# INNOVATIVE APPROACHES TO DEGENERATIVE JOINT DISEASE

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One of the most common conditions that family physicians and other primary care providers face in clinical practice is degenerative joint disease (DJD), more commonly known as osteoarthritis (OA).[1] DJD accounts for one of the greatest causes of disability, loss of productivity, suffering, health decline and social isolation in our society.[2] The general approach to diagnosing and treating DJD has, surprisingly, not changed a great deal over the past several decades. Apart from total joint replacement, treatment options are palliative at best, with symptom control playing a prominent role.[3] Yet, simple approaches utilizing diet, lifestyle and nutrition have been developed that make a profound difference in calming down inflammation not only in joints, but throughout the whole body.[4]

"Osteoarthritis is a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro and macro injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness."[5]

The prevalence of OA of the knee, hip or hand is estimated to be 20-30% of adults,[6] with an estimated lifetime risk of developing knee OA of 40% in men and 47% in women.[7] Risk factors for OA include person-specific factors, such as age, sex, obesity, genetics and race/ethnicity; as well as joint-specific factors related to abnormal loading of the joints, such as history of injury, level of activity, occupation, leg-length inequality, strength, and joint alignment/flexibility.[8] The main joints affected by OA include the knees, hips, interphalangeal joints, thumb base, first metatarsal-phalangeal joints and spinal facet joints. People who suffer with OA typically develop initial symptoms in middle age, with acceleration of symptoms after 50 years of age. Common symptoms include usage-related joint pain, morning or inactivity-related stiffness and movement restriction; with rest/night pain occurring with severe OA (Oarsi Primer Disease Diagnosis). Common signs of OA include crepitus, joint enlargement, reduced range of motion and joint line tenderness; with muscle weakness, atrophy and joint deformity in severe OA. Joint effusions may or may not be present.[9]

The diagnosis of OA remains clinical and may be made without radiographic or laboratory investigations.[10] OA is also a diagnosis of exclusion and the physician should rule out other forms of arthritis such as rheumatoid arthritis, psoriatic arthritis, septic arthritis, crystal arthropathies (which include gout), and so on.[11] The diagnosis of the severity of OA is based on quality-of-life questionnaires, physical examination and radiography.[12] A commonly used quality-of-life questionnaire is the Western Ontario McMaster Index (WOMAC), with higher scores indicating greater severity of OA.[13] In general, there is poor correlation between symptoms, disability and structural changes. Two large epidemiological studies – the Framingham Osteoarthritis Study[14] and the Osteoarthritis Initiative – demonstrated that

