

## Inflammation in Osteoarthritis

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**Advances in the understanding of chondrocytes and the synovial membrane as targets of and participants in the inflammatory process in articular joints have provided insights into the role of inflammation in cartilage and subchondral bone injury in rheumatic diseases. Reports that describe the inflammatory cellular infiltration of synovial membranes in patients with osteoarthritis, studies that associate cartilage structural injury with synovial membrane inflammatory status, the development of new imaging modalities that quantitatively measure synovial membrane inflammation and basic science advances that explore inflammatory pathways in the synovial cavity all suggest that inflammation plays an important role in cartilage injury in osteoarthritis. As a result there is a shift in the notion that osteoarthritis is a disease caused merely by mechanical forces that increase joint loading. In response to this change in the current paradigm, innovative treatments involving the use of medications that modify the body's immune response (i.e., biologic and disease-modifying agents) are being studied. Implications for the population of Puerto Rico are discussed herein. [P R Health Sci J 2017;36:123-129]**

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Osteoarthritis (OA) is the most prevalent type of arthritis in the world with an estimated 250 million persons in the world (27 million in the United States (US) suffering from it (1, 2). The economic burden and negative impact on quality of life are issues that are often underestimated. The World Health Organization's Global Burden of Disease initiative reports that in 2010 OA is associated with approximately 17 million disability-adjusted life-years (1 disability-adjusted life-year is equivalent to 1 year of healthy life lost) in the world (994 thousand in the US) (3). OA is the most common rheumatic disease diagnosed at the time of hip and knee total joint replacement (4). The costs linked to OA have been estimated to equal from 1-2.5% of the gross national products of Australia, Canada, France, the United Kingdom and the United States (5, 6). All this is expected to increase as the population of the world grows older and the prevalence of obesity continues to increase.

Traditionally OA has been thought of as a disease of wear and tear. Risks associated with OA development due to increased joint loading include obesity, muscle weakness, joint instability or excessive laxity, occupation and acute joint injury (7). Joint loading has many effects in cartilage biology. Chondrocyte apoptosis is increased. There is a decrease in the release of proteoglycans and collagen by chondrocytes. The density of aggrecan molecules is decreased with a resultant increase in cartilage water content. The structural integrity of the transverse collagen layer of cartilage is altered resulting in a reduction of its function as a semipermeable membrane. Subchondral bone stiffens and is unable to lower pressure for cartilage exposed to an increased load (8). The end result is a gradual loss of articular cartilage, leading subsequently to the development of

OA. However, recent studies have begun to clarify the role of inflammation in the pathophysiology of cartilage deterioration and the biochemical aspects of the same. As a result clinicians and basic scientists are gaining a new understanding of the mechanisms of inflammation-related cartilage damage.

As early as 1959 Nettelbladt and Sunblad studying inflammatory proteins present in the serum and synovial fluids of patients with OA and of those with rheumatoid arthritis (RA) suggested that both diseases may share similar pathogenic pathways (9). They found that inflammatory markers were increased in both, OA and RA. However, the concentration of inflammatory proteins in serum and synovial fluid was much higher in RA than OA patients. The investigators suggested that inflammatory pathways were present in both diseases, albeit with a lower intensity in the OA group, a notion that conforms with the current knowledge that low-grade inflammation is present in many pathogenic states. Many years passed before the concept of inflammation in osteoarthritis was re-explored.

### OA and Synovitis

In 1988, Revell et al (10) reported on the histological features of synovial membranes obtained from the hip or knee joints of patients with primary OA versus OA with a traumatic/

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mechanical (T/M) origin. Upon comparing the synovial membranes of patients with OA of T/M origin with those of patients suffering from primary OA, Revell and his team found that synovial mononuclear infiltration, fibrosis, and perivascular fibrosis-characteristics of the inflammation seen in RA synovial membranes-were observed more frequently in the former than the latter. The authors obtained a total of 20 frozen sections of synovial membranes from the 2 groups. They stained the frozen sections with monoclonal antibodies that identified macrophages/monocytes, CD4+T-cells (OKT4), CD8+T-cells (OKT8) and B-cells (pan B-cell). All cell types were represented in the mononuclear infiltrates present in patients with primary OA and OA of T/M origin in areas that ranged from the intimal layer to the deep synovial layer. In 5 cases the mononuclear infiltrates looked histologically like lymphoid follicles. Macrophages/monocytes and T- and B-cells were found to be present within the lymphoid follicles.

