

Pathogenesis and Epidemiology of Osteoarthritis

ROY K. AARON, MD; JENNIFER RACINE, BA

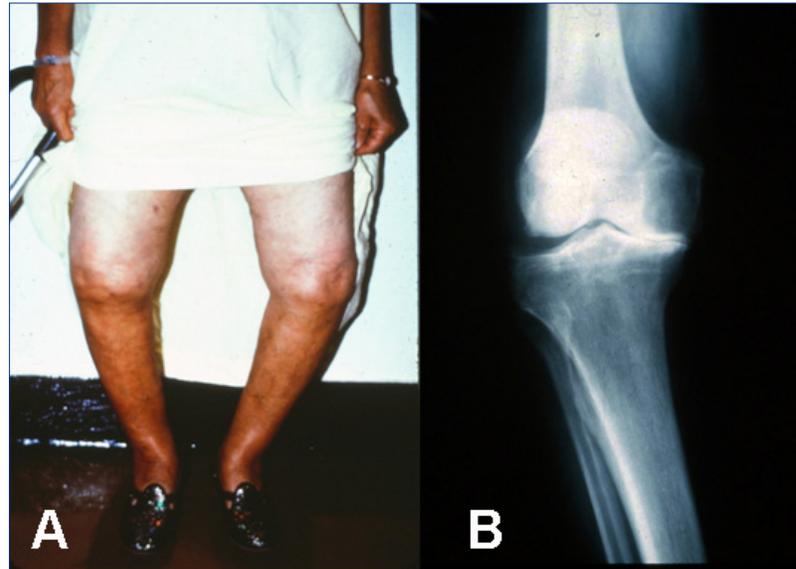
ABSTRACT

Osteoarthritis (OA) is a disease of high prevalence that produces substantial morbidity and is a leading cause of physical and psychological disability and expense, including time lost from work, medical care, and disability support. Until recently, the focus of research into the pathophysiology of OA has been on articular cartilage and has not resulted in either biomarkers of OA activity or effective targets for disease-modifying therapy. The contemporary paradigm of OA considers involvement of all joint tissues. It has been shown that, in later-stage OA, bone blood flow and oxygen content are markedly reduced and have a deleterious effect on bone cells, inducing them to release proteins (cytokines) that contribute to the bone remodeling and cartilage breakdown seen in OA.

KEYWORDS: Osteoarthritis, pathophysiology, articular cartilage

Pathogenesis

The contemporary paradigm of osteoarthritis (OA) is that its pathogenesis involves all joint tissues including cartilage, bone, synovium, ligamentous capsular structures, and surrounding muscle. It is characterized structurally by active bone remodeling, degradation of articular cartilage, and synovial inflammation resulting in loss of joint function and angular deformity or malalignment. A focus on the articular cartilage pathology has not led to novel biomarkers or therapeutic targets and many pharmaceutical manufacturers; notably, AstraZeneca, Pfizer, and Stryker Biotech have discontinued their OA research programs because disease modifying drugs were thought unlikely to be developed soon. Although a variety of synovial fluid markers provide insight into the biological response of joints to injury, no chemical or anatomic (imaging) biomarkers have been identified that monitor the development and progression of OA or the response to therapy. Certain factors increase the risk of developing OA, such as repetitive trauma/loading, joint injury, age, obesity, physical activity, bone mineral density (BMD), and in some subgroups, congenital anomalies. OA is thought to be highly cytokine-driven, and is associated with mechanical stress resulting from overloading of subchondral bone from dysplasias, malalignment, and trauma. Interest has been focused recently on small protein

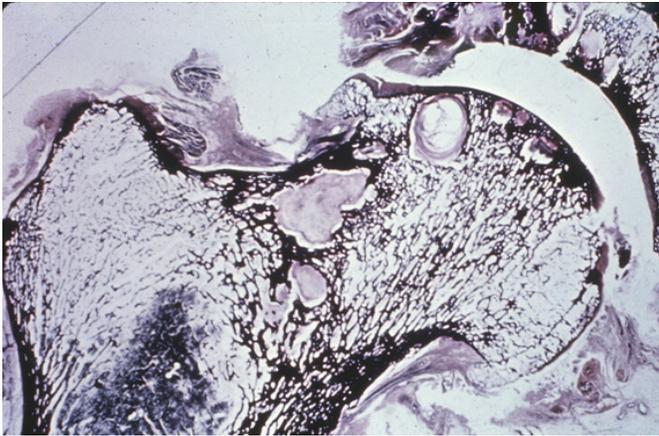


OA of the knee. Typical varus deformity is observed in the patient (A) with corresponding angular deformity in the joint due to asymmetric loss of cartilage (B).

