

## **DISEASE MECHANISMS IN OSTEOARTHRITIS**

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### **INTRODUCTION**

Osteoarthritis (OA) is the most prevalent joint disease worldwide. Although long considered as a result of mechanical wear and tear as one ages, OA can affect joints earlier and variably in those with significant joint trauma, and abnormal mechanics of joint loading from congenital and some heritable cartilage disorders. Its irreversible and chronic course makes it a frustrating disease to treat. To date, the clinician's treatment armamentarium consists mainly of pain relief and prevention or delay of disability.

The impact of arthritis in the next quarter of the century is expected to reach epidemic proportions, especially as an economic burden. This is already felt in industrialized countries where major health problems include those attendant to the longevity expected of the population - the so-called degenerative diseases. Moreover, the effects of fast, office-bound lifestyle, small nuclear families, and low population growth rates (inverted pyramid population profile) push the need for socialized care for the increasing number of people with non-fatal but disabling diseases like OA. Data show that arthritis affects more individuals than heart disease or hypertension combined. In persons 65 years and older, 50 percent report having arthritis while 33 percent report having hypertension, hearing impairment and heart disease.<sup>1-2</sup> These observations have fueled research in OA and related diseases. The declaration of the first 10 years of the 21<sup>st</sup> century by the United Nations as the Bone and Joint Decade (2000-2010), pushes the agenda even further into the international lay arena.

The increasing understanding of the mechanisms of disease has revolutionized diagnostic and treatment options. The role of bone, added to that of cartilage, synovial inflammation and genetics, is better understood and knowledge continues to expand. Clinical research has moved to standardize measures of disease and treatment outcomes. The race toward identifying a reversible phase of the disease is on. In recent years, organizations like the Osteoarthritis Research Society International (OARSI) have provided the venue for the exchange of information critical to this end.

### *Prevalence: Global and Philippine figures*

The definition of OA rests on both radiographic and clinical terms. Clinical disease consisting of joint pain on loading, crepitation, bony swelling, and occasional low grade synovitis, correlates with radiographic changes only 50 percent of the time. An estimated 6 percent of adults in the US above 30 years of age have symptomatic OA of the knee and 3 percent have symptomatic OA of the hips. Incidence and prevalence continue to increase after age 65. On the other hand, the rate of radiographic osteoarthritis is 50 percent for patients aged 60 years and rises close to 100 percent by age 75. The World Health Report Archives 1995-2025 estimates that "almost 80 percent of patients with OA have some degree of limitation of movement and 25 percent cannot perform their activities of daily life."

In the Philippines, the point prevalence of osteoarthritis is 4.1 percent of an urban population (mean age=34).<sup>5</sup> Manila, its capital city, with a population of 11 million, therefore has approximately half a million sufferers of OA. Considering population growth in the next 25 years as projected in the Summary of Philippine Demographic Data 2000, the number of individuals with OA will more than double by 2025.<sup>6</sup> Recently, the Food and Nutrition Research Institute in the National Nutrition Health Survey (NNHES) of 2003 noted a 0.5 percent prevalence of OA among individuals 40 years of age and above, a lower figure compared to the first study, perhaps an effect of the methods employed in this national survey. This figure reflects not only urban but also rural Philippines. In an 80 million strong population, this will easily be about 3.2 million plus Filipinos with the disease.

### *Factors affecting disease expression and prevalence*

There are several risk factors for OA. Considered as non-modifiable factors are age, gender, genetics and race; and the modifiable factors are trauma, vocational factors, congenital musculoskeletal abnormalities and obesity. The disease is considered heterogenous and affects different joint sites at different rates. The hands are most commonly affected, followed by the knees. Knee OA is more disabling and clinically significant. Hip OA is rare among Asians and more prevalent among whites.<sup>8-13</sup> Genetics are a major risk

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factor for specific sites, i.e., cervical and lumbar spine involvement has 70 percent heritability, hand OA, 65 percent and knee, 50 percent.<sup>9</sup> Rare sites of involvement can be due to vocation, as exemplified by OA of the metacarpophalangeal (MCP) joints, which have been reported among prize fighters.<sup>11</sup>

Several factors affect the reporting of clinical disease. One important phenomenon is what has been described as the “patient” and “non-patient” populations of individuals with OA. This phenomenon refers to health seeking behavior of individuals with OA which may be influenced by socio-cultural practices, coping mechanisms, and socioeconomic and educational status. The patient seeks medical help, while the non-patient is at large and living with the disability of OA without seeking medical help. Other observations describe patients as “participant” versus “non-participant” (Dieppe<sup>14</sup>) which refer to the effects of the disease on the individual in his social and interpersonal relationships.

