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Review Article

A New Paradigm for the Management of Knee Osteoarthritis: The Role of Hyaluronic Acid, Platelet-Rich Plasma (PRP) and Ozone in the Modulation of Inflammation: A Review

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ABSTRACT

Context: Osteoarthritis (OA) is the most common cause of arthritis. Traditionally, OA was considered a "wear and tear" disease. However, metabolic and inflammatory factors are now being considered as pathogenic factors to an extent that some authors are redefining OA as a "low-grade chronic inflammation" disease.

Evidence: In knee OA, many signaling pathways and inflammatory mediators are involved. The new paradigm of treatment is based on the assumption of signaling cell treatments, based on cellular and protein components to combat the inflammatory environment of the arthritic joint and regenerate damaged tissue.

Results: A treat-to-target approach (inhibitors of Nitric Oxide, nutraceuticals, urate lowering agents and biologic drugs) that has shown effectiveness in the management of inflammatory diseases such as in rheumatoid arthritis has not been effectively translated into OA. A multi-target approach would be capable of managing OA more efficiently. Standard Guidelines (AAOS, OARSI, ACR, NICE or EULAR) do not consider hyaluronic acid, platelet-rich plasma and Ozone, although these treatment options have shown immunomodulatory and healing properties. In that scenario, we hypothesize that hyaluronic acid, platelet-rich plasma and ozone are promising alternatives for the management of knee OA, because of their multi-target properties, as it was observed in this review.

Conclusion: The present study reviewed the pathophysiology of OA, focusing mainly on the inflammatory mechanism, the signalling pathways involved and the possible targets of treatment. Hyaluronic acid, Platelet-rich plasma and Ozone are postulated as multi-target treatment options for the management of knee OA.

Context

Osteoarthritis (OA) is a very usual source of arthritis. OA has a direct impact on quality of life to such an extent that it is the 11th global contributor to disability worldwide. The burden of the disease in terms of cost is such that it is estimated that 4 million people are affected in Spain, representing an annual cost of 4,378 million euros every year, representing 0.5% of Gross Domestic Product [1]. OA constitutes an important problem of Public Health. In people over 60 years, 13% refer symptomatic knee OA; in people over 70 years, 27% present radiological signs of OA and in people over 80 years, 44% present radiological signs and clinical symptoms [2].

Classically, OA was considered a "wear and tear" disease. However, metabolic and inflammatory factors are new pathogenic factors. In fact, some authors are redefining OA as a "low-grade chronic inflammation"

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disease [3]. Therefore, there is a change in paradigm for OA, from the biomechanical to the Inflammatory theory [2, 3]. The biomechanical theory states that OA is a mechanically induced disease. The joint cartilage gets overloaded as a result of malalignment, poor mechanics and impact. This overloading compromises the supporting structure of the cartilage, causing it to soften and degrade. Once the cartilage softens, the bone underneath stiffens, and the joint breaks down. If overloading is not reversed, OA would progress. Once subchondral bone elasticity is gone, progressive destruction of cartilage and bone leads to the formation of osteophytes to increase surface area, thereby diminishing load. Finally, progression of joint deformity moves the weight bearing axis into the opposite compartment, and additional joint destruction continues. At this stage, total knee arthroplasty is indicated, as final treatment [4].

The inflammatory and immune theory states that in the cartilage, cells are exposed to shear forces within the Extracellular Matrix (ECM) and at the joint surface. As a consequence, ECM is destroyed, releasing inflammatory cytokines such as IL-6, IL-8, matrix mineral metalloproteases (MMP), leukemia inhibitory factor (LIF) and Oncostatin M (OSM). These danger signals activate second messengers, enhancing the inflammatory environment. Moreover, the senescence of cartilage induces apoptosis and inflammatory responses are enhanced. This inflammatory cells and signals incite an inflammatory cascade that overwhelms the native healing response, leading to a catabolic state producing more cartilage destruction [4].

ECM can be destroyed by inflammation or by apoptosis mechanisms, which are mediated by immune or inflammatory responses [4]. In this inflammatory environment, acting on well-known signaling cascades, cell and protein signaling might encourage favorable healing responses [4]. Mesenchymal stem cells reduce inflammation, fight apoptosis (cell death), self-replicate and differentiate into multiple tissues. Platelet-rich plasma (PRP) contains almost 1200 proteins, included growth factors and anti-inflammatory cytokines [4]. They block inflammation and stimulate healing of cartilage [4]. The new paradigm of knee OA management is based on signaling cell treatments, based on cellular and protein components. It is expected that both components might interact with resident stem cells, inflammatory and immune cells to combat the inflammatory environment of the joint and regenerate damaged tissue [4].

