OSTEOARTHRITIS: UNDERSTANDING THE PATHOPHYSIOLOGY, GENETICS, AND TREATMENTS

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Risk factors for developing osteoarthritis include age, previous joint injury, obesity, and a genetic predisposition. An imbalance of joint functioning initiates the disease process, which is then worsened through biochemical changes in the collagen in the joint. Joint pain is the cardinal clinical presentation. Radiographic and lab testing do not correlate well with the disease; therefore, diagnosis is made by clinical findings. Treatment focuses on maintaining joint function through the use of directed activity, physical therapy, and medications. (J Natl Med Assoc. 2003;95:475-482.)

Key words: osteoarthritis ♦ degenerative joint disease ♦ chondrocytes ♦ osteotomy ♦ subluxation ♦ joint pain ♦ osteophyte ♦ NSAIDS ♦ symptomatic slow acting drugs for osteoarthritis (SYSADOA)

Osteoarthritis (OA) is a non-inflammatory disease characterized by progressive loss of joint articular cartilage that results in pain and deformity. The disease is also known as degenerative arthritis, degenerative joint disease (DJD), and osteoarthrosis. Epidemiologic data on OA varies depending on the source but the general consensus is that it is the most common joint disease affecting approximately 20-million Americans. Although people can be affected by OA at any age, is it most prevalent in the older population, with 65% of individuals over 65 years old having radiographic evidence of the disease in at least one joint.[1] The disease will become even more prevalent as the cohort of baby boomers grows older in the near future.

The disease can significantly affect one's quality of life. OA is the most common cause of disability in the United States, making up 17% of all disabled adults.[28] It results in trouble walking and climbing stairs, with approximately 100,000 Americans unable to independently walk from bed to bathroom because of OA of the knee or hip.[7] Even though the prevalence of OA is similar in both races, African Americans are about 1.5 times more likely to activity limitation attributed to OA.[37]

RISK FACTORS

Risk factors for primary OA include increasing age, history of injury to the joint (trauma, repetitive stress, inflammation, etc.), and obesity. Secondary OA can develop as a result of any physical, metabolic, or chemical injury to the joint such as congenital or developmental bone malformations (Legg-Calve-Perthes disease or SCFE),

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metabolic diseases (alcaptonuria, hemochromatosis, Wilson's disease), endocrine (acromegaly, hyperparathyroidism, DM, hypothyroidism), abnormal calcium deposition (calcium pyrophosphate dihydrate deposition, apatitie arthropathy), other bone/joint diseases (AVN, RA, gout, infection, osteoporosis), neuropathic (Charcot joints), and even such entities as frostbite, Caisson's disease, and hemoglobinopathies.

GENETICS

The details of genetics of OA are unknown at this time. There is, however, a significant genetic component. Spector et al. showed in 1996 in a classic female twin study that there was higher incidence of radiographic OA of hands and knees in identical twins than non-identical twins. Overall genetic influence on radiographic OA of hands and knees in women was estimated at 39-65%, independent of known environmental or demographic factors.[13] Demissie and colleagues took the Framingham Heart Study cohort and their offspring and tried to establish a genetic linkage of hand OA. They used LOD scores to establish the linkage based on the radiographic evidence and found evidence for presence of hand OA susceptibility genes on chromosomes 7, 9, 13, and 19.[2] Similar studies suggest loci in areas of chromosomes 2q for susceptibility to nodal OA and 11q for female-specific susceptibility to severe hip or knee OA.[14,15] Further investigations are needed to confirm these linkages and determine the exact genes.

ETIOLOGY AND PATHOPHYSIOLOGY

Despite the high prevalence and morbidity of primary OA, the cause is still unknown. The prevailing thought is that the imbalance in the joint loading or excessive joint loading causes the initial damage that slowly progresses. Numerous studies have uncovered the changes in biochemical, cellular, and metabolic processes in the osteoarthritic joint cartilage.[3] The general pathologic changes include softening and focal disintegration of the articular cartilage and the formation of osteophytes at the joint margins leading to joint pain and deformation. It has been shown that the water content of an osteoarthritic joint is increased due to the weakening of the collagen network, which normally prevents the highly hyrophilic proteoglycans from absorbing too much water. Type IX collagen, which is normally present in the joint cartilage, is thought to "glue" the main type II collagen fibers together and prevent their slippage over each other. Collagen analysis in the osteoarthritic joint shows marked decrease in type IX collagen content, which could explain the weakening of the collagen network. In addition, the concentration of proteoglycans falls sharply with advancing age and may decrease by over 50%.[4]

