential.

PATHOPHYSIOLOGY

Although the initiating events that trigger the development of OA are unknown, we will discuss recent advances that contribute to our current understanding of this disease and its pathogenesis.\(^{24–26}\) The importance of these recent advances is discussed further in the future therapies section.

Cartilage Constituents and OA

The viscoelastic and compressive properties unique to cartilage are imparted by its cellular and matrix constituents (shown in Figure 1). Under normal conditions, chondrocytes orchestrate the dynamic remodeling process and maintain extracellular matrix integrity by synthesizing type II collagen and glycosaminoglycans.\(^{24,25}\) OA, in simplistic terms, can be thought of as a process of cartilage matrix degradation to which an ineffectual attempt at repair is made. This degradative process depletes proteoglycans and compromises collagen ultrastructure integrity.\(^{25}\) Presumably in response to this degradative process, chondrocytes initially proliferate and secrete enhanced amounts of proteoglycan molecules.\(^{23}\) As the disease progresses, however, reparative attempts are outmatched by progressive cartilage degradation. Fibrillation, erosion, and cracking initially appear in the superficial layer of cartilage and gradually extend to deeper layers.\(^{25}\)

Aging and OA

The epidemiologic studies of OA discussed above suggest a strong association with aging. A critical question has been whether OA is a disease or a natural consequence of aging.\(^{28,29}\) Denatured type II collagen is found in both normal aging and OA cartilage although it is found more extensively in OA.\(^{29,30}\) OA and normal aging cartilage are also distinguished by relative differences in water content and the ratio of chondroitin-sulfate to keratan sulfate constituents.\(^{25,30,34}\) The expression of a chondroitin-sulfate epitope (846) in OA cartilage that is otherwise only present in fetal and neonatal cartilage provides further evidence that OA is a distinct pathologic process.\(^{31–33}\) A final but important distinction is that degradative enzyme activity is increased in OA but not in normal aging cartilage.\(^{28}\) Perhaps the association between aging and OA can be explained by the reduced functional chondrocyte density observed with aging that leaves cartilage vulnerable to the degenerative process that characterizes OA.

Mediators of Cartilage Remodeling

A number of soluble proteins have been implicated in the pathogenesis of OA because of their abilities to degrade, or induce repair of, cartilage (Figure 2). These include matrix metalloproteinases and proinflammatory cytokines that promote cartilage degradation and tissue metalloproteinases and cytokine inhibitors, growth factors, and, perhaps, oncogenes that foster reparative attempts.

*Matrix Metalloproteinases (MMPs)*\(^{24,27,35}\)

Cartilage degradation in OA appears to be primarily mediated by matrix metalloproteinases (MMPs) that are secreted by synovial cells and chondrocytes. Each of the three MMP enzyme classes (collagenase, gelatinase, and stromelysin-1) acts upon cartilage constituents with some specificity.\(^{24,27}\) Under normal conditions, MMP synthesis and acti-

![Figure 1. The cellular and matrix constituents of cartilage.](image-url)
Figure 2. The soluble proteins implicated in the pathogenesis of osteoarthritis. Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) mediate cartilage degeneration by stimulating metalloproteinase (MMP) and inflammatory prostaglandin synthesis and chondrocyte apoptosis. Growth factors such as Transforming Growth Factor-β (TGF-β) promote cartilage repair by directly stimulating collagen and proteoglycan (PG) synthesis and indirectly by stimulating synthesis and release of Interleukin-1 receptor antagonist (IL-1 RA) and tissue metalloproteinase inhibitors (TIMPs) that inhibit cartilage degeneration.

Interleukin-1 (IL-1)

IL-1 is a potent proinflammatory cytokine that is now believed to play a direct role in the pathogenesis of OA by inducing chondrocytes and synovial cells to synthesize MMPs, and inflammatory prostaglandins. Furthermore, IL-1 suppresses attempts of cartilage to repair itself by inhibiting synthesis of type II collagen and proteoglycans, and by interfering with transforming growth factor-β-stimulated chondrocyte proliferation. IL-1 also enhances nitric oxide production and induces chondrocyte apoptosis (programmed cell death). Under normal conditions, IL-1 activity is regulated by an endogenous IL-1 receptor antagonist. A relative excess of IL-1 and/or deficiency of the IL-1 receptor antagonist could conceivably result in the cartilage destruction that is characteristic of OA.