Today, there is no cure for OA. The goal of treatment on the short term is to decrease pain and to recover patients' quality of life and function; and in the long term, to slow/stop progression of the disease [1]. The latest treatment choices for knee OA management by intra-articular infiltrations include hyaluronic acid (HA), glucocorticoids, analgesics, and unproven alternative therapies, such as platelet-rich plasma (PRP) or even Ozone [1, 5]. The good results obtained by Biologic Drugs that fight inflammation as in Rheumatoid arthritis, based on a treat-to-target approach, have not been translated to the management of knee OA [5].

Since in the origin of Knee OA many signaling pathways and inflammatory mediators are involved, we postulate that a multi-target approach would be successful for the management of knee OA. HA, PRP and Ozone act on the modulation of inflammation via different mediators and signaling pathways; therefore, it is expected that these treatment options, considering their multi-target profile, might have a role in the management of knee OA in the near future [1, 4, 5]. The objective of the present study is to review the pathophysiology of OA, focusing mainly on the inflammatory mechanism, the signaling pathways involved and the possible targets of treatment, and to postulate HA, PRP and Ozone as multi-target treatment options for the management of knee OA.

Evidence Acquisition

I Pathogenesis and diagnosis of Osteoarthritis

As people age, people´s cartilage suffers histological changes and degenerates. As a result, catabolic enzymes (MMP1 [matrix metalloproteases], MMP10, MMP13, IL-1α, IL-6, IL-7, IL-8), glycation end products, ROS (reactive oxygen species), apoptotic and necrotic cells appear, and ECM breaks down [6]. ROS, inflammatory cytokines and catabolic proteins are involved in the aging process of articular cartilage [6].

For the reparation of cartilage, it is necessary to act on mesenchymal stem cells (MSC). Normally, some stimuli like TGF-β (transforming growth factor β), IGF-1 (insulin growing factor 1), mechanical load and hypoxia induce chondroblasts to differentiate into specific chondrocytes and to produce elastic cartilage, hyaline cartilage and fibrocartilage [6]. As a result, articular cartilage and collagen type II, IX and X is produced [6]. OA is produced by modifiable risk factors (obesity, occupation, injury, physical activity, sports) and by non-modifiable risk factors (gender, age, genetics, hormones and diet). OA is presented as a group of signs and symptoms, including pain, swelling, joint stiffness and muscle weakness [7].

According to the EULAR (European League against Rheumatism), for the diagnosis of OA, at least 3 symptoms and 3 clinical and laboratorial signs should be present. Clinical signs and symptoms include pain, stiffness, loss of function, crepitus, loss of range of motion and bony enlargement. Laboratorial signs include ESR (erythrocyte sedimentation rate) lower than 40mm/h, rheumatic factor lower than 1:40 and synovial fluid with leucocytes lower than 2000/uL [8]. OA is classified by Kellgren and Lawrence (KL) in 4 grades. In KL grade 1, there is suspicion of narrowing of joint space and possible osteophyte overgrowth. KL grade 2 shows possible narrowing of joint space and definite osteophytes. KL grade 3 depicts definitive sclerosis and narrowing of minimal joint space, and possible bony irregularity. KL grade 4 is characterized by great osteophytes, important narrowing of minimal joint space, major sclerosis, and certain bony irregularity [8]. OA diagnosis is clinical and radiological. Unfortunately, the beginning of OA is produced before radiological diagnosis is performed. In this stage, radiography is not capable of detecting early OA stages. Early diagnosis will let us stablish preventive treatment in order to slow or to stop cartilage destruction [9]. A biomarker is a quantifiable marker of a biological process. In OA, a biomarker should compromise osteogenesis and inflammation. A biomarker in OA quantifies the osteogenic or inflammatory changes observed in serum, urine or synovial fluid; and this change, whether growing or degrading of tissue, might even precede the radiographic changes [9].

