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### Osteoarthritis: “The Malady of the Masses” Re-Examined

Like the common cold and taxes, osteoarthritis (OA) sweeps so ubiquitously over humanity, and looms so complex in its etiology and cure, that it can seem to drop off the analytical radar. Not trendy or exotic, and taking a back seat to more mortal diseases, it nevertheless presents a scourge to a large percentage of the population.

This issue of *The WCC Note* discusses the prevalence and pathology of osteoarthritis, with specific emphasis on its most common focus of affliction – the knee. ■

#### OA: THE NUMBERS

#### How many people are afflicted with OA?

1. OA afflicts 13.9% of all people 25 years old and older and 33.6% of all people 65 years old and older. (1)
2. In 2005, a conservative estimate of U.S. adults with OA numbered 26.9 million. (1)
3. In 2006, an estimated 11.7 million ambulatory care visits were made for OA and allied disorders. (2)
4. Knee OA accounts for 1 of 5 primary factors of disability in non-institutionalized adults. (1)
5. Lifetime risk estimates project that nearly half of adults in a longitudinal osteoarthritis project in rural North Carolina will develop symptomatic knee OA by age 85. (3)
6. The estimated annual U.S. expenditure for OA treatment and lost work is more than \$33 billion. (4)

## Who gets OA? What risk factors are associated with OA?

Both avoidable and nonmodifiable factors influence the development of OA, as outlined below.

### 1. Modifiable risk factors:

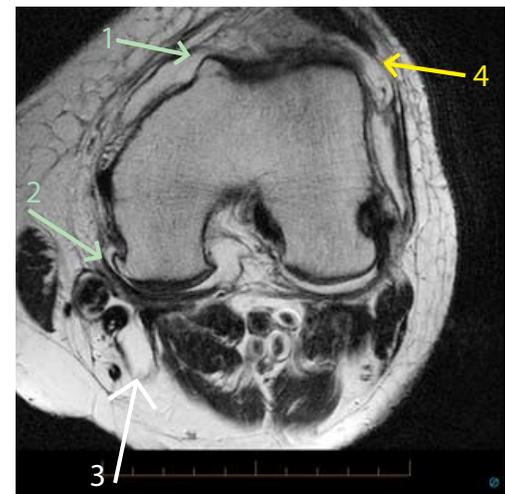
- a. Excess weight (1)
  - i. Especially with knee OA (1)
  - ii. For some women, weight loss of as few as 11 pounds can decrease the risk of developing knee OA by 50%. (5, 6)
- b. Joint injury (including occupational and sports-related)
- c. Occupation
  - i. Excess mechanical stress
  - ii. Repetitive injury
- d. Muscle weakness or structural malalignment (1)

### 2. Nonmodifiable risk factors:

- a. Gender (female risk is higher)
- b. Advancing age
- c. Race (risk lower in some Asian populations)
- d. Genetic predisposition (1)

## What is the genetic component of OA?

1. A clear genetic component has been apparent since it was first reported by Kellgren in 1963, who found that nodal OA was twice as likely to occur in first-degree relatives than in control subjects. (7, 8)
2. The genetic basis fails to follow typical Mendelian inheritance patterns, and multiple genetic alterations probably underlie the disease. (9)
3. The polygenic nature of OA, with its strong hereditary component, is supported by evidence from familial aggregation and classic twin studies. (10) Traits associated with OA, such as cartilage volume changes, also come under genetic control. (10)
4. The complex, multifactorial genetic basis has been partially revealed by genome-wide linkage scans. Thus far, implicated genes include (11):
  - a. Interleukin 1 gene cluster at chromosome 2q11.2-q13
  - b. Matrilin 3 gene at 2p24.1
  - c. IL-4 receptor alpha-chain gene at 16p12.1
  - d. Secreted frizzled-related protein 3 gene at 2q32.1
  - e. Metalloproteinase gene ADAM12 at 10q26.2
  - f. Asporin gene at 9q22.31
  - g. Growth differentiation factor 5 (12)
  - h. DVWA gene on human chromosome 3p24.3, found in OA in Japanese and Chinese patients (13,14)



1. Patellar femoral osteophyte at the medial trochlea; moderate effusion.
2. Posterior medial femoral osteophyte.
3. Posteromedial bursal cyst with chondral body (arrow head).
4. Lateral patellar tilt and subluxation.

5. A recent review of the science of OA by Abramson and Attur (8) describes the following:
  - a. Coexisting individual genes may give rise to an additive affect. (15)
  - b. Some genes that encode extracellular matrix articular cartilage proteins have links to early OA. (16)
  - c. Mutations in several genes expressed in cartilage and point mutations in type II collagen may cause inherited OA.
  - d. Genetically linked abnormal subchondral bone can cause OA in mice.