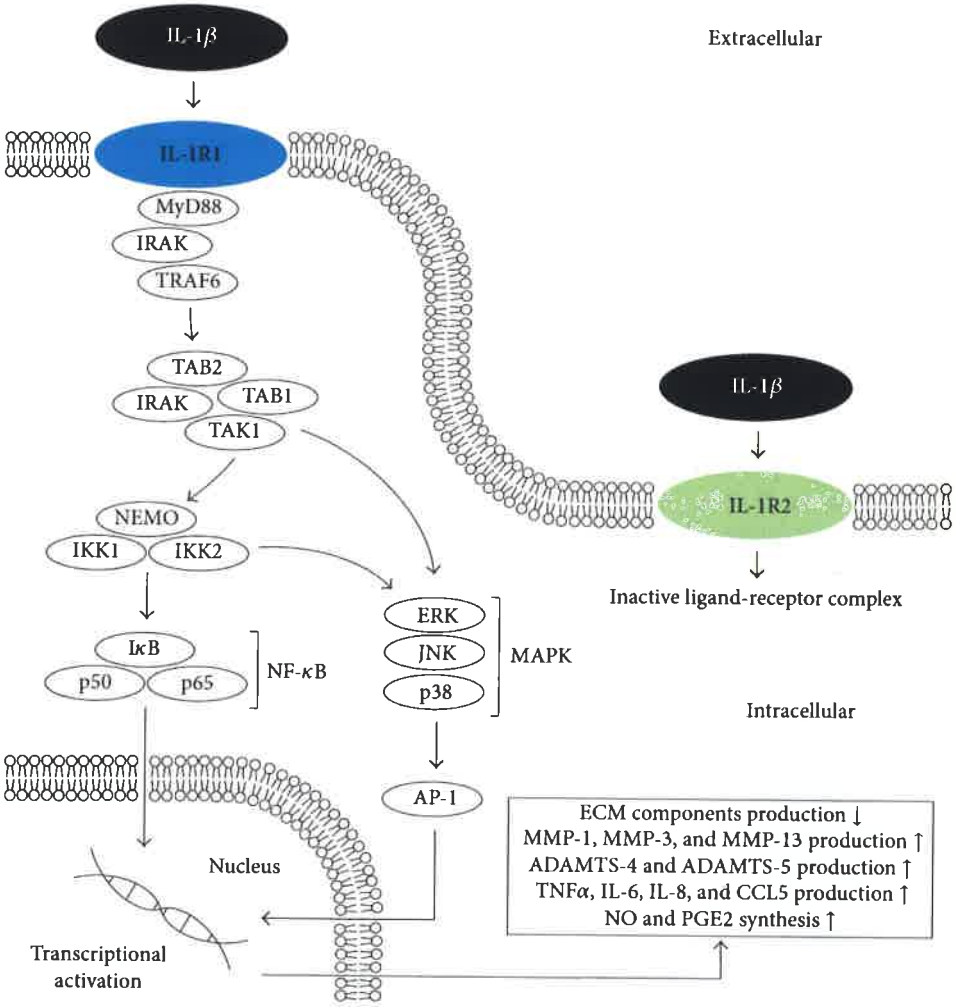



FIGURE 2: IL-1β associated intracellular signaling pathways and downstream cellular targets and effects. IL-1R1: interleukin-1 receptor, type 1; IL-1R2: interleukin-1 receptor, type 2; MyD88: myeloid differentiation primary response gene (88); IRAK: interleukin-1 receptor-associated kinase; TRAF6: TNF receptor-associated factor 6; TAK1: also known as mitogen-activated protein kinase kinase kinase 7 (MAP3K7); TAB1: also known as mitogen-activated protein kinase kinase kinase 7 interacting protein 1 (MAP3K7IP1); TAB2: also known as mitogen-activated protein kinase kinase kinase 7 interacting protein 2 (MAP3K7IP2); p50, p65: subunits of proteins forming NF-κB; IκB: (inhibitor of κB) an endogenous complex of proteins inhibiting the activation of NF-κB; IKK1,2/NEMO: NF-κB inhibitor kinase 1,2 (IκB kinase 1,2)/NF-κB kinase inhibitor (NF-κB essential modulator); ERK: extracellular-signal-regulated kinase; JNK: c-Jun N-terminal kinase; p38: p38 mitogen-activated protein kinases; MAPK: mitogen-activated protein kinases; AP-1: activator protein 1.

hip pain was not present most of the time when there was radiographic evidence of hip OA. Furthermore, many of the participants with painful hips did not have radiographic evidence of hip OA.[15]