Growth Factors, Oncogenes, and OA

Local growth factors are also thought to take part in cartilage remodeling by mediating reparative attempts. Transforming growth factor β (TGF-β) is best characterized and most potent of the chondrocyte growth factors, and it is the only growth factor identified to date which aging chondrocytes maintain a proliferative response. It also induces chondrocyte synthesis of collagen and PG while counteracting cartilage degradation by downregulating IL-1 receptor expression and by increasing IL-1 receptor antagonist release and TIMP expression.

Insulin-like growth factor (IGF-1), basic fibroblast growth factor (b-PGF) and oncogene proteins c-MYC, c-FOS, and c-JUN and bcl-2 have all been demonstrated in OA cartilage. Their significance is largely speculative at this point.

In summary, MMPs and proinflammatory cytokines (e.g., IL-1) appear to be important mediators of cartilage destruction in OA. Synthesis and secretion of growth factors and of inhibitors of MMPs and cytokines are apparently inadequate to counteract these degradative forces. Progressive cartilage degradation and OA result. These recent discoveries represent an important step toward the development of future therapies that can be halting, if not reversing, disease progression.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Osteoarthritis is diagnosed by a triad of typical symptoms, physical findings, and radiographic changes. Patients with early disease experience localized joint pain that worsens with activity and lessens with rest while those with severe disease may have pain at rest. Weight-bearing joints may "lock" or "give way" as a result of internal derangement that is a consequence of advanced disease. Morning stiffness and stiffness following inactivity, also known as gel phenomena, rarely exceed 30 minutes. Physical findings in osteoarthritic joints include bony prominence, crepitus, and deficits in range of motion. Tenderness on palpation at the joint line and pain on passive motion are also common although not unique to OA. Progressive cartilage destruction, malalignment, joint effusions, and subchondral bone collapse contribute to irreversible deformity. Radiographic findings in OA, as shown in Figure 3, include osteophyte formation, joint space narrowing, subchondral sclerosis, and cysts.

Osteophyte presence is the most specific radiographic marker for OA although it is not present in early disease. The American College of Rheumatology has set forth classification criteria to aid in the identification of patients with symptomatic OA that include, but do not rely solely on, radiographic findings (Table 2). Osteoarthritis is one of many causes of musculoskeletal pain in older patients. It is important to identify patients with symptomatic OA correctly and to exclude conditions that may be mistaken for or coexist with OA. Periarticular pain that is not reproduced by passive motion and direct joint palpation suggests an alternate etiology such as bursitis, tendinitis, or periostitis. The distribution of painful joints is also helpful to distinguish OA from other types of arthritis because MCP, wrist, elbow, ankle, and shoulder arthritis are unlikely locations for OA except after trauma. Symptoms including prolonged morning stiffness (greater than 1 hour) should raise suspicion for an inflammatory arthritis such as rheumatoid arthritis. Intense inflammation on examination suggests an infectious or microcrystalline processes such as gout or pseudogout. Weight loss, fatigue, fever, and loss of appetite should be sought out because these are clues to a systemic illness such as polymyalgia rheumatica, rheumatoid arthritis, lupus, or sepsis.
DISEASE MARKERS

There has been considerable interest in identifying a biological marker for OA. Several investigators have searched actively for the ideal marker that is sensitive enough to detect early OA yet retains specificity for the disease, and reflects disease activity reliably. Current radiographic techniques lack the sensitivity required to detect early OA but remain useful in confirming the presence of more advanced disease. Routine laboratory studies (sedimentation rates, c-reactive protein) have proven uniformly useless as specific markers for OA.

Several of the cartilage constituents and degradative metalloprotease enzymes discussed earlier have been tested as potential markers for OA and are summarized in Table 3. The synovial fluid to serum ratio of cartilage-derived PG fragments has been shown to correlate more accurately with the presence of OA than single values isolated from source alone. Elevated serum hyaluronan levels have also been shown to correlate with radiographic OA. Discovery of a chondroitin sulfate epitope and its preferential elevation in the synovial fluids of patients with OA has been a promising development. Synovial fluid levels of this epitope correlate with both disease duration and extent of local inflammation; Serum levels appear to parallel the extent of systemic inflammation and are lower in patients with OA than in patients with inflammatory arthritis. The evidence of elevated cartilage oligomeric protein (COMP) levels in synovial fluid after traumatic joint injury may portend development of OA in the injured joint. Of the degradative enzymes, stromelysin (MMP-3) levels in serum and synovial fluid is the most promising because it correlates well with symptomatic joint involvement. However, MMP-3 is found at higher levels in patients with RA and, therefore, lacks specificity for OA. Others markers are listed in Table 3 but are either not easily accessible or lack the sensitivity and specificity required to consider them as potential OA markers.