## OA PATHO- GENESIS

### What is the pathogenesis of OA?

Abnormal biochemical processes occur in the cartilage, bone, and synovium, instigated by the risk factors delineated above. Progressive cartilage damage occurs, with accompanying osteophyte formation, meniscal degeneration, bone-marrow and subchondral lesions, synovial proliferation, and effusion.

The following list outlines the proposed mechanisms causing OA, segregated by risk factor — a subject elegantly reviewed by Abramson and Attur. (8)

#### 1. Obesity

- a. Increased mechanic force: Obese individuals commonly exhibit varus knee malalignment, increasing forces in the medial compartment. (8, 17)
- b. Adipocytes play roles regulating cells in bone, cartilage, and joint tissue.
- c. Adipocyte-derived factors may encourage catabolism for chondrocytes.

#### 2. Joint injury

- a. Chondrocytes act as mechano-sensors and osmo-sensors, changing their metabolism depending upon local physical and chemical alterations.
- b. Response to mechanical stress can change gene expression, resulting in increased formation of inflammatory cytokines and matrix-degrading enzymes.
- c. A focal cartilage injury can result in matrix disruption and chondrocyte apoptosis, or both, which begins a vicious cycle. Trauma can cause chondrocyte death by two mechanisms: via mechanical load or via disruption of extracellular matrix leading to chondrocyte physical isolation. Detached chondrocytes undergo apoptosis (programmed cell death) and injured areas make degradative enzymes. Load transfer to normal peripheral regions then undergo abnormal forces, resulting in their apoptosis. (18)
- d. An enzyme called Smurf2 (**Smad Ubiquitination Regulatory Factors**) controls whether a chondrocyte matures and calcifies and, in the setting of cartilage injury, may cause a chain reaction that deteriorates cartilage. (19)

#### 3. Joint malalignment

- a. This is debated as an etiological factor, but altered joint geometry may interfere with cartilage nutrition or change load distribution. Knee malalignment may be a marker of disease, and the literature is conflicting about its role as an OA instigator. (20, 21)

#### 4. Gender

- a. Estrogen receptors exist in joint chondrocytes.
- b. It has been hypothesized that the markedly increased risk of knee OA in women after age 50 is due to estrogen insufficiency, though this is actually poorly understood and evidence for such a relation is reported as inconsistent.

## 5. Age

- a. This factor may alter mechanical stress on cartilage because of changes in muscles, gait, etc.
- b. Aging probably decreases chondrocytes' ability to maintain and repair tissue, as they sustain "decreased responsiveness to anabolic growth factors, and synthesize smaller and less uniform large aggregating proteoglycans and fewer functional link proteins." (8, 22)
- c. Aging predisposes chondrocytes to apoptosis.
- d. Deviant chondrocyte behavior in age-related cartilage destruction has recently been found to be associated with altered signaling via ALK1. (23)

## 6. Genetic predisposition

- a. The newly identified DVWA genetic link to OA, found in certain populations, has been further revealed as the human gene encoding for collagen VI alpha4 chain. (14)

## 7. Inflammation and angiogenesis

- a. Challenging the notion that osteoarthritis is primarily a disease of the cartilage, newer findings relating to inflammation and angiogenesis postulate that these factors modulate chondrocyte function and contribute to abnormal tissue growth and perfusion, ossification, and endochondral bone development. (24)

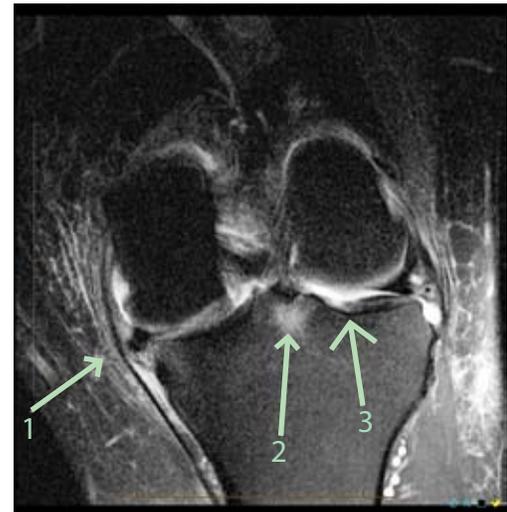
## 8. Diet

- a. Increased fatty acid consumption may increase the risk of developing bone-marrow lesions. (25)