BIOCHEMISTRY

The metabolic changes affecting the joint in OA include an increase in synthesis and secretion by chondrocytes of active matrix-degrading enzymes, such as stromelysin and collagenase. These enzymes are able to break down all of the components of the extracellular matrix and rapidly degrade the articular cartilage. Such derangement in the joint cartilage structure and metabolic state is thought to be due to activation of chondrocytes by increased levels of interleukin-I (IL-1) to produce matrix-degrading enzymes. At the same time there is a decrease in the concentration of the substances such as TIMP-1, TIMP-2, and PAI-1 that are inhibitory to the metalloproteases stromyelisin and collagenase. It is not known why the IL-1 level increases while TIMP and PAI levels decrease. The overall result is gradual but irreversible degradation of the artricular cartillage, formation of osteophytes, and subsequent pain and deformity.

The key question is why and how this process begins. The data is very limited due to the inability to study the early asymptomatic phase of disease in humans. All of the existing data is based on secondary osteoarthritis in animal models. The first alteration seems to be an increase in water content of the cartilage—indicating weakening of the collagen network as described above. This is followed by initial increase in proteoglycan content but eventual decrease below the baseline.

This, in turn, leads to loss of compressive stiffness and elasticity and an increase in water permeability (improving diffusion of degradative enzymes).

Another insight given by the research in animal models of OA is the importance of the inflammatory component, which was previously thought to be only a secondary phenomenon. IL-1 plays the key role, as mentioned above. TNF-alpha also seems to play a significant role. Both cytokines upregulate production of metalloproteinases, as well as blunt the chondrocytes' mechanisms for the extracellular matrix repair. Further exacerbating the metabolic picture is the fact that the IL-1 receptors are upregulated in the OA tissues and that the production on the IL-1 receptor antagonists is decreased, making the cytokine even more effective at cartilage degradation.[27]

STRUCTURAL CHANGES

The reasons for formation of the osteophytes, that are at least partially responsible for the joint deformity and pain in OA, are unclear. Some possibilities include increase in vascularity of the basal layers of the degenerating cartilage, improperly healing stress fractures in subchondral trabculae near subchondral margins, or venous congestion in the bone.[3] In animal models, joint immobilization seems to prevent osteophyte formation, glucocorticoid administration decreases their size and prevalence, and biphosphonate therapy does not affect their formation.

The prevalent opinion on the cause of OA is that it results from progressive fatigue failure, or, in other words, prolonged wear and tear. This would explain geometric increase in incidence of OA with age, as well as prevalence of OA in joints that are most used, not necessarily weight bearing (ankle in ballet dancers, MCPs in boxers, elbow in baseball pitchers, etc.). Some studies supporting this idea show that articular cartilage alone cannot handle the entire force load during the joint movement. Much of the force is transmitted to and absorbed by the subchondral bone and periartricular muscles. Some recent studies suggest that in OA the elasticity of the subchondral bone is decreased due to increase in its mineral density.[5,6] Several other studies suggest quadriceps strengthening is beneficial in prevention and treatment of knee OA.[10,11,12]

Others argue that the cause is not the wear and tear itself but the decrease in reparative abilities with age. Some biochemical findings listed above point to this, namely elevation in IL-1 and decrease in TIMP and PAI leading to unopposed degradation of the cartilage matrix by metalloproteinases.

A third opinion is that osteoarthritis is not a single disease but separate entities with a common final pathway. They separate primary OA into knee OA and hip OA, explaining that they have different risk factors and, therefore, could be distinct diseases, generalized OA, which is more dependent on systemic factors (such as genetic predisposition) than on local (i.e. mechanical) factors. They further divide the hip OA into hypertrophic, associated with pyrophosphate crystal deposition and diffuse idiopathic skeletal hyperostosis, and atrophic, associated with basic calcium phosphate crystals and osteoporosis.[9]

CLINICAL PRESENTATION

The main feature of the clinical presentation of OA is joint pain. The pain is usually a deep ache localized to the joint. It is typically aggravated by joint use and relieved by rest (in advanced OA the pain might be constant). If stiffness of the involved joints after rest is present, it usually lasts less than 20 minutes. It should be noted that the articular cartilage has no nerve endings and the pain comes from such structures as nerve endings in periosteum of osteophytes, microfractures of the subchondral bone, stretching of the joint capsule, periartricular muscle spasm, or synovitis in advanced OA.