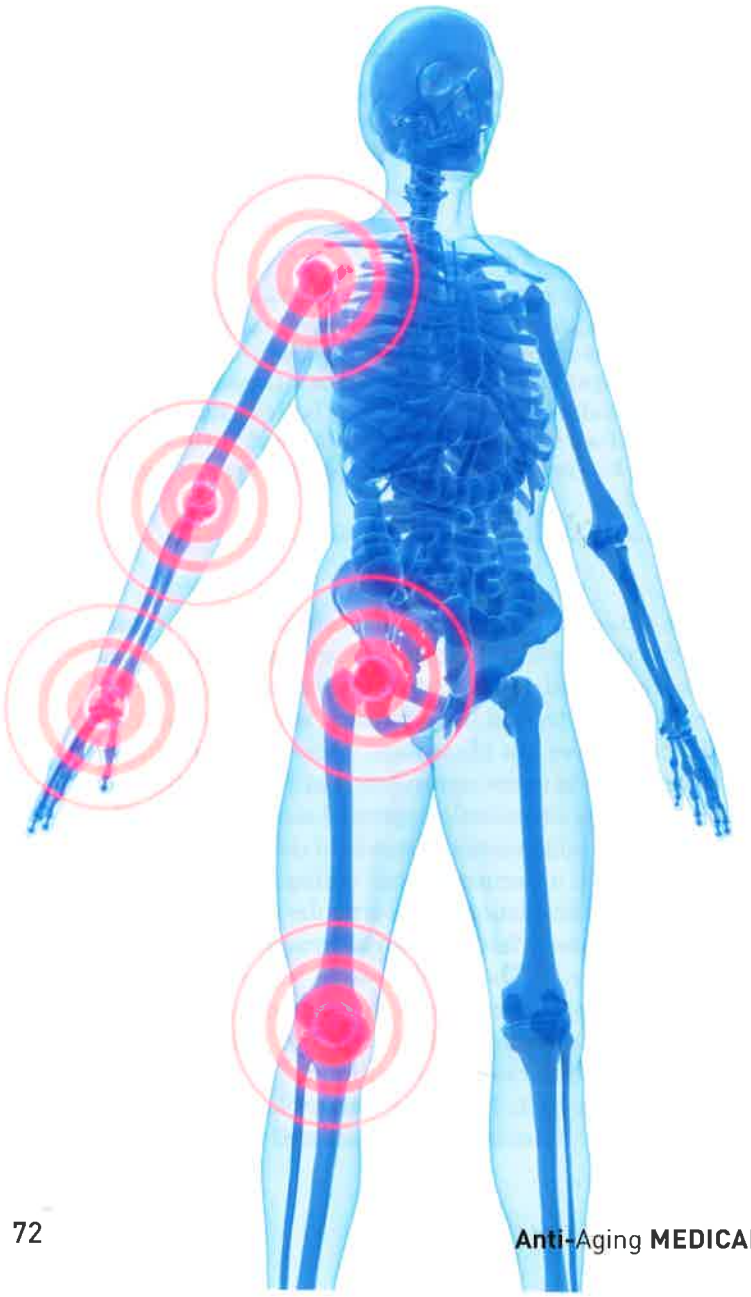
There is ongoing research attempting to find biomarkers useful in the diagnosis of osteoarthritis.[16] These biomarkers fall into 2 classes: biomarkers of joint tissue turnover and biomarkers of inflammatory status, which include cytokines, chemokines and cell type markers important in the pathology of OA. Unfortunately, there has been little clinical validation of these biomarkers and there remains a large, unmet medical need to identify, test, validate and qualify biomarkers for clinical use.[17]

Osteoarthritis results when there is an imbalance between the mechanical forces within a joint and the ability of the articular cartilage to withstand those forces. All the tissues in a joint – cartilage, bone, synovium, ligaments and adipose tissue – are involved in the osteoarthritic process. Once the tolerance of the articular cartilage to mechanical forces is exceeded, inflammatory mediators are released from chondrocytes and the synovium, which may result in the progressive loss of cartilage. Synovial macrophage activation results in the upregulation of NFkB, with many cytokines being abundantly expressed and released.[18] The feed-forward, inflammatory cascade of cellular responses to injury results in inflammatory cell infiltration, which leads to erosion and fibrillation of the articular cartilage, fibrosis, subchondral bone sclerosis, synovial hyperplasia and osteophyte formation.[19] The problem arises when the catabolic/inflammatory processes surpass the matrix anabolic/synthetic activities, leading to the progressive destruction of the articular cartilage in osteoarthritic joints.[20]