For knee OA, inflammatory and non-inflammatory biomarkers are considered. Non inflammatory biomarkers include collagen metabolic biomarkers (CTX-I [C-terminal telopeptide], CTX-II), non-collagen

metabolic biomarkers (proteoglycans, aggrecanases [chondroitin sulphate, queratan sulphate], non- aggrecanases [hyaluronic acid, osteocalcin, osteopontine, folastine]. Inflammatory biomarkers are divided in pro-inflammatory and anti-inflammatory. Pro-inflammatory biomarkers include adipokines (leptin, adiponectin, visfatin and resistin), interleukins (IL-1β, IL-6, IL-15, IL-17, IL-18), chemokines (TNF-α), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and uric acid. Anti-inflammatory biomarkers include cytokines such as IL-4, IL-7, IL-8, IL-10 and IL-13 [9].

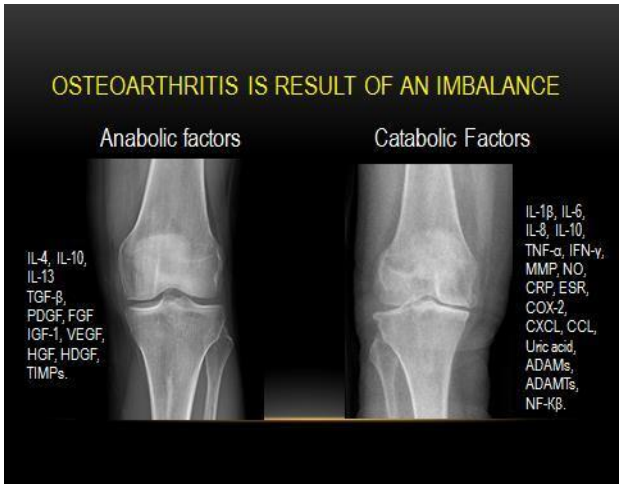

Figure 1: Osteoarthritis is the result of an imbalance between anabolic and catabolic factors where pro-inflammatory cytokines and catabolic chemokines predominates over anti-inflammatory cytokines and anabolic chemokines.

MMP: matrix mineral metalloproteases, ADAMs: disintegrin and metalloprotease, ADAMTS: disintegrin and metalloprotease with thrombospondin motifs, NO: nitric oxide, TNF-α: tumor necrosis factor α, iNOS: Inducible Nitric Oxide Synthase, COX-2: cyclooxygenase-2, CXCL: chemokine receptor, CCL: chemokine ligand, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TGF-β: transforming growth factor β, HGF: hepatocyte growth factor, VEGF: vascular endothelial growth factor, EGF: endothelial growth factor, IGF-1: insulin growing factor 1, HDGF: hepatocyte derived growth factor, TIMPS: Tissue inhibitor of metalloprotease, NF-Kβ: nuclear factor Kβ.

The pathophysiology of OA is very complex. In knee OA there is an imbalance between anabolic and catabolic factors. Catabolic factors include inflammatory cytokines (IL-1β, IL-6, IL-15, IL-17, IL-18, TNF-α, LIF [leukemia inhibiting factors]) and proteolytic enzymes (MMP-1, MMP3 and aggrecanases [ADAMTs]). Anabolic factors comprise anti-inflammatory cytokines (IL-4, IL-10) and anabolic cytokines (TGF-β, IGF-1, FGF-18 [fibroblast growth factor] and PDGF [platelet derived growth factor]) [10]. Inflammatory and catabolic factors produce and imbalance leading a healthy articulation to develop knee OA (Figure 1) [11].

Leptin is an adipokine with inflammatory effect. An increase in body weight and an expansion of white adipose tissue leads to a rise in mechanical load; then, cartilage degradation is the final result, triggering OA development. On the other hand, Leptin derived by adipose tissue (overproduction in obese patients) is related to dysregulation of osteoblast at subchondral bone tissue, producing joint wear and tear damage. In addition, leptin releases pro-inflammatory cytokines derived by adaptive and innate immune cells, creating an inflammatory milieu that favors cartilage destruction and OA [12].

Apart from Leptin, others adipokines such as Visfatin produces ROS and pro-inflammatory cytokines lead to inflammation and degradation of the cartilage [13]. Obesity and metabolic syndrome is related to low-grade chronic inflammation, leading to articular lesion, pain and disability. Metabolic syndrome/obesity releases IL-1β, IL-6, PgE2, TNF-α, Adipokines. The catabolic factors produce synovitis, subchondral sclerosis and articular lesion [13].