While OA diagnosis is made clinically, the x-ray findings include asymmetric joint space narrowing, subchondral bony sclerosis in most loaded areas due to bones rubbing on each other (eburnation), and in advanced cases, subchondral bony cysts from leakage of synovial fluid into the subchondral bone. The laboratory findings in primary OA are usually normal except for possible mild

leukocytosis in the synovial joint fluid (less than 2000 WBC/L, mostly mononuclear cells). The laboratory specimens are usually obtained to rule out other causes of joint pain.

OA can affect any movable, synovial-lined joint, but the location is mostly influenced by which joint has been overloaded in the past, as discussed above. Weight-bearing joints are considered the most important ones affected, but not the only ones. The DIP and PIP joints in the hand are common sites for primary (idiopathic) OA. It is characterized by development of bony enlargements over distal interphalangeal joints (Heberden's nodes) and proximal interphalangeal joints (Bouchard's nodes). These nodes can be painful, especially if they develop fast, but once present, they are usually non-tender and do not interfere with the range of motion in the joints. Absence of the nodes does not, however, rule out OA.

The second most common site of OA in hand is the 1st CMC joint (thumb base). Patients usually complain of swelling, tenderness, and crepitus on movement. Osteophyte development may lead to "squared" thumb base. Pain on motion of this joint also can lead to contracture of the first web space and hyperextension of the first metacarpophalangeal joint, which is similar to the swan-neck deformity seen in rheumatoid arthritis.

OA in the hip is most commonly secondary to congenital or developmental malformations such as acetabular dysplasia, Legg-Calve-Perthes disease, and SCFE. The pain is usually referred to the inguinal area and is worse on internal rotation. Gradual capsular fibrosis and growth of osteophytes result in progressive decrease in the range of motion of the hip joint.

The knee joint has been found to be involved more frequently in females than in males. The osteoarthritic knee joint is usually tender to palpation, contains osteophytes, and has bony crepitus on movement. Depending on which compartment is involved, the knee could go into either valgus or varus deformity. If the patellofemoral compartment is involved, one can elicit positive "shrug" test (pain on manually pressing patella against femur). However, in this case the evaluating physician must rule out another disease—chondromalacia patellae, which is characterized by bilateral patellofemoral compartment pain in teenagers and young adults (more commonly women). It is usually non-progressive, caused by patellar misalignment, and is treated by NSAIDs, physical therapy, and corrective surgery.

OA of the spine is characterized by involvement of apophyseal joint, localized pain, and stiffness. It can also involve intervertebral disks and paraspinous ligaments. Notably, the cervical spine involvement is more common in women. Possible neurologic complications include compression of nerve roots by osteophytes, disk prolapse, and subluxation of an apophyseal joint, resulting in radicular pain and motor weakness.

COMPLICATIONS

The general complications of OA include loss of range of motion, extremity deformity due to asymmetric loss of joint space, subluxation, ankylosis or complete bony fusion of a joint, and intraartricular loose bodies related to subchondral fractures.

TREATMENT

OA remains an irreversible disease of unknown etiology. The goal of the treatment is to reduce pain, improve or maintain mobility, and minimize disability. The initial step is to reduce joint loading by discontinuing the offending activity (i.e. pitching, working with the jackhammer, etc.), improving posture, losing weight if obese, wearing splints and/or braces, using wedged insoles to correct abnormal biomechanics due to varus deformity of the knee, and using cane, crutch, or walker. Physical therapy should be aimed at increasing the range of motion and improving strength in periartricular muscles. Ettinger and colleagues showed that quadriceps strengthening and aerobic exercises for patients with knee OA resulted in approximately 10% improvement in functional outcomes, even though there was no radiographic evidence of recovery[11] Angst et al. also measured outcomes in patients with hip and knee OA undergoing a three-month structured exercise program. They showed greatest responsiveness to exercise in women and

in knee OA and less in men and hip OA.[29]

There are numerous studies showing benefits of weight loss. For example, Felson and colleagues showed that decrease in weight by 5.1 pounds over 10 years resulted in 50% decrease in risk of developing OA.[30] Another study showed that weight loss combined with exercise resulted in improvements in both functional and pain outcomes, as well as health-related quality of life status.[31]

From the beginning, the patients should be educated on the disease, treatment options, and prognosis and encouraged to participate in a self-management program such as the Arthritis Foundation Self-Management Program. Occupational therapy can also be useful, if needed, to assist patients with activities of daily living.