Interleukin-1 (IL-1) was the first cytokine discovered in the 1980s.[21] It has long been considered the most potent

catabolic cytokine. It coordinates systemic host defense responses to pathogens or various injuries. In the joint, it is released by synovial macrophages,[22] as well as by chondrocytes.[23] It results in the down-regulation of chondrocyte type II and proteoglycan synthesis. It also stimulates and enhances the release of chondrocyte-mediated cartilage destructive enzymes including matrix metalloproteinases and A Disintegrin And Metalloproteinase with Thrombospondin Motifs (ADAMTS), which is a family of peptidases. IL-1 has two known isoforms – IL-1α and IL-1β – and both bind to the IL-1R1 (IL-Receptor type 1). IL-1α is released intracellularly upon cell death and IL-1β is considered to act as an extracellular cytokine (Figure 2).[21]

Cells that are activated by IL-1 produce and release small amounts of the IL-1 inhibitor IL-1Ra (receptor antagonist), which has a down-regulating effect on the IL-1 inflammatory cascade.[24] It is understood that high levels of IL-1Ra are needed to effectively balance the impact of IL-1.[25] There is growing evidence that the introduction of IL-1Ra into joints results in significant down-regulation of the inflammatory cascade.[26]



Since OA of the knee is the most common presentation of osteoarthritis in clinical practice, the management will focus on this joint. Consensus-based treatment guidelines were developed by the Osteoarthritis Research Society International (OARSI) and provide the current, evidence-based approach for family physicians and primary care providers in the management of knee OA.[27] Looking carefully at these guidelines, it should be noted that there is no listing of intra-articular injections of hyaluronic acid. This treatment approach remains controversial, with proponents on either side. A recent systematic review concluded that "meta-analysis of only the double-blinded, sham-controlled trials with at least 60 patients did not show clinically important differences of hyaluronic acid treatment over placebo."[28]

Furthermore, based on the current understanding of the pathophysiology of osteoarthritis, none of the recommended treatments effectively address the upregulated inflammatory cascades and are considered palliative. The problem with oral anti-inflammatory-type agents is the significant and systemic adverse effects that occur and are routinely observed by family physicians and primary care providers. Finally, these guidelines make no mention of one of the most important and foundational treatment approaches as taught by Hippocrates: "Let Food Be Thy Medicine."

Using a focus on food to modulate the highly complex cascades of the inflammatory orchestra is the wisest approach. "Food first" is a foundational tenet of an Integrative/Functional approach to medicine. A simple and profound way to help patients discover which foods or beverages are up-regulating the inflammatory cascades, is to have them (and preferably those they live with) go through a Comprehensive Elimination Diet.[29] This is a foundational step towards health recovery that should not be skipped. It is an important tool that allows patients to become their own "medical detectives" and to discover for themselves which foods and/or beverages are triggering and mediating inflammation in general and, specifically, in their joints. This approach takes approximately 4-6 weeks and is a step-by-step, methodical elimination and then reintroduction of various food families. Foods to remove include: corn, dairy, eggs, gluten, simple processed sugars, shellfish, soy, beef, pork, processed meats, coffee, tea, chocolate and nightshades (tomato, white potato, bell peppers, eggplant, gogi berries, ashwaganda and tobacco). Foods to include: fruits, healthy oils, lean meats, legumes, nuts, seeds, vegetables and non-gluten grains. Instead of just giving lists of foods to patients, a new set of tasty recipes is introduced, making it easier to implement change. This program is given to the patient on the first visit and gives them "homework" to do prior to the second visit, which is usually 6 weeks later. This program helps to engage the patient and, when they discover for themselves the link between consumption of foods/beverages and joint inflammation, they become empowered and are much more likely to eliminate dietary triggers and mediators on an ongoing basis.

Besides eliminating dietary triggers and mediators of inflammation, it is also important to introduce foods, herbs and spices that have inflammation-modulating properties. Extra virgin olive oil has been shown to significantly reduce joint edema as well as cartilage destruction by down-regulation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-17.[30] Piperine from black pepper has a down-regulating effect on IL-1β in human osteoarthritis chondrocytes.[31] Piperine also increases the bioavailability of curcumin.[32] Cordyceps, a genus of ascomycete fungi, has a similar effect on down-regulating IL-1β.[33]