Denoble has stated that uric acid is related to OA degradation via inflammasome (NLRP3) [14]. OA joints release nucleating agents that promote crystallization of urate. As OA progresses, the death of cells releases uric acid. In hyperuricemic patients, uric acid diffuses from blood to synovial fluid at the joint. Theses mechanisms, diffusion or apoptosis produce subacute inflammation and favors OA progression by activation of inflammasome pathway [14]. Similarly, Mc Alister states that NLRP3 (inflammasome) might be activated via the NF-Kβ [nuclear factor-Kβ] pathway or via caspases, releasing inflammatory cytokines (IL-1β and IL-18), leading to chronic inflammation, favoring the progression of OA [15]. Wehmeyer states that OA and rheumatoid arthritis (RA) share the RANKL [Receptor activator of nuclear factor kappa-β ligand] or NF-Kβ signaling pathway and blocking that pathway would be a valid treatment option [16]. Pulsatelli states that OA is not only a cartilage but a subchondral bone and a synovial tissue disease [17]. Various signaling pathways act upon chondrocytes, leading to cartilage derangement and bone formation in OA [16]. Blocking those signaling pathways could avoid OA progression [17].

Kennedy states that inflammatory cytokines (IL-1β, IL-6, TNF-α) may act on several signaling pathways. They may release ROS and act over cartilage degradation. They may also act over matrix MMPs leading to degradation of collagen type X. Inflammatory cytokines may also act on RANKL membrane ligand, activating nuclear NF-Kβ pathway, acting over transcription factor SOX-9 (chondrogenic protein) and COX-2 (cyclooxygenase), degrading collagen type II [18].

Mobasheri states that not only pathogenesis of OA is complex, but OA phenotypes are varied [19]. There are several phenotypes in arthrosis (ageing-driven, cartilage-driven, traumatic injury-driven, synovitis-driven, metabolic and subchondral bone phenotype); metabolism is involved in several of them; and also share similar signaling pathways [19]. In this regard, Berembaum argues that the metabolic syndrome releases inflammatory mediators to the blood, which are harmful to joint tissues and initiate or perpetuate this process. Once the arthritic cells are activated, they release inflammatory mediators to the joint and the blood, amplifying low-grade inflammation, accelerating other chronic, low-grade systemic diseases [20].

Therefore, not only does metabolic syndrome worsen OA, but acute trauma, aging and crystal diseases also, releasing systemic mediators of inflammation that would worsen diseases such as Alzheimer's, arteriosclerosis or acute myocardial infarction [20]. As a resume, OA is affected by low-grade chronic inflammation as presented in metabolic syndrome (obesity, insulin resistance, lipid abnormalities, hypertension), and OA development contributes to low-grade chronic inflammation, via

systemic effects of OA-derived inflammatory mediators, inducing and accelerating other chronic diseases (Alzheimer disease, stroke, myocardial infarction) [20].

The altered body composition, the altered metabolites and inflammation derived from fatty tissue and synovial tissue release inflammatory mediators that worsen OA. Abnormal dietary factors and dysfunctional fat tissue produce and increase of adipokines which lead to a greater risk for OA development, due to release of mediators of inflammation (complement, CRP, cytokines) [21]. Guisasola and Ortiz demonstrated that in acute polytraumatism there is an elevation of inflammatory cytokines (IL-1β, IL-6, TNF-α and the Heat Shock Proteins) [22]. The perpetuation of an acute aggression that results in chronic inflammation can induce post traumatic OA. Lieberthal states that the resolution of the inflammation with specific cytokine blockade would solve the problem [23].