LATE COMPLICATIONS

Older people are at high risk for developing disability, gait impairment, and recurrent falls. Difficulties with mobility, upper extremity function, household management, and self-care activities have been associated with arthritis and joint pain in several studies of community-residing older persons. It has also been shown clearly that arthritis acts synergistically with other concurrent chronic conditions, rather than simply additively, in impairing mobility in older adults. The high prevalence of OA in older people has led to its implication as an important contributor to these deficits in function.

Several studies have implicated OA as a cause of impaired ambulation and disability in performing self-care activities. A plethora of tools, including the self-report questionnaires and objective performance-based measurements listed in Table 4, have been used in various combinations to provide an accurate assessment of mobility and self-care in older people, but seldom have these studies defined OA with the same rigor. Unfortunately, these investigations have not pursued radiographic confirmation of OA, nor have these studies excluded other potential causes of functional impairment adequately. Therefore, the role of OA in the evolution of disability and functional decline requires further investigation.

This problem is also illustrated in studies of falls that are a leading cause of injury and death among older people. Because ambulation can be painful in patients with knee and/or hip OA, disturbances of gait, such as an adductor lurch or antalgic gait, are common and may themselves predispose to falls. King and Tinetti recently reviewed four prospective studies of risk factors for recurrent falls in older adults. Indeed, a self-reported history of “arthritis” and physical findings of painful or limited range of motion were predictive of recurrent nonsyncopal falls among community-residing older people, but again no radiographic confirmation of the diagnosis of OA was provided. Furthermore, these and other studies demonstrate clearly that a number of intrinsic and environmental factors other than OA contribute to risk of falling. These include lower extremity muscle weakness, deficits in balance, impaired visual, proprioceptive, and cognitive function, sedative medications, and comorbid medical conditions. Accurate estimation of the relative contribution of a single factor such as hip or knee OA, among this complex interplay of variables to the risk of falling, is daunting and has not yet been clearly ascertained. This problem also applies to residents of nursing homes and assisted living facilities, many of whom experience difficulty with ambulation or recurrent falls but in whom the prevalence of weight-bearing OA is unknown.
Table 2. Does the Clinical Presentation Meet ACR Criteria for the Diagnosis of OA?

<table>
<thead>
<tr>
<th>HAND OA</th>
<th>KNEE OA</th>
<th>HIP OA</th>
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<tbody>
<tr>
<td>Hand pain, aching or stiffness</td>
<td>Knee pain</td>
<td>Hip pain</td>
</tr>
<tr>
<td>And</td>
<td>And</td>
<td>And</td>
</tr>
<tr>
<td>Hard tissue enlargement of 2+ select joints</td>
<td>Radiographic osteophytes</td>
<td>2 or more of the following:</td>
</tr>
<tr>
<td>And</td>
<td>And</td>
<td>ESR &lt; 10mm/hour</td>
</tr>
<tr>
<td>Radiographic femoral or fewer than 3 swollen MCP joints</td>
<td>1 or more of the following:</td>
<td>acetabular osteophytes</td>
</tr>
<tr>
<td>And</td>
<td>Age ≥ 50</td>
<td>Radiographic joint space narrowing</td>
</tr>
<tr>
<td>2 or more DIP hard tissue enlargement</td>
<td>Morning stiffness &lt;30 minutes</td>
<td></td>
</tr>
<tr>
<td>Or</td>
<td>Crepitus on motion</td>
<td></td>
</tr>
<tr>
<td>Deformity in 2 or more select joints</td>
<td></td>
<td></td>
</tr>
</tbody>
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Select Joints = DIP, PIP, 1st CMC.