The spice with the most profound impact on inflammatory modulation is turmeric, which has been used in Ayurvedic medicine for over 4,000 years. It is the rhizome of the plant Curcuma longa and contains over 20 different active compounds, with the most prevalent being the curcuminoids.[34] Curcumin modifies over 80 molecular targets involved in the inflammatory orchestra.[35] A recent randomized controlled trial[36] studied the effects of taking 1 g per day of an oral curcumin formulation (curcumin plus phosphatidylcholine for better absorption) over 8 months. The 50 patients in the treatment group had a >50% decrease in WOMAC score and a threefold increase in treadmill walking distance as compared to the control group. Inflammatory biomarkers such as serum IL-1β, IL-6, soluble CD-40 ligand, soluble VCAM-1 and ESR were significantly decreased in the treatment group.

Avocado and soybean oils are often used in the manufacturing of soap. The unsaponifiable fraction of these oils is called avocado/soybean unsaponifiable or ASU.

ASU contains a number of inflammation-modulating phytochemicals such as phytosterols. Human clinical trials have been published showing improvement of OA in the test subjects as compared to the controls.[37]

Boswellia, also known as Frankincense, is a group of resins from the Boswellia Serrata tree. One of these resins, acetyl-keto-beta-boswellic acid, inhibits the lipooxygenase pathway and thus decreases inflammation. Nine clinical trials have been published demonstrating some benefit for OA.[38] Boswellia is often combined with other plant extracts such as curcumin for synergistic effect in OA.

A common antecedent, trigger and mediator for OA is ongoing obesity, which is an important modifiable factor when it comes to addressing OA.[39,40] Other mediators of inflammation could include overuse or misuse of joints, ongoing biotoxin exposure from overgrowths of certain organisms in the microbiome, ongoing exposure to other toxic influences such as heavy metals, chemicals and so on. When formulating a treatment approach for OA, it is important to think in terms of an anti-inflammatory lifestyle.

### Leading-Edge Approaches for OA

There is great concern that, in the not-too-distant future, the need and demand by the aging, general population will outstrip the availability of total joint replacements. As well, better approaches than palliation need to be developed that are safe and effective. To this end, ways to modulate the inflammatory cascades have been in development over the past few decades. The focus in the past has been to block the inflammatory pathways in order to decrease the catabolism within joints. Currently, the focus also includes looking at ways to cause tissue to regenerate, increasing the anabolic events within joints. The following are a few of the leading edge approaches that are now being utilized.

#### IL-1Ra (Interleukin-1 Receptor Antagonist protein)

IL-1Ra was first discovered in 1986 and, as previously mentioned, cells such as the chondrocytes, which produce and release IL-1β, also release small amounts of IL-1Ra. Other cells such as mononuclear cells and macrophages in the blood also produce and release cytokines as well as IL-1Ra.[41] Strategies to inhibit the biological activities of IL-1β have been developed. A recombinant IL-1Ra, known as Anakinra, has demonstrated the effective blockade of the IL-1 inflammatory cascade. A double-blind, placebo-controlled study (n = 170) concluded that it was safe to use in humans, but was not associated with improvements in OA symptoms as compared to placebo.[42] In 1994 it was discovered that if peripheral whole blood is drawn into a syringe containing glass beads coated with CrSO4 to initiate monocyte activation, incubated at 37.0°C for 24 hours and then centrifuged, the resulting serum is selectively enriched with the anti-inflammatory cytokines IL-1Ra, IL-4 and IL-10.[43] Subsequent research has shown that not only is the autologous conditioned serum (ACS) rich in these anti-inflammatory cytokines, but also contains over 35 other factors including fibroblast growth factor b (FGFb), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), IGF-1, platelet-derived growth factor (PDGF) and transforming growth factor β (TGF β) – as well as a number of the pro-inflammatory cytokines IL-1β and TNF-α.[44] The net effect is anti-inflammatory when the ACS is injected into osteoarthritic joints. This has been demonstrated in animal and human clinical trials with levels 1 and 2 scientific evidence – knees,[45] hips,[46] TMJ.[47] A recent prospective, observational study demonstrated the therapeutic power of collaboration using ACS and physiotherapy.[48]