II Treat-To Target Approach

Since there is no cure for OA, there are many therapeutic targets in study for the treatment of OA. [24]. The standard treatment in advanced OA is total replacement arthroplasty, with an efficiency of 95% at 10 years and 90% at 15 years [1]. However, this approach is not exempt of risks and complications [1]. For the management of early OA many targets are proposed as therapeutic options. Therapeutic targets include: a) regulators of mitochondrial function, b) nutraceuticals, c) regulators of apoptosis, d) iNOS [Inducible Nitric Oxide Synthase] inhibitors, e)analgesics and NSAIDs[non-steroidal anti-inflammatory drugs], f) MMP inhibitors, g)pro-inflammatory cytokine blockers, h)herbal medicines, i)bone density conservation agents, j)bisphosphonates and k)strontium ranelate [24].

i Inhibitors of Nitric Oxide and Antioxidants

Inhibitors of Nitric Oxide and antioxidants are capable of modulating inflammation, but they are not useful for the management of OA [25, 26].

ii Nutraceuticals

Curcumin was able to slow OA progression and to decrease OA-related pain symptoms in post-traumatic OA mouse model. Unfortunately, these findings were not corroborated on humans yet [27].

iii Urate Lowering Agents

OA, rheumatoid arthritis and gout share similar signaling pathways. Unfortunately, drugs that decrease levels of uric acid (such as allopurinol or uricosuric drugs) do not diminish risk for total knee replacement [28]. Colchicine is an antimitotic and anti-inflammatory drug. In a recent study, colchicine showed a reduction of inflammation and of biomarkers of bone turnover (both factors related to progression and severity in OA patients); but on the long-term (16-week follow-up), colchicine was not capable of reducing knee OA symptoms [29].

iv Biological Therapy

Biological Therapy directed to specific cytokines or interleukins such as Anakinra, Infliximab, Etanercept, Adalimumab, Tocilizumab, or Denosumab has demonstrated effectiveness in the management of Rheumatoid Arthritis (RA); unfortunately, biological drugs have not demonstrated effectiveness on the management of OA, there is no disease modifying effect in the progression of OA [20]. Biologic drugs target inflammatory processes, but their excellent results observed in RA have not been successfully translated to OA [30].

v Targeting IL-1

IL-1β is a cytokine related to inflammation and catabolic process that favor joint cartilage degradation and destruction [30]. Anakinra (an antagonist of IL-1β) did not produced improvement in OA symptoms if compared to placebo [20, 30].

vi Targeting TNF-α

TNF-α is a pro-inflammatory cytokine that targets chondrocytes producing cartilage loss [30]. Infliximab (Remicade®) showed initial tolerability in early exploratory trials but was not effective in the management of knee OA [20, 30]. Etanercept (Enbrel®) showed effectiveness in the relief of pain, but the effect lasted only 4 weeks [30]. Adalimumab (Humira®) was safe and improved symptoms in OA, but it has not progressed in the management of knee OA [30].

III Multi-Target Approach

i Exercise and Loss of Weight

Exercise increases anti-inflammatory IL-10 in peri-synovial and intra-articular site of the knee [31]. Weight loss decreases IL-6 and Leptin and improves pain, function, quality of life, muscular strength and endurance in symptomatic knee OA patients [32]. Exercise and loss of weight might act as a multi-target approach decreasing inflammatory cytokines and adipokines (IL-6, Leptin) and increasing anti-inflammatory cytokines (IL-10) [31, 32].

ii Hyaluronic Acid

Hyaluronic acid (HA) is a component of the synovial fluid and it is responsible for its viscoelasticity fluid [33]. In OA, the concentration and molecular weight of HA is decreased, leading to a reduced mechanical protection of the joint [33]. Intra-articular (IA) infiltration of HA might restore the elasticity of the synovial fluid, adding shock absorption, lubrication and protection of the joint [33]. Moreover, HA increased proliferation of chondrocyte and decreased its apoptosis, decelerating destruction and progressive joint space narrowing, which is related to OA, acting as a chondroprotective agent [33]. HA anti-inflammatory and analgesic effects have also been reported in literature [33].

Nichols has stated that HA is possible to act on ECM degradation and on inflammation and pain [34]. Depending of molecular weight, HA might act on different degradation and inflammation cytokines [34]. In Nichols study, Low Molecular Weight (LMW) HA inhibited MME (macrophage metalloelastase) and MMP-10 (matrix metalloproteinase), responsible