Table 3. Potential Markers of OA

<table>
<thead>
<tr>
<th>Cartilage Staining</th>
<th>Synovial Fluid or Serum</th>
<th>Urine</th>
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<tr>
<td>Denatured type II collagen</td>
<td>Pyridinoline crosslinks</td>
<td>Deoxypyridinoline crosslinks</td>
</tr>
<tr>
<td>Chondroitin sulfate 846 epitope</td>
<td>Type II procollagen peptide</td>
<td></td>
</tr>
<tr>
<td>Cartilage oligomeric protein</td>
<td>Cartilage oligomeric protein</td>
<td></td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Stromelysin (metalloproteinase 3)</td>
<td></td>
</tr>
<tr>
<td>IGF-1</td>
<td>Osteocalcin</td>
<td></td>
</tr>
<tr>
<td>Chondroitin sulfate 846 epitope</td>
<td>Chondroitin sulfate 846 epitope</td>
<td></td>
</tr>
<tr>
<td>Synovial/serum ratio</td>
<td>Synovial/serum ratio</td>
<td></td>
</tr>
<tr>
<td>Keratan sulfate</td>
<td>Keratan sulfate</td>
<td></td>
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</tbody>
</table>

Thus, although OA can impair mobility significantly, its contribution to overall disability, recurrent falls, and need for nursing home care requires further investigation. It is also important to understand whether OA-associated mobility and other functional impairments are mediated by painful symptoms, muscle weakness, structural damage, or other factors so that intervention strategies directed at modifying these mediators can be developed and implemented.

MANAGEMENT

Effective management of OA in older people should include concurrent pharmacologic and nonpharmacologic interventions (shown in Figure 4), with targeted goals of pain relief, and preservation of functional independence, mobility, and quality of life. Nonsteroidal anti-inflammatory agents exert their anti-inflammatory and analgesic effects by inhibition of prostaglandin synthesis via inactivation of cyclooxygenase (COX) enzyme(s). In addition to their inflammatory capacity, however, prostaglandins serve important physiological roles in the stomach and kidney. Consequently, reduction of prostaglandin levels in these organs can result in the well recognized side effects of NSAIDs, that is, gastric ulceration and renal impairment. Older people are at higher risk for these side effects by virtue of multiple comorbidities and diminished physiologic reserve. For example, adults older than age 60 who are taking NSAIDs have a 4.2- to 5.5-fold higher risk of gastrointestinal bleeding or ulceration then their age-matched counterparts. Furthermore, approximately 20 to 30% of all hospitalizations and deaths attributable to peptic ulcer disease in adults 65 years and older are NSAID related.

Renal toxicities include azotemia, proteinuria, and renal failure requiring hospitalization. Hematologic and cognitive abnormalities have also been reported with several NSAIDs.

Several of the newer NSAIDs may have less gastrointestinal and renal toxicity in older people. In short-term studies,
4. Functional Assessment Measures

Osteoarthritis specific indices
Lequesne algofunctional index
Western Ontario McMaster University (WOMAC) osteoarthritis index

General measures of function
Self report
Katz Activities of Daily Living
Instrumental Activities of Daily Living
Geriatric Arthritis Impact Scale

Objective performance upper body
Grip Strength
Pinch Strength
Dexterity

Objective performance lower body
Balance

Speed & Mobility
Gait evaluation

Squeeze the examiner’s fingers or maximum pressure squeezed with a rolled sphygmomanometer cuff inflated to 30mmHg
Patient firmly holds a piece of paper between the thumb and index finger while the examiner tries to pull the paper out.
Patient picks up a coin or small object from a table top or floor
Tandem gait and stance
Functional reach
"Get up and go" test
Tinetti Balance and Gait evaluation
Walk speed
Time to rise from a chair
Antalgic gait due to pain from weight bearing joint (knee or hip)
Trendelenberg lurch indicates gluteus medius weakness; often accompanies hip arthritis
Tinetti Balance and Gait evaluation

ibuprofen and etodolac, for example, were as effective as comparator NSAIDs in the relief of pain of knee OA but used fewer serious adverse events, including gastrointestinal ulcers, bleeding, and perforation. This apparent protective effect may be caused by the enhanced COX-2 selectivity of these agents compared with other NSAIDs (discussed later in Future Therapies section). However, although somewhat safer than nonselective agents, it would be best to avoid any NSAID in patients with known ulcer disease or nail impairment and in patients who would not endure these implications should they occur. Currently, acetaminophen remains the drug of choice for treatment of OA-related pain in older people. If acetaminophen proves inadequate for pain management, an NSAID in low dose or a nonacetylated salicylate is a reasonable second step in patients with normal nail function who have no prior history of gastrointestinal bleeding. Higher (anti-inflammatory) doses of NSAIDs should be reserved in this group for difficult-to-treat pain.