### *The Joint in Osteoarthritis*

#### *Bone*

Subchondral bone changes occur early in OA. Bone is recognized as the major shock absorber of joints, serving to absorb energy, mechanically accommodating heavier loads applied to the joint. It is elastic, but is about 10 times more stiff than cartilage.<sup>15</sup> Osteophytes and subchondral bone sclerosis are seen in radiographs before joint space narrowing. Osteophyte formation has been shown to antedate x-ray changes in joint space or bony sclerosis by three to four years. Scintigraphy studies confirm this very early involvement of bone. The anterior cruciate ligament (ACL) model for OA has shown that rupture of the ACL leads to thickening of the subchondral horizontal trabeculae.<sup>16</sup> The process of bone modeling is activated in the subchondral bone plate (SBP) resulting in direct appositional growth of bone in the side away from cartilage. This causes thickening of the plate or what is called corticalization of the SBP. The process of bone production also occur in the trabecular subchondral bone proper in a way that does not result in thickened trabeculae but causes trabecular redirection and reordering. In adults, bone remodeling is seen to cause thickening of subchondral bone plate and stiffening.<sup>18</sup> Thickening and stiffening of subchondral bone is now believed to change loading mechanics in a way that puts abnormal stresses on cartilage.

Later in the disease, characteristic x-ray findings of osteophytes, subchondral bone sclerosis, microfractures and bony cysts are seen, in addition to joint space narrowing. These changes are recognized

as sources of pain in OA: osteophytes impinging on capsular and other peri-articular structures or the occurrence of trabecular microfractures. Osteophytes are clinically associated with pain and predict pain more accurately than joint space narrowing in all radiological views. Osteophyte formation is linked to growth factors, partly secreted by activated synoviocytes and chondrocytes. This involves upregulation of transforming growth factor (TGF-1) and basic fibroblast growth factor (bFGF) from osteophytes.<sup>18</sup>

Formerly, changes in bone were considered as end results of mechanical loading forces applied to thinned-out or ulcerated cartilage. Now, evidence points to bony changes occurring first, causing stiffening of bone resulting in extra stress to cartilage on loading.

### *The Bone- Cartilage Interphase*

The junction of cartilage and subchondral bone provides clues as to how bony changes proceed in OA. The critical histologic portion of the cartilage-bone junction is composed of the zone of calcified cartilage (ZCC), subchondral bone plate (SBP), both making up the tidemark, and the subchondral trabeculae. The tidemark on scanning electron microscope, is dotted with tiny defects containing chondrocytes and larger defects that carries blood vessels from the more distal subchondral bone vessels into cartilage.<sup>17</sup> The more loaded sites showed higher numbers of vessels, perhaps allowing for better nutrition and as supporting evidence of the observation that the loaded sites are stronger compared to the chondromalacic less loaded sites.

Data on bone growth and modeling has collaborating evidence on continued bone growth at the region of the tidemark.<sup>18</sup> Growth is normally marked by endochondral ossification in the growth plate but in adults, continued ossification occur in ZCC in the tidemark area (Lane, 1981 and Bullough, 1983). Histologic data show a step-like advancement of ZCC into the body of the cartilage and increase in their numbers, seen mostly in the central convex surfaces of joints. The advancing mineralized fronts are in areas showing more vascular canals perforating the subchondral cortical layer. Joint space narrowing on x-ray can therefore be due to the advancing mineralized front of the ZCC, and not to actual thinning of cartilage.