for ECM degradation [34]. Low Molecular Weight (LMW) HA also inhibited CCL-2 (Chemokine ligand), CCL-3, CCL-4, CXCL-2 (chemokine receptor), CXCL-9, CXCL-10 and IL-12, responsible for the presentation of inflammation/pain [34]. High Molecular Weight (HMW) HA inhibited ADAM-17(disintegrin and metalloprotease), ADAMTS-4 (disintegrin and metalloprotease with thrombospondin motifs), ADAMTS-5, and MMP-1, MMP-2, MMP-3, related to ECM degradation. High Molecular Weight (HMW) HA also inhibited IL-6, NF-Kβ (nuclear factor), phospho-Akt (Ak strain transforming), phospho-JNK (c-jun N-terminal kinase) and TLR-4 (toll-like receptor), cytokines related to presence of pain and inflammation. Both LMW HA and HMW HA might act on MMP-9 and MMP-13, inhibiting ECM degradation. LMW HA and HMW HA inhibit IL-1β, IL-8, TNF-α, CCL-5, iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase), responsible for the presentation of pain and inflammation (Table 1) [34]. HA acts on symptomatic (pain and inflammation) and disease modifying (ECM degradation) effects in OA, therefore HA might constitute a multi-target drug and a valid option for the management of knee OA [34].

Table 1: Multi-target profile of Hyaluronic acid, Platelet-rich plasma and Ozone with stimulation (↑) and inhibition (↓) effects.

Cytokines, molecules, signaling pathways	Hyaluronic acid	Platelet-rich plasma	Ozone
Catabolic chemokines	↓MMP, ↓ADAMs, ↓ADAMTS [34].	↓NO [18], ↓MMP, ↓ADAMTS-5 [35].	↓MMP, ↓NO [1,42].
Inflammatory cytokines	↓IL-1β, ↓IL-6, ↓IL-8, ↓IL-12, ↓TNF-α, ↓iNOS, ↓COX-2, ↓CXCL1,2,9,10, ↓CCL2,3,4 [34].	↓IL-1β [2], ↓TNF-α [18,38], ↓IL-6, ↓COX-2 [35].	↓IL-1, ↓TNF-α, ↓IFN-γ, ↓IFN-β [1,40], ↓COX-2 [12], ↓CRP, ↓ESR, ↓Uric acid [41,42].
Anabolic chemokines	↑TGF-β, ↑PDGF [49].	↑TGF-β, ↑HGF, ↑VEGF, ↑EGF, ↑IGF-1, ↑HDGF [2,18,37], ↑TIMPS [35].	↑TGF-β, ↑IGF-1 [1,40].
Anti-inflammatory cytokines	↑IL-10 [47].	↑IL-4, ↑IL-10, ↑IL-13 [35].	↑IL-4, ↑IL-6, ↑IL-10 ↑IL-13 [1,42].
Signaling pathway	↓NF-Kβ [34].	↓NF-Kβ [2,37,38].	↓NF-Kβ [12]

↓ : Inhibition, ↑ : Stimulation, MMP: matrix mineral metalloproteases, ADAMs: disintegrin and metalloprotease, ADAMTS: disintegrin and metalloprotease with thrombospondin motifs, NO: nitric oxide, TNF-α: tumor necrosis factor α, iNOS: Inducible Nitric Oxide Synthase, COX-2: cyclooxygenase-2, CXCL: chemokine receptor, CCL: chemokine ligand, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, TGF-β: transforming growth factor β, HGF: hepatocyte growth factor, VEGF: vascular endothelial growth factor, EGF: endothelial growth factor, IGF-1: insulin growing factor 1, HDGF: hepatocyte derived growth factor, TIMPS: Tissue inhibitor of metalloprotease, NF-Kβ: nuclear factor Kβ.

iii Platelet-Rich Plasma (PRP)

Platelet-rich plasma is an autologous product that by means of centrifugation elevates the level of platelets several times from that observed in blood serum [30]. PRP carries several mediators that communicate with joint cells [30]. Some authors state that PRP contains 300 molecules or proteins identified by proteomics in the α-granules, while others sustain that PRP contains almost 800 proteins and even 1200 proteins, included growth factors (GFs) and anti-inflammatory cytokines [4, 35-37]. Those GFs and cytokines might block inflammation and stimulate healing of cartilage [4, 30, 35-37].