#### Mesenchymal Stem Cells (MSCs)

A promising approach to cartilage regeneration in joints is the use of MSCs. MSCs occur in numerous tissues including bone marrow and adipose tissue.[49] MSCs have the ability to differentiate into bone, cartilage, muscle, as well as adipose tissue.[50] There is a growing scientific literature demonstrating that MSCs can successfully regenerate cartilage in animals and humans.[51] Adipose tissue-derived stem cells (ADSCs) in the form of stromal vascular fraction (SVF) contain stem cells that can differentiate into cartilage, bone, muscle and adipose tissue, similar to MSCs.[52] Recent studies have demonstrated that ADSCs can regenerate cartilage in the osteoarthritic knees of human patients.[53] Even more promising is the use of MSCs from bone marrow aspirate concentrate (BMAC), as it is an approved procedure by the FDA. BMAC, besides being

a source of MSCs, also contains various growth factors including PDGF, TGF-b, as well as bone morphogenetic protein (BMP)-2 and BMP-7, which are known to have both anabolic and anti-inflammatory effects.[54] A recently published review of the BMAC literature[55] concluded that overall, the outcomes reported with the use of BMAC for the treatment of early knee osteoarthritis are good to excellent. However, this field is in its infancy and the level of scientific evidence in the studies published varied from grades 2-4. There is a need for large, randomized controlled trials to evaluate the efficacy of BMAC for the treatment of knee pathologies.

### Case Study

A 64-year-old, married woman presented with a many-year history of progressive osteoarthritis affecting both knees (right > left), the lower back, neck, and small joints of her hands. She also had one kidney. Over the years, the pain and stiffness in her joints led to an inability to cook and do housework, loss of sleep, fatigue, anxiety and inability to golf, garden and line dance – which she was passionate about. She was careful about her diet and had previously gone through the comprehensive elimination diet. She also avoided gluten and nightshade foods; and since she had one kidney, she was careful to avoid medications such as NSAIDS and other analgesics. She had tried a number of oral herbal remedies with little improvement. On examination, she appeared tired, moved carefully and walked with a right-sided limp, was unable to flex her fingers more than 50%, and demonstrated decreased range of motion in her cervical and lumbar spine regions. Her right knee had a mild-moderate effusion and was warm to the touch, with tenderness over the joint lines and lacking full flexion. All standard laboratory work was within normal limits including CRP. X-rays showed moderate changes of osteoarthritis in the medial compartment of the right knee, as well as many of the PIP and DIP joints in both hands. Her initial WOMAC score was 44/96 or 45%. She met with the Family Nurse Practitioner in my clinic for three 1-hour educational sessions, reviewing the functional medicine anti-inflammatory lifestyle. She was assessed by an excellent physiotherapist for structural and functional problems that she had developed over the years as a result of the OA. She was then coached and supervised on specific flexibility and strengthening exercises by the physiotherapist. She was placed on oral curcumin twice daily with food and began twice-weekly intravenous curcumin treatments over 3 weeks. A total of five Autologous Conditioned Serum injections to the right knee were given over 3 weeks and tolerated well. An important component of the treatment program was ONDAMED® (German electromagnetic, focused electromagnetic field device) over 3 weeks. Following her third ACS injection, she reported the ability to line dance for 2 hours with no triggering of inflammation in her knees. The following 2 days she played 18 holes of golf each day, again without triggering inflammation. She had regained full function of her hands and had no further back and neck pain. Over the subsequent weeks she noted that she was able to sleep deeply, had increased energy, was able to do housework, cooking and gardening. Importantly, her chronic anxiety also resolved. At the end of the 3-week program, her WOMAC score had dropped to 11/96 or 11%; and one month later, the WOMAC score had dropped to 6/96 or 6%. At the 3-month follow-up she was clinically doing very well and the WOMAC score had dropped to 0/96, and this was maintained at the eighteen-month follow-up. This case demonstrates the importance of a multimodal approach combining the functional medicine anti-inflammatory lifestyle, Autologous Conditioned Serum joint injections, judicious use of curcumin, ONDAMED® and supervised exercise.

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