Monitoring of renal function should always accompany treatment with NSAIDs in older people; in addition, uphylectic treatment to reduce risk of gastrointestinal ulceration, perforation, and bleeding is recommended in patients more than 60 years of age with prior history of peptic ulcer disease, anticipated duration of therapy of more than 3 months, moderate to high dose of NSAIDs, and, concurrent corticosteroids. Several studies have demonstrated a significant protective effect of misoprostol when given as 200 mcg four times daily although it was poorly tolerated as a result of diarrhea. Initiation of cytotec may be better tolerated at 100 mcg, increasing, as tolerated, to 200 mcg two to three times daily although the lower dose is not protective. A histamine-2 blocker or omeprazole can be substituted in those intolerant to misoprostol; however, the efficacy of these drugs is limited to prevention of duodenal, but not gastric, ulcers.

Local therapies may include topical capsaicin and methyl salicylate creams as adjunctive agents in the management of knee pain and hand OA. Judicious use of intra-articular glucocorticoid injections is appropriate for older OA patients with effusions or local inflammatory signs. Periarticular injections may be effective in treating bursitis or tendinitis that may accompany OA. The need for four or more intra-articular injections suggests the need for orthopedic intervention.

NONPHARMACOLOGICAL MANAGEMENT

Recent guidelines set forth by the American College of Rheumatology (ACR) for the management of hip and knee OA highlight the importance of nonpharmacologic modes of therapy to relieve pain and improve joint biomechanics and overall function. These include local heat or ice, ultrasound, and stimulation with electrical devices (TENS) and weight
reduction in obese patients may also significantly relieve pain by reducing biomechanical stress on weight-bearing joints. The use of proper orthotic devices and shock-absorbing shoes compensate for permanent functional deficits and are protective. The ACR guidelines also acknowledge the importance of exercise as an integral part of OA management. Recent evidence indicates that joint loading and mobilization are essential for articular integrity. In addition, quadriiceps weakness develops early in OA and may contribute to progressive articular damage. Recent studies of community-residing older adults with symptomatic knee OA have shown improvements in physical performance, painful symptoms, and reports of disability after 3 months of aerobic or resistance exercise. Others have shown that resistive strengthening and weight-bearing range of motion improves gait, strength, and overall function. Low-impact or gravity-limiting activities, including water-resistive exercises or bicycle training, may achieve increased muscle tone and strength, neuromuscular function, and cardiovascular endurance without excessive force across, or injury to, joints. Studies of nursing home and community-dwelling older adults demonstrate clearly that one additional important benefit of exercise is a reduction in the number of falls.

SURGICAL MANAGEMENT

Patients whose function and mobility remain compromised by persistent pain despite maximal medical therapy, and those with structural instability, may be considered for surgical intervention. Surgical options in management of osteoarthritis include arthroscopy, osteotomy, and arthroplasty. Surgical removal of intra-articular loose bodies and resection of torn tissue can be achieved by way of arthroscopy in knee OA and, less often, in hip OA. Tibial osteotomy may achieve significant pain relief for patients with knee OA that has a relatively small varus angulation (less than 10 degrees) and stable ligamentous support. Total knee arthroplasty is recommended for patients with more severe varus or any valgus deformity and ligamentous instability. Joint replacement is also an option for patients with knee OA with significant deformity or ligamentous instability, those who have ineffective pain relief following a tibial osteotomy, and patients with advanced hip OA. Total joint prostheses are used most commonly in surgical replacement in older adults, largely because of the extent and severity of disease. Patients who have not yet developed appreciable muscle weakness or generalized or cardiovascular deconditioning and who could medically withstand the stress of surgery are ideal surgical candidates. In contrast, full mobility and function may not be realistically achieved in the presence of significant cognitive impairment or function-limiting cardiopulmonary disease because these conditions can impede postoperative rehabilitation. Furthermore, patients with genu recurvatum associated with muscular weakness and paralysis, gross quadriiceps weakness, and active sepsis should not undergo joint replacement.

FUNCTIONAL ASSESSMENT

Accurate and reliable assessment of function is the foundation for the preservation of mobility and self-care function and is important to the management of OA in older people. Two outcome measures (the Lequesne index and the WOMAC scale) have been validated and reliably assess pain and functional limitations attributable to weight-bearing OA. Although most clinicians have some familiarity with the self-report questionnaires of daily activities and arthritis impact questionnaires, performance-based measures may detect functional deficits earlier than self-report measures. Although not specific to OA, performance-based measures — including grip strength, timed walk, sequential chair-stands, and others listed in Table 4 — can provide the clinician with valuable information about the patient's current level of function. Studies are currently under way to evaluate the utility of these and other performance-based measures in the evaluation of OA related disability.