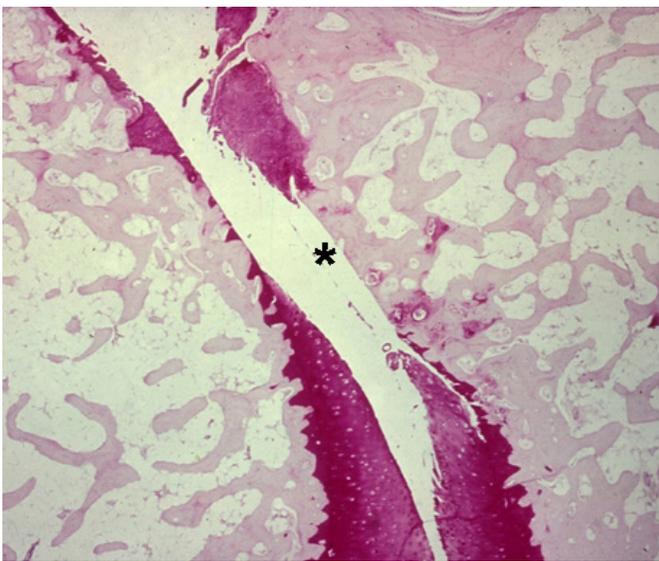
mediators (cytokines) that provide chemical signaling or “cross-talk” among involved tissues. These signaling molecules incite inflammation in the synovium, remodeling subchondral bone, and enzyme activation and extracellular matrix degradation in articular cartilage.

Subchondral Bone

Interest in structural remodeling, vascular biology, and osteoblast cytokine expression of subchondral bone in OA has been stimulated by a large number of studies suggestively associating a role for subchondral bone changes in the pathogenesis of OA. Active bone remodeling is associated with the initiation and progression of OA including sclerosis of the subchondral bone plate, alterations in trabecular structure, osteophytes and bone marrow lesions.²⁻⁵ Some studies with a guinea pig OA model suggest that subchondral bone changes precede degradation of articular cartilage.^{6,7} Additionally, several cytokines have been found in subchondral bone that play major signaling roles associated with cartilage degradation including IL-1, TNF- α and those of the fibrinolytic system including plasminogen, tissue and urokinase plasminogen activators (tPA, uPA), and plasmin.⁸



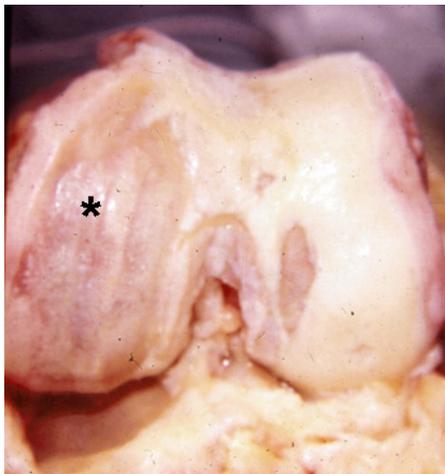
OA of the hip. Coronal, histological section of an osteoarthritic hip showing the hallmarks of OA including loss of articular cartilage, osteophytes, subchondral cysts, osteoporosis, and osteosclerosis.



OA joint surfaces. Histochemical section of opposing osteoarthritic joint surfaces showing focal cartilage loss, subchondral sclerosis and eburnation (asterisk).

Distal femur at knee replacement.

Focal nature of OA is evident with loss of articular cartilage (eburnation) on one femoral condyle (asterisk).



Vascular Biology of Subchondral Bone in OA

Intraosseous hypertension, venous stasis, and outflow obstruction are associated with bone pain and produce physiologically relevant reductions in perfusion and pO_2 . These relationships are of extreme importance in understanding the physicochemical environment of OA and its pathologic significance. Collective observations suggest that the physicochemical environment consisting of pressure, blood flow, and oxygen, among others, may constitute signaling mechanisms to osteoblasts resulting in alterations in cytokine expression. Changes in perfusion, then, bear a functional relationship to bone remodeling and cartilage degeneration.