Kennedy states that PRP modulates inflammation inhibiting IL-1β and TNF-α. PRP favors the proliferation and cell renewal by stimulation of TGF-β (transforming growth factor) and HGF (hepatocyte growth factor), VEGF (vascular endothelial growth factor), EGF (endothelial growth factor), IGF-1 (insulin growing factor) and PDGF (platelet derived growth factor) [18]. Indeed, HGF inhibits NF-Kβ and decreases NO (nitric oxide) synthesis [18]. Ornetti published that PRP, via HGF inhibits the NF-Kβ pathway [37]. PRP via IGF-1 is also capable of inhibiting the NF-Kβ pathway [37]. HGF limits the inflammatory response within the synovial membrane [37]. Demange stated that PRP is capable of attenuating pro-inflammatory cytokines such as NF-Kβ and IL-1 (Table 1) [38]. PRP may act over different cytokines and signaling pathways, modulating inflammation and decreasing cartilage degradation and promoting cartilage healing [4, 30, 35-38]. The multi-target profile of PRP makes this intervention as a promising alternative for the management of knee OA.

iv Ozone (O2-O3)

Ozone (O2-O3) modulates inflammation and pain in knee OA patients [39]. Moreover, the anabolic effect of Ozone (O2-O3) could play an important role in modifying the natural history of OA disease, as recently reported in a clinical case [40, 41].

Lately, Fernández-Cuadros et al reported the immunomodulatory and anabolic properties of Ozone (O2-O3) by means of upregulation of anti-inflammatory cytokines (IL-4, IL-10), growth factors(TGF-β, IGF-1) and stem cells and down-regulation of inflammatory and catabolic cytokines (MMPS, NO [nitric oxide], PgE2 [prostaglandin E2]) (Table 1) [1, 41]. Manoto has stated that ROS activate NF-Kβ pathway leading to apoptosis of cartilage. He has proven that Ozone might block NF- Kβ, decreasing inflammatory cytokines such as IL-1β, IL-6, TNF-α, and COX-2, considering Ozone (O2-O3) as a promising option for cartilage in knee OA patients [12]. Fernández-Cuadros has observed that intra-articular Ozone is capable of decreasing CRP, ESR (erythrocyte sedimentation rate) and uric acid, recognized as inflammation biomarkers in knee OA patients, confirming that Ozone modulates inflammation (Table 1) [39, 42]. For the previous statements, it is expected that Ozone (O2-O3) may play a role in the treatment of knee OA patients [41, 43].

Results

This is the first article that reviews the role of inflammation as the leading cause in the pathogenesis of OA and postulates HA, PRP and Ozone as possible treatment options because of its multi-target profile in the modulation of inflammation. OA pathophysiology is very complex. There are many signaling pathways involved. Proteolytic molecules and inflammatory mediators are compromised in the initial progression of the disease [2]. OA was classically defined as a "wear and tear" disease, but now biochemical, biomechanical, metabolic and genetic variables are considered key factors for the progression of the disease [30]. For that reason, the paradigm has changed from the biomechanical theory to the inflammatory theory [3]. The therapeutic aims in OA are to: a) slow down the degradation-inflammation cycle, b) inhibit mediators of inflammation, c) decrease catabolic chemokines and d) stimulate anabolic chemokines [35].

In this review, drugs that have a treat-to-target profile, included biologic therapies (such as Anakinra [anti IL-1β] or Infliximab, Etanercept, Adalimumab [anti-TNF-α], Tocilizumab [anti IL-6] and even Denosumab [RANKL-a]), which demonstrated effectiveness in the management of RA, blocking specific inflammation cytokines, has not been translated to knee OA [20]. For the management of knee OA, recognized Guidelines are stablished by the ACR (American College of Rheumatology), OARSI (Osteoarthritis Research Society International), EULAR (European League Against Rheumatism) and the AAOS (American Academy of Orthopedic Surgeons) [33]. However, none of the Guidelines has included neither PRP nor Ozone as treatment options yet [30, 33].

In the case of HA, there is controversy for its use. The AAOS (2013 recommendation) and the NICE (National Institute for Health and Care Excellence 2104 recommendation) does not support its use; whereas the OARSI (2014 recommendation) and the ACR (2012 recommendation) are inconclusive with respect to HA use [30].There is only one Systematic Review that has stated that intra-articular treatments showed greatest effect on the management of knee OA, including PRP and HA with a molecular weight greater than 1500 kDa [44]. In the case of Ozone, one updated meta-analysis and a review published separately by Nori-Zadehh et al and Vazquez et al have defined Ozone (O2-O3) as a valid option for knee OA management because of their effectiveness in the management of pain [45, 46]. In the case of PRP, three recent meta-analysis (Chang 2013, Khoshbin 2013, Tietze 2014) have stated that PRP offers better outcomes if compared to HA or corticosteroids, and the effect is sustained for at least 6 months. Ornetti and Andía, in two recent reviews state that PRP has a role in the treatment of knee OA because of its anti-inflammatory and regenerative properties and clinical benefits observed in randomized and non-randomized controlled trials [2, 36, 37].