## What is the gross anatomic and cellular pathology of OA?

The morphology of OA initially shows that:

- Chondrocytes proliferate with increased water and decreased proteoglycans.
- Then, vertical and horizontal fibrillation and matrix cracks occur.
- Next, full-thickness cartilage areas are lost.
- Friction smooths exposed bone (bone eburnation).
- Sclerosis and rebuttoning of underlying bone happens.
- Small fractures of subjacent bone lead to dislodged pieces (loose bodies).
- Synovial fluid is forced through the fractures into subchondral bone.
- The fluid forms subchondral cysts with fibrous walls.
- Bone outgrowths grow at articular margins (osteophytes).
- Synovium becomes congested and fibrotic, and may have inflammatory cells. (4)



1. *Pseudoextruded medial meniscus, deformed, with meniscofemoral and meniscotibial lax attachments, slight medial tibial plateau stress edema, tibial-collateral ligament stretched medially due to underlying degenerative changes with mild reactive surrounding swelling.*
2. *Stress edema intertibial spine, pericruciate insertion.*
3. *Full-thickness lateral tibial cartilage linear fissure.*

Further details include:

### **1. Cartilage:**

- a. Normal articular cartilage contains water (75% by weight), collagen (predominantly type II; 20% by weight), aggrecan (5% by weight), and other extracellular matrix molecules, all maintained by chondrocytes.(18) As reviewed by Biswal, *et al.*, collagen provides tensile strength, while aggrecan (glycosaminoglycan molecules) affords compressive strength.
- b. In OA, articular cartilage loss occurs due to proteolytic enzymes that destroy proteoglycans and collagen. Increased cartilage degradation occurs with insufficient repair.
- c. OA cartilage shows the presence of hypertrophic chondrocyte phenotype, leading to type II collagen degradation, endochondral ossification, and chondrocyte apoptosis.
- d. Normal cartilage extracellular matrix has two main constituents: a type II, collagen-rich network providing tensile strength; and aggrecan, a cartilage-specific proteoglycan that is highly hydrated and helps cartilage resist compressive loads. In OA, the degeneration of extracellular matrix outpaces its creation, leading to exposure of cartilage and, subsequently, bone. (26)
- e. In early OA, cartilage degenerates and contains increased water and decreased proteoglycans. The collagen network weakens, due to decreased synthesis of type II collagen and increased preexisting collagen breakdown. Apoptosis decreases functional chondrocytes. (4)

### **2. Inflammation**

- a. Inflammatory mediators like IL-1beta and tumor necrosis factor induce chondrocytes to make proteases, chemokines, nitric oxide, prostaglandins, and leukotrienes, which drive catabolism, impair cartilage substance generation, and encourage cell death. Oxygen and nitrogen-derived free radicals promote chondrocyte cell death, probably by mitochondrial dysfunction.

### **3. Abnormal bone**

- a. Osteophytes are theorized to develop from penetration of blood vessels into degenerating cartilage basal layers, or from the abnormal healing of stress fractures at the joint margins within subchondral bone.
- b. Subchondral bone sclerosis may arise from excessive loads leading to microfractures in the trabeculae that go on to heal with callus and remodeling.
- c. The histopathology of bone-marrow lesions in OA is unclear, but microfractures, cysts, and avascular necrosis may give rise to findings appreciable by MRI.

### **4. Synovial proliferation and inflammation**

- a. Synovial hypertrophy and hyperplasia have been noted by arthroscopic studies in up to 50% of OA patients. (27)
- b. Cartilage breakdown products from mechanically or enzymatically destroyed cartilage can provoke release of collagenase and other enzymes from synovial cells and macrophages, lead to mononuclear cell infiltration and vascular hyperplasia in synovium, and induce synovial IL-1beta and tumor necrosis factor that continue the cascade of degradation. (8)

### **5. Meniscal tears**

- a. Degenerative meniscal tears may signal the first symptom of OA. When an isolated meniscal tear has undergone limited meniscectomy treatment, there is a high risk of tibiofemoral OA at 16-year follow-up. (28)
- b. Meniscal damage without surgery is also a high-risk factor for subsequent OA. (29)

## CONCLUSION

**Conclusion:** Osteoarthritis currently seems inevitable and unavoidable for a large swath of the population. Its etiology relates to a strong, but complex, non-Mendelian genetic basis, combined with mechanical and metabolic factors that cause molecular alterations – the end results of which affect the whole joint.

The next issue of *The WCC Note* will continue this three-part series with a discussion of the MRI appearance of OA. The third and final article will review available treatments, clinical trials, and research developments. ■

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