The most recent American College of Rheumatology recommendations came out in 2000. The pharmacologic therapy for now is limited to pain relief and should always be preceded by or combined with nonpharmacologic strategies listed above. The first line agent for relief of mild-to-moderate joint pain may be acetaminophen, since it is comparable with the pain relief provided by the previous first line agents—NSAIDs.[8] Even though a number of patients do not respond to acetaminophen, it should be attempted first because of its efficacy, low cost, and low toxicity profile. It should be noted that daily dose should not exceed 3 gm to avoid liver toxicity. If acetaminophen fails to bring pain relief, the next agent should be a cyclooxygenase 2 (COX-2) specific inhibitor. This class of drugs has a similar mechanism of action as NSAIDs, lower GI toxicity, and convenience of once-daily dosing.

The next class of agents to be tried is nonsteroidal anti-inflammatory drugs (NSAIDs), since they have proven efficacy in treating joint pain. These drugs are especially useful if there is an inflammatory component, such as joint effusion. However, before starting on NSAIDs, patients must be evaluated for risk factors for serious upper gastrointestinal and renal toxicity (such as active peptic ulcers or renal failure). Those with an increased risk of GI side effects may take such GI-protective agents as misoprostol or proton pump inhibitors. It should be noted that some patients may achieve pain relief with some NSAIDs, while others may not. Therefore, at least six NSAIDs are usually tried before declaring a patient unresponsive to this class of drugs. A new alternative to the classic oral NSAIDs is the topical formulation. Existing data shows that topical NSAIDs are just as effective for treatment of joint pain and carry lower risk of serious side effects than their oral counterparts, as would be expected, considering their low systemic circulation.[17]

Other oral agents to treat joint pain in OA include paracetamol, an acetaminophen-like analgesic.[18] Pure analgesics such as tramadol and opioids also are recommended in cases refractive to other oral therapies. Finally, other topical analgesic agents for OA include capsaicin and methylsalicylate.

The new category of drugs for OA are called symptomatic slow acting drugs for osteoarthritis or SYSADOA and include glucosamine sulfate, chondroitin sulfate, diacerein, and hyaluronic acid. These agents are new and the evidence of their efficacy is incomplete. Intraartricular injections of hyaluronan have been shown to delay progression of knee OA, decrease pain, and increase functionality.[19] Oral chondroitin sulfate and glucosamine sulfate has been shown to decrease OA pain and improve function.[20,21] These agents might be useful in patients who cannot take or have already failed therapy with acetaminophen, NSAIDs or COX-2 inhibitors.

For short-term management of acute exacerbation of pain with or without effusion, an intraartricular injection of long-acting steroid may be beneficial.[18] The effect lasts only several weeks. However, care should be taken to avoid excessive injections (more than twice a year) as they could lead to steroid arthropathy and tendon rupture.

Current advances in research on pathophysiology and biochemical derangements in OA, reviewed above, have resulted in numerous new pharmacological targets, offering a possibility to not only improve the symptoms by also modify the disease. Neutralization of inflammatory agents,

such as IL-1 and TNF-alpha, is one of the possibilities. Soluble IL-1 receptor antagonists have been shown to decrease metalloprotease transcription in a rabbit model.[27] Another potential strategy is to stimulate chondrocyte compensatory biosynthesis pathways with such agents as TGF-beta or insulin-like growth factor-1. There are also anti-inflammatory cytokines, such as IL-4, IL-10, and IL-13. IL-4 has been shown to be just as effective as low-dose dexamethasone in suppressing IL-1 and TNF-alpha synthesis.[27] Futher animal, and eventually human trials are necessary to confirm efficacy of these agents. Future research in OA pathophysiology is necessary as it is likely to produce even more drug targets for an eventual medical cure for OA.