Findings by Revell et al were validated and further characterized in latter studies using monoclonal antibody panels broader in spectrum and of greater specificity (11-13). Studies showed that Th-1 lymphocytes predominated and that mononuclear cells showed membrane receptors that identified macrophages, T- and B-cells and plasma cells at different stages of activation. All these findings are similar to those in RA synovial membranes, although occurring at a lesser intensity in OA, and strongly support the idea that inflammation is an important factor in cartilage injury in OA patients.

### Synovitis and Cartilage structural injury

The association of articular cartilage injury in OA with the presence of synovitis has been recently reported. In 2005 Ayral et al (14) reported on a longitudinal, 1 year prospective study in 422 patients with primary OA of the knee in which articular cartilage structural status, using well-defined and validated scores, was evaluated at the time of arthroscopic surgery (baseline) and 1 year after the initial arthroscopy. The severity of cartilage injury was evaluated in association with the arthroscopic pattern of the synovial membrane. Three synovial patterns were identified: the absence of synovitis; the presence of a reactive, non-inflammatory synovitis; and the presence of inflammatory synovitis. Primary OA patients with inflammatory synovitis had worse scores at baseline and greater amounts of articular cartilage structural damage 1 year after the initial arthroscopy than did those without synovitis or with reactive synovitis. The authors, however, did not find statistically significant differences between the groups. The percentage (%) of patients whose articular structural score progressed (based on predetermined criteria) was also studied. Over the course of the 1-year study period, articular cartilage damage was seen to progress in 12% (without synovitis), 13% (with reactive, non-inflammatory synovitis) and 28% (with inflammatory synovitis) of the patients. That a relatively higher percentage of patients suffering inflammatory synovitis (compared to those either without synovitis or with reactive synovitis) saw their articular

cartilage structural injury worsen was significant and suggests that inflammation contributes to articular damage in OA.

Reports that magnetic resonance imaging (MRI) and ultrasonography (US) reliably detect synovial inflammation led to studies in which the progression of OA (as assessed by x-ray) is associated with the presence and degree of synovial inflammation as detected by MRI or US. When MRI is used to detect synovitis in hand joints, high- grade synovitis (grade 2-3) is found to be significantly associated with joint space narrowing (JSN) and the development of erosion. This association is not significant when low- grade synovitis (grade 1) is detected (15). Similar findings have been reported when synovitis and joint effusion in hand joints are detected through US. Synovitis or synovial effusion grade 2 or 3 (as detected by US) was significantly associated with the progression of JSN. This association was not seen if the synovitis or synovial effusion detected was grade 1 (16).

MRIs are able to measure knee OA progression with precision (17). The association between the presence of synovial effusion, as a marker of synovitis, and Hoffa's fat pad synovitis of the knee (as assessed by MRI) and the progression of medial JSN seen in x-rays of the knee over a period of 4 years has been reported. Synovial effusion and Hoffa's fat pad synovitis were measured at baseline (P-0) or 1 year prior to baseline (P-1). Patients with synovial effusion or Hoffa's fat pad synovitis had significant progression of JSN compared to controls without knee effusion or knee synovitis when the effusion and synovitis were seen at both P-1 and P-0 (18).

### Basic science studies

Clinical and radiological studies that link synovial inflammation to articular cartilage structural injury and JSN have been complemented by basic science studies that explore this relationship. Basic science studies have suggested that pathogenic pathways in which inflammation contributes to cartilage injury in OA may exist. The presence of inflammatory mediators in the sera and synovial fluids of patients with OA (in comparison to the presence of same in subjects without arthritis or RA) has been studied. In OA multiple inflammatory and anti-inflammatory mediators have been reported to be present in both compartments, and in concentrations above those found in subjects with no arthritis but below those of subjects with RA (19, 20). Elevated levels of interleukin (IL)-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-7, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and vascular endothelial growth factor (VEGF), among many other cytokines, have been found in both the sera and synovial fluids of OA subjects. The effects of these inflammatory mediators in articular cartilage, chondrocytes and synoviocytes have been reported.