What about the effects of external forces on the joints? The group of Radin looked at potentially harmful forces applied to joints calling the phenomenon “microklutsiness” (lecture delivered in the 2<sup>nd</sup> International Workshop for Osteoarthritis,

Indiana University, 2002). Normally, joints are protected by an intact joint and neuromuscular “shock absorbers”. This hypothesis considers early subchondral bone changes to be caused by forces normally applied to joints, that may have lost the dampening effect of these shock absorbers, either temporarily or permanently. A good example is the jolt one feels in the knee upon stepping down on a step of stairs expected to be there but was not. Here, the knee is extended as the foot lands at an unanticipated distance, so that force is received by the knee faster than the visco-elastic and neuromuscular protective properties of the joint can dampen. These phenomena happen in the course of normal daily activities and microdamages created this way later accumulate and exceed the capacity of the joint to heal resulting in thickening of subchondral bone and thinning of cartilage.

Studies (Bullough et al, 2001) also explored the role of joint architecture in early OA. Data show that in the younger individual, the apposing bones of a joint is incongruent in the manner of a “ball-in-gothic arch” configuration. This allows for loads to be applied in the periphery contact points of the apposing cartilage. At these contact points, the cartilage is found to be normal in thickness and histologic character while those in the less loaded portions the cartilage exhibit early chondromalacic changes. In aging, bone to bone congruence increases and makes possible for loads to be applied to previously less loaded, chondromalacic portions of the overlying cartilage. These findings could explain the initial trigger of cartilage fibrillation, the long observed initial change in cartilage.

### *Synovium*

Osteoarthritis clinically presents with episodes of low grade inflammation. Inflammation of osteoarthritic joints are known to coincide with disease progression. These so-called disease flares are results of synovitis.

Studies confirm that the synovium is involved in osteoarthritis and that inflammation is an important part of the disease. Histologic studies show significant hypertrophy and hyperplasia of the synovium, and in severe disease, have been reported to reach the degree of hyperplasia seen in rheumatoid arthritis.<sup>22</sup> Aside from these changes, cytokine are upregulated, among these are IL1 $\beta$ , TNF $\alpha$ , IL 6, IL 8, LIF, IL-17 and IL-18. Known to stimulate their own production by activated inflammatory cells, IL1 $\beta$  and TNF can induce both synoviocytes and chondrocytes to produce the other cytokines like IL 6, IL 8, leucocyte inhibitory factor (LIF), insulin-like growth factor (IGF), TGF  $\beta$  and bone morphogenic proteins

(BMPs). Likewise these result in production of nitric oxide synthase (NOs) and tissue metalloproteinases (MMPs). One important effect of TNF is stimulation of osteoclast activity in bone, a phenomenon seen during bone remodeling in subchondral trabeculae. IL1 $\beta$  and TNF $\alpha$  also stimulate production of proteases and prostaglandins. BMPs and TGF  $\beta$  stimulate bone reaction resulting in osteocyte formation.

Together with the increased production of inflammatory cytokines, there is also observed upregulation of their individual receptors. Two receptors for IL1 has been identified with the type 1 receptor having slightly higher affinity for IL1 $\beta$  than IL1 $\beta$ . This type 1 receptors have been detected in increased amounts in OA chondrocytes and synovial fibroblasts rendering these cells sensitive to stimulation by the cytokine. Activation of synoviocytes therefore is key to the activation of chondrocytes. Once interaction is established, chondrocytes generate nitric oxide (NO) that activate matrix metalloproteinases (MMPs) and at the same time cause decreased production of matrix proteins and aggrecan. The net effect is accelerated degradation of cartilage matrix.

Activated synoviocytes are also shown to elaborate anabolic cytokines like IGF-1, OP-1, TGF- $\beta$  and IL-4. Anti-inflammatory cytokines IL10 and IL13 are likewise upregulated and shows the balance that the synovium tries to maintain. This much understanding has led to the consideration that antagonizing these mechanisms at the earliest time, perhaps a time of reversibility, can actually render the disease curable.