Osteoblasts (bone-forming cells) alter their cytokine expression profile in response to their physicochemical environment, and changes in the physical environment in subchondral bone in OA are well within the range to which osteoblasts are sensitive. Several studies have demonstrated a 2- to 3-fold increase in venous outflow obstruction in late stage OA of the hip.⁹ One study, using intraosseous phlebography, also demonstrated markedly delayed venous drainage and occlusion of retinacular veins, with drainage of the proximal femur through diaphyseal intramedullary vein.¹⁰ Several observations have suggested that intraosseous hypertension is caused by increased venous resistance resulting in outflow obstruction and venous stasis.

Intraosseous hypertension produced experimentally by venous ligation results in the histopathological hallmarks of OA – focal avascular necrosis (AVN), trabecular remodeling, thickening of the subchondral bone plate, endosteal and periosteal new bone formation and sclerosis.¹⁰⁻¹² The pathophysiological consequences of intraosseous hypertension may lie in its association with diminished perfusion and hypoxia, which could serve as parts of a signaling complex to osteoblasts. Several studies describe linear relationships between perfusion and intraosseous pressure.¹³ An elevation in intraosseous pressure from 26 to 45mm Hg results in a reduction of intraosseous blood flow by 60%. A decrease in perfusion of 60% has been shown to reduce the pO_2 from 75 to 50mm Hg, within the range of hypoxia measured in OA bone. Measurement of intraosseous pO_2 shows significant hypoxia in OA.¹⁴⁻¹⁶

Osteoblasts Recognize and Respond to Altered Perfusion and Hypoxia

Osteoblasts derived from OA bone express increased amounts and types of cytokines that are related to bone remodeling and cartilage breakdown. The cytokine expression profile of osteoblasts is altered in response to changes in pressure, perfusion, and oxygen concentration of the type and magnitude seen in OA, raising the hypothesis that physicochemical changes observed in OA subchondral bone may serve as disordered signaling pathways to osteoblasts which, in response, alter their cytokine expression profile in ways relevant to bone remodeling and cartilage breakdown.

The relationship between increased bone remodeling and

cartilage degradation in OA has been recognized for many years but understanding the role of subchondral bone in the pathophysiology of OA remains elusive. In particular, the role of the osteoblasts in subchondral bone remodeling and cartilage breakdown remains unclear, as does the significance of recent descriptions of bone marrow edema and altered perfusion. Osteoblasts are also responsive to hypoxia. Osteoblasts subjected to hypoxic conditions with pO_2 of 35-40 mmHg, markedly alter the expression profile of growth factors associated with the pathologic findings of OA, increased bone remodeling and cartilage degradation.

Epidemiology and Economic Impact

The prevalence of OA is difficult to determine because symptomatic OA (joint pain, swelling, and stiffness) does not always correlate with the pathology of OA.¹⁷ Prevalence of pain associated with joint degeneration varies among joints and among individuals.¹⁸ Individuals with advanced degeneration of the joints may have minimal pain and disability, and for this reason, investigations of the prevalence of OA based on evidence of joint degeneration by itself, such as imaging studies or direct inspection of joints, yield larger numbers of affected individuals than do studies that require evidence of joint degeneration and joint pain together for the diagnosis of OA.^{19,20}

Recent information on the epidemiology of OA originates from population-based radiographic surveys.²¹ Population-based studies in the United States suggest prevalence rates comparable to those in Europe, increasing from 1% for severe radiographic disease among people aged 25-34 to 30% in those aged 75 and above.²¹ In 1997, a study in the Netherlands demonstrated that of the 1040 participants (aged 55-65), only 13% (135) were free from radiographic evidence of OA studied in the knees, hips, hands, wrists, and thoracolumbar spine.²² According to some population surveys, evidence of radiographic OA of the knee increases up to 80% for adults over the age of 65.²³

While most studies have focused on information from radiographic OA, there is increasing interest in the prevalence of symptomatic conditions of OA. This is important in order to determine the healthcare needs and options for patients. Symptomatic OA affects nearly 27 million Americans and is the most common form of arthritis. It is the leading cause of disability in the US.^{24,25} OA has a higher incidence in the hips and knees resulting in pain and stiffness and because these are large weight-bearing joints, it often leads to significant problems with mobility and disability requiring expensive surgical treatments.²⁶ In the United States alone, more than 350,000 knee and hip replacements are performed each year.²¹