Receptors for IL-1 $\beta$ , TNF- $\alpha$  and IL-6 have been found in chondrocytes and synoviocytes. When stimulated there is an increase in cell expression in the chondrocytes of several matrix metalloproteinases (MMPs) such as MMP 1, 3 and 13, and prostaglandin E-2 (PGE-2), and aggrecanases such as a disintegrin and metalloproteinase with thrombospondin motif

4 (ADAMTS-4). In vitro cultures of chondrocytes with IL-1 $\beta$ , TNF- $\alpha$  or IL-6 consistently show decreases in proteoglycan and collagen synthesis by chondrocytes and increases in chondrocytes apoptosis (21-25). Studies of cartilage explants report decreases in the density of glycosaminoglycan within the proteoglycan molecule, decreases in aggrecan molecule size and density, and increases in cartilage matrix degradation products such as low molecular weight hyaluronic acid and biglycan (25).

Pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) 2 and 4, present in synovial fibroblasts and macrophages can recognize cartilage degradation products (biglycan, fibronectin, low molecular weight hyaluronic acid). Danger-associated molecular patterns (DAMPs) can recognize intracellular stress molecules (S-100 proteins or high mobility group 1). The recognition by PRRs and DAMPs of cartilage degradation substances are linked to the activation of the innate immune response and, as a consequence of this activation, in the release of inflammatory cytokines (such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6), chemokines and the recruitment of immune cells (19, 26-30).

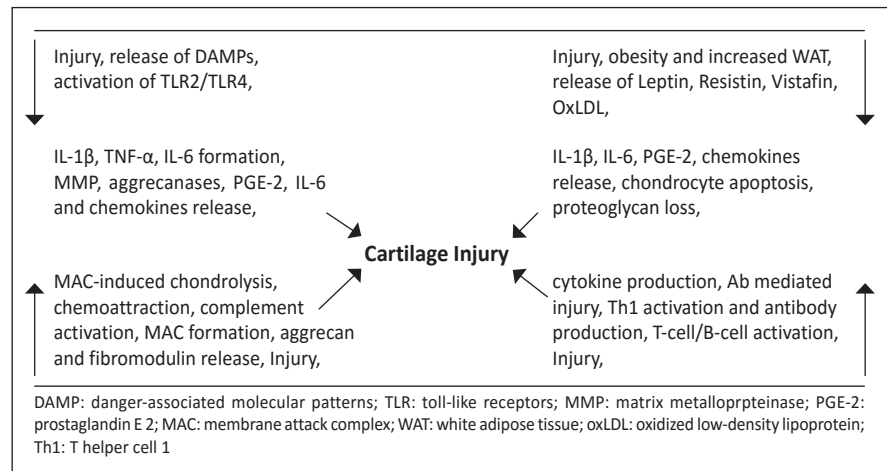
Complement has been found to be increased in the serum of OA subjects and is considered by some a biomarker of the arthritic process (31). It is also found to be elevated in the synovial cavity. The complement cascade in the synovial cavity is believed to be activated primarily through the mannan-binding lectin pathway by cartilage degradation molecules such as aggrecan and fibromodulin. The C5b-C9 membrane-attack complex causes direct injury to chondrocytes through formation of a pore and is believed to play an important role in cartilage injury in OA (32). Furthermore, complement molecules amplify the inflammatory cascade and further increase the recruitment of immune cells (33). Antigen-specific antibodies that form in response to the adaptive immune response are present in the synovial fluid of OA subjects and may activate the complement system. However, their contribution to cartilage injury is not believed to be significant.

Obesity and metabolic syndrome are identified as risks for the development of OA. They are also identified as risks for low-level inflammation which itself increases the risk of cardiovascular diseases and Alzheimer's disease. Leptin, resistin, and visfatin, formed and released by white adipose tissue, and oxidized low density lipoprotein (OxLDL), have actions in the cartilage that are similar to those of IL-1 $\beta$ , TNF- $\alpha$  and IL-6. Increased production of MMP, ADAMTS-4, IL-6 and PG-2 (all due to synovial-cells activation) has been reported. Increased proteoglycan and cartilage turnover (and decreases in their synthesis), increased chondrocyte apoptosis and chondrocyte depletion have been observed as results (34-37).