### *Cartilage*

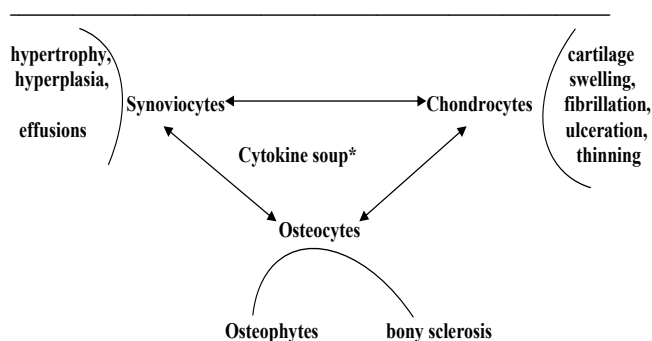
In weight-bearing joints, cartilage acts as one of the shock absorbers of applied loads. This observation influenced the focus of early researches on cartilage pathology as the major mechanism of disease in OA. The avascular, alymphatic and aneural character of this tissue explained the seeming inability of cartilage to repair damage brought on by aging or injury, hence the degenerative or wear and tear paradigm. Indeed, data show that early in the disease, cartilage water content increases, and proteoglycan structure reverts to immature forms that have less affinity for water.<sup>13</sup> These changes cause disruption of the collagen fibers that results in loss of strength of cartilage. Consequently, the surface of cartilage fibrillates. These fibrillations deepen and later full thickness defects in cartilage are created.

Chondrocytes, are now known to be metabolically active in OA. Electron microscopic studies show

increased numbers of cytoplasmic organelles, notably, the endoplasmic reticulum. Chondrocytes are known to undergo increased rates of secretion of cartilage matrix constituents like proteoglycans and collagen. The proteoglycan molecules secreted by these active chondrocytes are those seen in immature cartilage where the glycosaminoglycan (GAG), chondroitin-4 sulfate predominates over chondroitin-6 sulfate molecules. Likewise, the keratan sulfate secreted are shorter than those seen in mature cartilage. This phenomenon accounts for the decrease in affinity of proteoglycan (or its aggregates in the aggrecan molecule) for water. Chondromalacia develops consisting of surface fibrillations that later deepen and ulcerate, leading to full thickness loss cartilage at some point. Significantly, these changes are seen in only one of the apposing cartilage in joints and therefore, could not be explained by the wear and tear theory of disease.<sup>14</sup>

By the mid-80's, the concept of cartilage repair became increasingly recognized as relationships between biochemical and mechanical processes were identified and defined. Recognition of bone and synovial membrane events and the active cellular activity of chondrocytes have made for a paradigm shift away from the wear and tear mechanism of osteoarthritis. The presence of significant amounts of pro-inflammatory and anti-inflammatory cytokines and degradative enzymes in the osteoarthritic joint shows that the disease creates cellular and tissue responses that at first maintain balance and holds off disease expression, but later ultimately fails.

#### Pathogenesis of osteoarthritis. The Bone-Synovium-Cartilage Osteoarthritis Link



**Fig.1.** Interaction of cells in subchondral bone, synovium and cartilage creating a cytokine network that tip the balance toward pro-inflammatory processes. The cytokine soup\* includes: IL1  $\beta$ , TNF  $\alpha$ , IL 6, IL 8, LIF (pro-inflammatory); IL 4, IL 6, IL 10, IL 13 (anti-inflammatory); TGF  $\beta$ , IGF-1, OP-1 (Growth factors)

#### New Treatment Targets

Identifying the structural, histologic changes and cytokines in OA ultimately identifies treatment targets. The concept of disease modification has brought about the term disease modifying osteoarthritis drugs (DMOADs). Agents that inhibit the MMPs, the earliest studied being the antibiotic family of tetracycline, as well as naturally occurring MMP inhibitors like the tissue inhibitor of metalloproteinases (TIMP) have been on the bench. Tetracyclines act by chelating zinc in active sites of MMPs and by inhibiting iNOS. Other possible DMOADs can target cytokines. The up-regulation of IL 4, 10 and 13 mechanistically can decrease production of IL1 $\beta$  and TNF  $\alpha$ . Use of nonsteroidal anti-inflammatory drugs NSAIDs for the episodes of synovitis offer pain relief and resolve inflammation. They inhibit the generation of prostaglandins and reduce inflammatory symptoms. Upstream, cytokines that stimulate prostaglandin production might be target for treatment.