FUTURE THERAPIES

Exciting new developments in the formulation of NSAIDs may prove effective in reducing their gastrointestinal and renal toxicities. Two forms of the COX enzyme are now recognized. COX-1, which is constantly (or constitutively) expressed in most cells, generates the protective prostaglandins of the stomach and kidney. The expression of COX-2, on the other hand, is induced only in states of inflammation. This discovery has generated intense interest in identifying or developing drugs that selectively inhibit COX-2. Several drugs that satisfy this requirement (i.e., demonstrate a 1000-fold higher sensitivity for inhibiting COX-2 compared with COX-1) are now in clinical trials and appear to be effective analgesics (ACR abstracts). If these studies confirm a reduction in gastrointestinal and renal toxicity, as would be predicted with selective COX-2 inhibition, it is likely that this new class of agents will displace currently available NSAIDs (all of which are either nonselective or demonstrate only mildly the selective inhibition of COX-2) from the market. It should be kept in mind, however, that NSAIDs, no matter what their selectivity, do not alter the natural history of OA, and a disease-modifying therapy is still needed.

Advances in our understanding of the factors that contribute to the pathogenesis of OA (discussed earlier) provide a foundation on which we can develop innovative therapies...
n suppress cartilage degradation and/or enhance car-
age repair and, thereby, halt disease progression. To
suppress degradation, the putative imbalance in TIMP to
MP levels (defined above) must be shifted in favor of
the former. This could be accomplished by enhancing articular
levels of TIMP through the use of recombinant gene therapy
by administration of exogenous TIMP. Studies to date in
high recombinant TIMP was given to animals with arthritis
we had inconclusive results, however, perhaps because of
effective penetration of this relatively high molecular
weight protein into the cartilage matrix. 109, 110 The develop-
ment of synthetic small molecular weight inhibitors of MMPs is
proceeds more rapidly; in fact, several of these oral
inhibitors have proven to be effective in animal models of
arthritis and should soon be entering Phase I clinical trials in
humans. 111, 112 The potent MMP inhibitory properties of
traceycline and its semisynthetic derivatives, doxycycline
and minocycline, have prompted investigations of these
gents in the treatment of both OA and RA. 113 Finally,
bilateral of IL-1, via administration of a soluble IL-1 recep-
tor or receptor agonist, represents another rational strat-
agy for suppressing MMP synthesis, and preliminary studies
on RA are also promising. 114

Replenishment and maintenance of the extracellular ma-
xix of cartilage is a second desirable goal in the treatment of
OA. Administration of growth factors, such as IGF and
FGF, to stimulate chondrocyte proliferation and/or matrix
esis has had beneficial effects in animals models of OA,
GF-β has the added advantage of suppressing MMP
ynthesis. 40, 114 Another approach is to transplant healthy
urologic chondrocytes that have been genetically engi-
neered to overexpress one or more of these growth factors,
the cartilage repair site. 36, 114 Because the area of
articular loss in OA can be quite extensive and because older
chondrocytes are likely to be less metabolically active than
young chondrocytes, it remains doubtful that this transplanta-
tion approach will be practical in the treatment of OA
finally, as suggested recently by Brandt, 116 we should not
exclude preliminary interventions directed at modifying dis-
ase process in subchondral bone, joint capsule, ligaments,
and periarticular muscles as a means to managing OA.

CONCLUSIONS

Osteoarthritis remains the most prevalent articular dis-
ase in older people. Disease markers that will detect early
disease and allow early intervention with pharmacologic
gents that modify, if not halt, disease progression are much
needed, but, at present, they are unavailable. Current man-
agement should include safe and adequate pain relief using
systemic and local therapies, and it should also include med-
cal and rehabilitative interventions to compensate for, if not
prevent, functional deficits. Although OA clearly causes
impaired mobility and decreased lower extremity function, its
contribution to recurrent falls and impaired self-care, among
other comorbid conditions, remains to be fully clarified.

Interventions into the determinants of disability, loss of
mobility, and falls in older patients with OA are currently
under way.

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