Radiographic and symptomatic OA have been compared with age and gender. Using the Kellgren/Lawrence scale, they found that among different populations (NHANES study, Boston, MA, and Johnston County, NC) the prevalence of symptomatic OA was higher in women (62.9%) than men (46.5%).²⁷ Nearly half of the participants from the Johnston

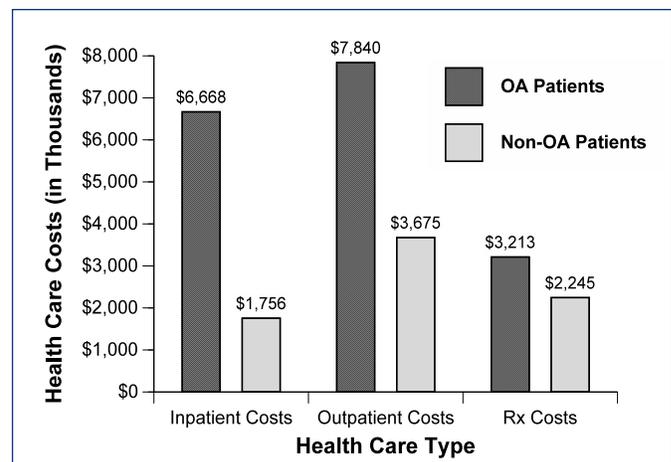


Figure 1: Regression-adjusted healthcare costs over one year. Non-OA patients had comorbidities shown to be prevalent among OA patients (eg, hypertension, diabetes, obesity, injuries, peptic ulcers, etc).¹ (Source: Graphic data from T.K. Le, *Journal of Pain and Research*, 31 January 2012.)

County, NC, study are expected to develop symptomatic OA by age 85.²⁸ Another study used age and sex prevalence in persons ≥ 26 years old and, using 2005 Census Bureau data, estimated that 9,267,000 adults have symptomatic knee OA.²⁷ As the population over 40 increases, the number of people experiencing symptomatic OA will rise as well.²⁹

OA contributes to a decrease in activities of daily living, and quality of life, and an increase in loss of work days, all of which result in out-of-pocket costs to the patient. The World Health Organization (WHO) has estimated that 10% of the world's population over 60 years old suffers from OA; 80% of people with OA experience limitation of movement; and 25% cannot perform major daily activities.³⁰ One observation reported that of 9,933 participants from the Medical Expenditures Panel Survey (MEPS) who have OA, 92% see physicians during the year, 34% visit at least one OA specialist, 25% see an orthopedist, 11% a physical therapist, and 6% a rheumatologist.³¹ Another study found that OA accounted for 7.1 million (19.5%) of all arthritis-related ambulatory medical care visits, of which 4.9 million were female patients, while 2.2 million were male.²⁵ OA is a major contributor to the total economic burden (1 to 25% of the gross national product of Western nations).³² In addition, another study reported that OA costs more than \$60 billion per year in the US.^{29,31} In 1997 alone, \$7.9 billion estimated costs were attributed to knee and hip replacements.³³ In 2000 it was estimated that the total costs in the United States were calculated at \$254 billion.³⁰ Le et al. recently reported that OA patients incur annual total direct costs that were \$10,941 higher, on average, than patients without OA.¹ In their article, the total average healthcare costs (outpatient, inpatient, and Rx) for OA patients is \$18,435 compared to \$7,494 for non-OA patients (Figure 1). Direct costs included hospitalizations, emergency department visits, office visits

(primary and specialist), physical/occupational therapy, and medications. This figure does not include the costs due to decreases in productivity, such as time out of work for both patient and non-patient (i.e. care taker).

CONCLUSION

There is currently no biological cure for OA. The number of U.S. adults with OA is expected to increase, affecting the healthcare system and society as a whole. Because of these reasons, it will be necessary to find ways of preventing and reducing the progression of OA. Translational research should be directed toward understand how aging and mechanical loading may lead to joint degeneration, how some joints are resistant to primary OA, and how joints can partially reverse the degenerative process.¹⁸

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Authors

Jennifer Racine is an academic coordinator and research associate in the Department of Orthopaedics.

Roy K. Aaron, MD, is Professor of Orthopedic Surgery and Director, Orthopedic Cell Biology Laboratory and Clinical Research, Department of Orthopaedics, The Warren Alpert Medical School of Brown University.

Correspondence

Jennifer Racine
100 Butler Drive
Providence RI 02906
401-330-1432
Fax 401-861-5812
jracine@lifespan.org