Further upstream, inhibition of cytokine production by CSAIDs or cytokine suppressive anti-inflammatory drugs is now being studied. Inhibition of iNOS in canine experiments has also been shown to retard progress of cartilage destruction, and decrease chondrocyte apoptosis.

In summary, OA is a disease that clearly show the cytokine footprints of active cellular and tissue reaction instead of simply just being a “wear and tear” phenomenon. External loading forces coupled with failure of joint and neuromuscular shock-absorbing mechanisms, continued cellular activity and ossification at tidemark sites, evidence of inflammation in synovium and cartilage cellular reaction, are described and new treatment targets are generated by this fresh body of knowledge.

#### REFERENCES

1. The World Health Report 1995-2003. <http://www.who.int/en/>
2. National Institutes of Health, NIAMS: Arthritis Prevalence Rising as Baby Boomers Grow Older. May 5, 1998.
3. Top Ten Causes of Morbidity and Mortality in the Philippines, Department of Health Report, 2000.
4. Eullaran, R, Penserga, Economic Burden of Osteoarthritis in the Philippine General Hospital, 2002, unpublished.
5. Dans LF, Tankeh-Torres S, Amante CM, Penserga, EG: The Prevalence of Rheumatic Diseases in A Filipino Urban Population: A WHO-ILAR COPCORD Study. *The Journal of Rheumatology*; 24:9:1814, 1997.