SURGICAL THERAPY

For now, however, the only definitive treatment for OA is surgical. Such treatment on OA joints should be attempted only if all the non-operative options have been exhausted, and the goal should be to decrease pain and improve mobility. The least extensive treatment is tidal irrigation. It is mostly performed on knee and shoulder joint and involves washing the joint space with large amounts of saline to remove fibrin and debris (usually while performing arthroscopy of the joint). Other surgical options include osteotomy, which is used in mild cases of OA and mostly involves removing painful osteophytes. The most intensive procedure is total joint replacement, which is used in severe cases and is considered to be the definitive treatment. There also is the new and experimental technique of abrasion arthroplasty. This involves stripping the damaged cartilage off of the entire joint surface and allowing it to be replaced by new cartilage. However the new cartilage is weaker and immature. There is no concrete data yet to show that this procedure is effective and further studies are needed.[9]

It should be noted that there are marked racial disparities in the surgical treatment of OA. White men are 3 to 5.1 times more likely than African American men to receive a total knee replacement.[32] Similar disparity is found in total hip replacements.[33] The differences in access to healthcare were not enough to explain such a disparity. Ibrahim and colleagues surveyed African American and white VA patients with chronic knee or hip pain on their willingness to undergo a total joint replacement.[34] African American patients were found to be less knowledgeable about the procedure, had worse expectations of outcome, and were less willing to undergo a joint replacement surgery if it was needed and recommended by a physician. This difference in willingness was attributed to the worse post surgical expectations. These perceptions could, at least in part, be based on truth. Katz has shown that African American patients are at higher risk of complications from joint replacement therapy.[35]

ALTERNATIVE THERAPIES

There are many alternative therapies for OA, ranging from herbal remedies, to massage therapy, to chiropractic manipulations, to acupuncture.[22] Despite their immense popularity, alternative therapies are still poorly researched and their benefits are unclear due to scarcity of traditional randomized, placebo-controlled, double-blind studies. Institute of Health & Community Studies in Bournemouth, UK, recently conducted a meta analysis of such studies to determine benefits of various herbal therapies for treatment of osteoarthritis.[23] In general, the review showed that all herbal remedies were well tolerated by the patients, without significant side effects. However, overall scarcity of well-designed studies made it difficult to reliably assess efficacy of herbal remedies in treatment of OA. They found sufficient evidence for beneficial effect of avocado/soybean unsaponifiables (ASU) in improving function and decreasing pain. The studies showed 39% improvement with ASU vs. 18% with placebo at the end of trial and 48% improvement with ASU vs. 26% with placebo at a two-month follow-up. Of note: patients with hip OA had significantly greater improvement than patients with knee OA. The reviewers did

not find sufficient evidence to prove anti-OA benefit of such herbs as capsaicin topical cream, tipi tea, and Reumalex tablets (a combination of five herbs: guaiacum resin, black cohosh, white willow, sarsaparilla, and poplar bark).

In addition to clinical trials, there is some basic science evidence of benefits of herbal remedies in treatment of OA. Choi et al. have recently showed that the natural product named SKI 306X (a combination of Clematis madshurica, Trichosanthes kirilowii, and Prunella vulgaris) had beneficial effect on cartilage in collagenase-induced rabbit OA model.[24] SKI 306X inhibited proteoglycan degradation *in vitro* and protected rabbit joints from OA-like changes *in vivo* when given prophylactically.

Some non-pharmacologic alternative medicine modalities, such as acupuncture, T'ai Chi and even application of leeches at periartricular sites have also been found to benefit patients with OA.[25,26,36]

CONCLUSION

OA is a serious illness that affects one's quality of life and could have lethal complications. It is a very common disease and, with the aging population, it is becoming an even greater public health concern. Currently, extensive work is being done to determine the etiology of the disease and refine prevention strategies, as well as to design better medical and surgical treatments that will provide further symptomatic relief, and possibly, stop or reverse the degenerative processes in the joint cartilage. Considering that more and more evidence is coming out about efficacy of alternative therapies in treatment of OA, as well as their safety profile and popularity among general population, a physician should seriously consider including these options in their general treatment plan for OA.

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