Four inflammatory pathways in OA are depicted in Figure 1. Cartilage injury, secondary to any cause, is believed to antecede the inflammatory process. Non-inflammatory injury to cartilage that results in the increased release of cartilage degradation products and increased chondrocyte stress and cellular death with the release of intracellular stress proteins triggers the different inflammatory pathways. Of the 4 inflammatory pathways described, the innate response pathway is believed to be the primary contributor to cartilage injury in OA. Regardless of the pathway, the end result of the inflammatory component is to accelerate cartilage degradation and, as a result, OA severity with an increase in pain, and decreases in joint functionality and quality of life. Thus, inflammation in OA is a process that increases disease burden and health care costs.

**Treatment**

As data of the role of inflammation in OA have become robust, studies that evaluate the effects of the treatment of OA with biologic agents and drugs that block the effects of IL-1 $\beta$ , TNF- $\alpha$  and other inflammatory cytokines have been conducted. These agents have been found to control damage to cartilage and bone, decrease pain, and increase joint function in RA. While small patient studies have suggested similar benefits in OA (38), clinical trials have failed to demonstrate that the use of biologic agents in the treatment of this disease will result in statistically significant improvements (Table 1). Two prospective, randomized, double-blind clinical trials using adalimumab have been published (39, 40). In one study, 40 mg of adalimumab or placebo was administered every 14 days for a period of 12 months to patients with hand OA. The study failed to demonstrate a decrease in the rate of joint space narrowing in patients who received adalimumab. In addition, there was no improvement in pain. In a second study 40 mg of adalimumab or placebo was administered at day 0 and 14 to subjects with hand OA. A global pain assessment was made by each patient at week 6. Thirty-five percent of the subjects who received adalimumab (versus 27.3% in the placebo group) experienced improvements greater than 50% in global hand pain, which was the study's



**Figure 1.** Potential inflammatory pathways in osteoarthritis

**Table 1.** Human trials evaluating the effect of biologic agents and methotrexate in osteoarthritis.

Biologic/DMARD	Type of Trial	Length	Findings
Adalimumab(38) : 40 mg subcutaneously every 14 days	Randomized, double- blind, prospective; 60 patients with HOA and 60 controls	12 months	No difference in structural progression or improvement in pain.
Adalimumab(39) : 40 mg subcutaneously days 1 and 14	Randomized, double- blind, placebo-controlled; 41 adalimumab and 37 controls with HOA	6 weeks	No difference in pain, global assessment of hand function or painful/swollen joints
Infliximab and incident hand OA in RA patients(40) (BeST study data analysis)	Observational, longitudinal study, to evaluate incident and progressive OA in 416 RA patients: infliximab versus DMARDs	Baseline and year 3 evaluation of hand X-rays	Reduced incident and progressive OA in DIP but not statistically significant; association between inflammation and progression of OA seen
Methotrexate(41) : 25 mg weekly	Prospective, randomized, primary KOA in 72 subjects and 72 controls	28 weeks	Statistically significant reduction in pain and improvement in ADL and synovitis confirmed by US

HOA: hand osteoarthritis; OA: osteoarthritis; DMARDs: disease modifying anti-rheumatic drugs; DIP: distal interphalangeal hand joints; KOA: knee osteoarthritis; ADL: activities of daily living; US, ultrasonography

primary outcome. However, differences were not statistically significant. In addition, no differences were seen in secondary end points such as the number of painful or swollen joints, the duration of morning stiffness and hand functionality indexes.

The effect of another TNF- $\alpha$  blocker, infliximab (INF), in incident and progressive secondary OA in patients with RA was studied in a 3-year observational, longitudinal study in which hand x-rays were evaluated at the time of recruitment and again 3 years after starting INF or a disease-modifying anti-rheumatic drug(s) (41). Subjects with worsening incident or progressive secondary OA of the distal interphalangeal joint (DIP), but not of the proximal interphalangeal joint (PIP), had higher inflammatory states than those who did not progress. INF had a tendency (relative risk 0.5 [95% confidence interval 0.5-10];  $p=0.059$ ) to decrease incident, but not progressive, hand OA in the PIPs only. This tendency to reduce incident OA was independent of inflammatory status and suggested to the authors that a non-anti-inflammatory effect of the drug may have been acting to decrease incident OA in RA patients treated with INF.