6. Summary of Philippine Demographic Data, 2000: *U.S. Census Bureau, International Database July 2003 version*. <http://www.census.gov/cgi-bin/ipc/idbsum?cty=RP>
7. Peat G, McCarney R, Croft P: Knee Pain and Osteoarthritis in Older Adults: A Review of Community Burden and Current Use of Primary Health Care. *Annals Rheum Dis*; 60:91, 2001.
8. Hart DJ, Doyle, DV, Spector T: Incidence and Risk Factors for Radiographic Knee OA in Middle-aged Women. *Arthritis Rheum* 42:1 January 1999, pp 17-24.
9. Holderbaum D, Haqqi TM, Moskowitz RW: Genetics and Osteoarthritis: Exposing the Iceberg. *Arthritis and Rheum*; 42:397, 1999.
10. Spector TD, MacGregor J: Risk Factors for Osteoarthritis Genetics. *Osteoarthritis and Cartilage* , 12, S39, 2004.
11. Brandt KO: "Osteoarthritis" Harrison's Principle of Internal Medicine, 16th Ed.; Mc Graw Hill USA. pp 2036, 2005.
12. Ingvarsson, *et al.*: The Inheritance of Hip Osteoarthritis in Iceland. *Arthritis and Rheum.*; 43:12:2785, 2000.
13. Sambrook PN, MacGregor AJ, Spector TD: Genetic Influences on Cervical and Lumbar Disc Degeneration. *Arthritis Rheum.*, 42:2, 336, Feb 1999.
14. Dieppe P: Relationship Between Symptoms and Structural Change in OA. What are the Important Targets for OA Therapy? International Workshop on Osteoarthritis Outcomes. Ruth Lilly Learning Center, Riley Hospital Outpatient Center, Indianapolis , Indiana, Dec 13-14, 2002.
15. Brandt, Handbook OA, 2004.
16. Buckland-Wright C: Subchondral Bone Changes in Hand and Knee Osteoarthritis Detected by Radiography, *Osteoarthritis and Cartilage* (2004) 12 S10-19.
17. Bullough PG: The Role of Joint Architecture in the Etiology of Arthritis. *Osteoarthritis and Cartilage*, 12, S2, 2004.
18. Burr D: Anatomy and Physiology of Mineralized Tissues: Role in the Pathogenesis of Osteoarthritis. *Osteo Cart* (2004) 12 S20-S30.
19. Mankin, Brandt: Pathogenesis of Osteoarthritis, In Ruddy, Harris, Jr, Sledge eds. *Kelley's Textbook of Rheumatology*. WB Saunders Company, Philadelphia; 1395, 2001.
20. Bulloughs P: Pathology of Osteoarthritis. In Hochberg, M, Silman, A, Smolen, J, Weinblatt, M, Weissman, M. Eds, *Rheumatology* 3rd ed. 2003 Elsevier Limited. Spain. p1838.
21. Spector T, MacGregor A: Risk Factors for Osteoarthritis: Genetics. *Osteoarthritis and Cartilage* 12, S339, 2004.
22. Felson DT, Coupromitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, *et al.*: Evidence for A Mendelian Gene in A Segregation Analysis of Generalized Radiographic Osteoarthritis: The Framingham Study. *Arthritis Rheum* 1998;1064-71
23. Huch H, Kuettner K, Dieppe P: Osteoarthritis in Ankle and Knee Joints. *Seminars in Arthritis*, Vol 6 No. 4 (Feb):667, 1997.
24. Martel-Pelletier J: Pathophysiology of Osteoarthritis. *Osteoarthritis and Cartilage*, 12, S31, 2004.
25. Lajeunesse J: The Role of Bone in the Treatment of Osteoarthritis. *Osteoarthritis and Cartilage*, 12, S34, 2004.
26. The Mazzuca SA, Brandt K, German NC, Buckwalter KA, Lane KA, Katz BP: Development of Radiographic Changes of Osteoarthritis in the "Chingford Knee" Reflects Progression of the Disease or the Non-Standardized Positioning of the Joint Rather than Incident Disease. *Annals of the Rheumatic Diseases*; 62:1061, 2003.
27. Pham T, *et al.*: OMERACT-OARSI Initiative: Osteoarthritis Research Society International Set of Responder Criteria for Osteoarthritis Clinical Trials Revisited. *Osteoarthritis and Cartilage*, 12, 389, 2004.
28. Arden NK, Griffiths GO, Hart DJ, Doyle DV, Spector TD: The Association Between Osteoarthritis and Osteoporotic Fracture: The Chingford Study. *British J Rheumatol*; 35:1299, 1996.
29. Sharma L, *et al.*: Does Laxity Alter the Relationship Between Strength and Physical Function in Knee OA? *Arthritis Rheum* 42:1 January 1999, pp 17-24.
30. Chaisson CE, Zhang Y, Sharma L, Kannel W, Felson DT: Grip Strength and the Risk of Developing Radiographic Hand OA, Results from the Framingham Study. *Arthritis Rheum* 42:1 January 1999, pp 17-24.
31. Hochberg M, Silman A, Smolen J, Weinblatt M, Weisman M.: eds. *Rheumatology*, 3<sup>rd</sup> edition 2003 Mosby, London pp 1781 ff.
32. Jordan, *et al.*: EULAR Recommendations 2003: An Evidence Based Approach to the Management of Knee Osteoarthritis: Report of Task Force of the Standing Committee for the International Clinical Studies Including Therapeutic Trials (ESCSIT). *Ann Rheum Dis* 62(12):1145.
33. Loeser RF: A Stepwise Approach to the Management of Osteoarthritis. *Bulletin on the Rheumatic Diseases*. <http://www.arthritis.org/research/Bulletin/Vol52No5>
34. Aggarwal A, Sempowski I: Hyaluronic Acid injections for Knee Osteoarthritis, Systematic Review. *Canadian Family Physician*, Feb 2003.
35. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the Medical Management of the Hip and Knee: 2000 Update. *Arthritis Rheum*, 43:1905, 2000.
36. Pelletier JP: Rationale for the Use of Structure Modifying Drugs and Agents in the Treatment of Osteoarthritis. *Osteoarthritis and Cartilage* (2004) 12 S63-S<sup>^</sup>\*
37. Pelletier JM: Pathophysiology of Osteoarthritis. *Osteoarthritis and Cartilage* (2004) 12 S31-S33
38. Menkes C-J, Lane N, Workshop on Are osteophytes good or bad? *Osteoarthritis and Cartilage* (2004) 12 S53-S54.
39. Dougados, M: Monitoring osteoarthritis progression and therapy. *Osteoarthritis and Cartilage*. *Osteoarthritis* (2004) 12 S55-S60.