Zamboni has stated that HA and PRP may promote regeneration and reduce inflammation [47]. HMW HA (50-120 kDa) added to PRP (infiltrated in combination) reduces cytokines and chemokines responsible for OA progression [48]. The combination of intra-articular injections of HA and PRP may decrease immune-related cells and may recover cartilage breakdown and may repair meniscus tears [49]. Moreover, HA has shown to upregulate the production of GFs if added simultaneously to PRP infiltration, reducing the time needed for healing. The combination of PRP plus HA enhances the release of TGF-1 and PDGF, favoring the healing effect [49].

In this review, HA, PRP and Ozone have showed to have anti-inflammatory, immunomodulatory, and regenerative properties because of their multi-target profile. For all the reasons exposed previously, we postulate HA, PRP and Ozone as drugs with a multi-target profile for the management of knee OA, as it has been observed in this review.

Conclusion

OA is a disease of complex pathophysiology that involves cartilage, subchondral bone and synovial tissue. New studies suggest that inflammatory mechanisms are involved in the pathogenesis of OA even more than biomechanical factors, to an extent that a change of paradigm has been proposed in this review. OA has no definitive cure nowadays. The objective of treatment is to interrupt the vicious cycle of inflammation-degradation by blocking specific inflammatory and catabolic pathways. Treat-to-target options that block single pathways have not produced significant results in the management of knee OA as it was observed in the management of rheumatoid arthritis. The multi-target profile of Ozone, PRP and HA offer a promising alternative for the management of knee OA, since these alternatives might act on inflammatory cytokines and catabolic chemokines, and they might stimulate anabolic chemokines and anti-inflammatory cytokines, as it was observed in the present review. It is time for Standardized Guidelines to consider these drugs for the management of knee OA.

Conflicts of Interest

None.

Funding

None.

Ethical Considerations

The review article complies with current ethical considerations.

Abbreviations

OA: Osteoarthritis
ECM: Extracellular Matrix
MMP: Matrix Mineral Metalloproteases
LIF: Leukemia Inhibitory Factor
OSM: Oncostatin M
HA: Hyaluronic Acid
PRP: Platelet-Rich Plasma
MSC: Mesenchymal Stem Cells
ROS: Reactive Oxygen Species
TGF-β: Transforming Growth Factor B
IGF-1: Insulin Growing Factor 1
EULAR: European League Against Rheumatism
ESR: Erythrocyte Sedimentation Rate
KL: Kellgren and Lawrence
CTX: C-Terminal Telopeptide
IL: Interleukins

TNF-α: Tumor Necrosis Factor A
CRP: C-Reactive Protein
ADAMTS: Aggrecanases
FGF: Fibroblast Growth Factor
PDGF: Platelet Derived Growth Factor
PgE2: Prostaglandin E2
NLRP3: Inflammasome
[NLR]: Nucleotide-Binding Oligomerization Domain-Like Receptor. family pyrin domain-containing 3 inflammasome
NF-Kβ: Nuclear Factor Kβ
RA: Rheumatoid Arthritis
RANKL: Receptor Activator of Nuclear Factor Kappa-B Ligand
COX-2: Cyclooxygenase-2
iNOS: Inducible Nitric Oxide Synthase
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
HGF: Hepatocyte Growth Factor
VEGF: Vascular Endothelial Growth Factor
EGF: Endothelial Growth Factor
NO: Nitric Oxide
LMW: Low Molecular Weight
HMW: High Molecular Weight
ADAMTS: ADAM Disintegrin And Metalloprotease, disintegrin and metalloprotease with thrombospondin motifs
TIMPS: Tissue Inhibitor of Metalloprotease.
AAOS: American Academy of Orthopedic Surgeons
EULAR: European League Against Rheumatism
OARSI: Osteoarthritis Research Society International
ACR: American College of Rheumatology
NICE: National Institute for Health and Care Excellence

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