The effect of methotrexate (MTX) on OA of the knee has been recently published (42). In one clinical trial 144 patients with primary OA of the knee were randomized to receive MTX 25 mg once a week or placebo for 24 weeks. At the end of the study period knee pain was compared using a VAS pain scale (0-100); functional assessments were made using the Western Ontario and McMaster Universities Osteoarthritis Index and activities of daily living scores. Compared to controls, the subjects treated with MTX experienced improvements in all 3 primary endpoints ( $p$ -scores of 0.009, 0.001 and 0.032, respectively). In subjects with OA, MTX was found to be highly effective, both in the treatment of pain and in terms of the improvement of knee function. However, it has to be pointed out that this article has been voluntarily retracted due to unintentional errors in data statistical evaluation. The study protocol of a second methotrexate trial exploring knee OA has been published, is currently ongoing and may help clarify if MTX is truly effective in control of knee pain and knee function (43).

Hydroxychloroquine (HCQ) and colchicine have been suggested as treatments for OA. HCQ at a dose of 200 mg twice a day has been found to be effective in reducing pain in mild to moderate OA of the knee compared to placebo (44). In this double-blind randomized clinical trial OA patients treated with HCQ (versus those in the placebo group) had significant reductions in pain, and stiffness and improvements in knee function from weeks 8 to 24, with  $p$ -values of 0.049, 0.005 and 0.032 respectively. HCQ has been reported to be effective in the treatment of erosive OA of the hand, though prior reports of its effectiveness had not been confirmed. In a recent open randomized pilot study comparing clodronate to HCQ in erosive OA of the hand (45) the bisphosphonate was found to be effective in reducing pain and increasing function of the hand while HCQ was found ineffective in improving either end point. Two study protocols for randomized, double-blind, placebo-controlled studies that aim to evaluate the effectiveness of HCQ in erosive OA of the hand in an intention-to-treat analysis have been published. Both randomized clinical trials have been completed. The research findings of neither trial have been published. The first of the two studies, Hydroxychloroquine in patients with inflammatory and erosive osteoarthritis of the hands (OA TREAT, ISRCTN46445413) evaluated the efficacy of HCQ using clinical and radiological criteria, and explored as well HCQ safety over 12 months. The Hydroxychloroquine effectiveness in reducing symptoms of hand osteoarthritis (HERO, ISRCTN91859104) study evaluated improvement in hand pain and hand joints cartilage structural integrity over 12 months of HCQ or placebo treatment. An important aspect of the HERO study was the inclusion of hand USs when data were interpreted. Authors proposed to evaluate efficacy of HCQ versus placebo in the whole population of patients, but planned to do sub-analyses of efficacy based on joint inflammation as determined by US at the time of patient recruitment.

The results of a double-blind randomized controlled clinical trial (46) and a randomized controlled trial (47) evaluating the effectiveness of colchicine in controlling the symptoms



of knee pain due to OA have been published. Both studies used a dose of 0.5 mg twice a day of colchicine. In the first study significant improvements in patients' and physician's global assessment (at 12 weeks) were recorded compared to placebo ( $p=0.000$  and  $p=0.000$  respectively). In the second study (at 20 weeks) there was significant improvement in terms of pain compared to placebo ( $p=0.012$ ). The Colchicine effectiveness in symptom and inflammation modification in knee osteoarthritis (COLKOA, NCT02176460) trial protocol was published and the trial has been completed. Its findings and conclusions have not been published. This is an ambitious randomized controlled trial that proposed evaluation of clinical parameters; inflammatory biomarkers in serum, urine and synovial fluid; and cartilage degradation biomarkers, prospectively.

### Conclusions and Relevance to the Puerto Rican population

Osteoarthritis has long been considered a disease of wear and tear in which joint injury is believed to be caused by the force exerted to the joint throughout life. The presence of inflammatory infiltrates in synovial membranes of joints with primary OA, the association between synovial inflammation and structural joint injury and OA progression, the presence of inflammatory mediators in blood and synovial fluid of patients with OA and "in vitro" studies that have identified potential mechanisms by which inflammatory mediators cause cartilage injury linking it to OA progression are providing new insights in the pathogenesis of this particular type of arthritis. Understanding unsuspected pathogenic mechanisms of injury provides the opportunity to study new treatment options in a rheumatic disease that so far lacks a safe and effective treatment in terms of both, its prevention and the control of pain.

Although the use of biologic agents in OA have not been shown to reduce the progression of structural damage to articular cartilage, as seen in an intensely inflammatory arthritis such as RA, further studies are warranted since a tendency towards reduced structural damage in this type of arthritis was observed with the use of low-dose INF infusion in a relatively short time-frame. The intra-articular injection of INF is being studied as an alternative to systemic infusion in OA, with success in small pilot studies, but data from clinical trials have not been reported. The finding that pain relief and increased knee function in patients with OA may be obtained with the use of MTX at a well-tolerated dose may open new treatment avenues in a disease that for many decades has rapidly and progressively increased incapacity and decreased quality of life in afflicted persons around the globe. Several clinical trials have studied the efficacy and toxicity of HCQ and colchicine (though not in the same trial). Publications of the results are pending.

The implications of an inflammatory component as a risk for the development of OA are significant for society as a whole and for Puerto Rico's population in particular. The Centers for Disease Control and Prevention (CDC) National Diabetes Statistics Report 2014 reveals that the prevalence of diabetes in adults in Puerto Rico is 14.8%. A cross-sectional study done in

Puerto Rico and published in 2013 (48), reported that there is a significantly increased prevalence of OA in diabetics versus non-diabetics ( $p$ -value  $<0.01$ ). In diabetics the odds of having OA was 2.18 times greater than that of non-diabetics, particularly in females, whose odds ratio was 5.06-times greater than that of their male counterparts.

Metabolic syndrome is an inflammatory condition that may increase risk for the development of OA. As discussed in the basic science section cytokines released by white adipose tissue and OxLDL increase the production of MMPs and other proteins and cytokines that are injurious to cartilage. Perez et al (49) published their cross-sectional findings of 368 adults in the San Juan metropolitan area in 2012. Their group found that 42.9% of the population studied fitted the definition of metabolic syndrome. Levels of highly sensitive C-reactive protein (hs-CRP) were measured and found to be significantly associated with the syndrome when in the mid to upper tertiles. Elevated hs-CRP is a reflection of the low level inflammatory status found in this syndrome.

In 2014 the CDC's Division of Nutrition Physical Activity and Obesity reported a prevalence of obesity (defined as a body mass index above 30) in 28.3% of the adults in Puerto Rico. A sample of 5743 adults was studied. Obesity is considered a risk for OA secondary to increased joint loading. It is also a risk because of the low-grade inflammatory status present in obesity through increased white adipose tissue and the attendant increased risks for both diabetes and the metabolic syndrome.

Clinicians who care for patients with OA must be made aware that the current treatment of this type of arthritis is not restricted to pain control through the use of analgesics, intra-articular joint infiltration with corticosteroids or hyaluronic acid, exercise, reduction of joint load by use of devices such as a cane or weight loss. Care of these patients must include measures to decrease the inflammatory state. This is particularly relevant in Puerto Rico where high prevalence rates of obesity, diabetes and metabolic syndrome exist. In addition, clinicians must be attentive to publications describing results of randomized clinical trials with medications that reduce the inflammatory state in OA. These medications may finally provide new and effective treatments that reduce the severity of joint injury and pain in this specific type of arthritis.

## Resumen

Avances en el entendimiento del rol de los condrocitos y la membrana sinovial como blanco y participante del proceso inflamatorio en coyunturas ha provisto ideas novedosas sobre el rol de la inflamación en el daño al cartílago y hueso subcondral en enfermedades reumáticas. Reportes que describen la infiltración de células inflamatorias en membranas sinoviales de pacientes con osteoartritis, estudios que asocian daño estructural al cartílago y estatus inflamatorio de la membrana sinovial, desarrollo de modalidades de imágenes que permiten medir cuantitativamente el estatus inflamatorio de la membrana

celular y avances en las ciencias básicas que exploran los senderos inflamatorios en la cavidad articular sugieren que el proceso inflamatorio juega un papel importante en el daño al cartílago en osteoarthritis. Como resultado de estos avances, ha ocurrido un cambio en la noción que la osteoarthritis es una enfermedad ocasionada únicamente por fuerzas mecánicas que ocasionan un aumento en la fuerza aplicada al complejo articular. Como consecuencia de este cambio en paradigma, tratamientos que modifican la respuesta inmunológica del cuerpo tales como agentes biológicos y agentes modificantes de la respuesta inmune se están estudiando. Se discuten las implicaciones para la población de Puerto Rico.

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