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Review

Degenerative osteoarthritis a reversible chronic disease

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ABSTRACT

Osteoarthritis (*OA*) is the most common chronic musculoskeletal disorder. It can affect any joint and is the most frequent single cause of disability in older adults.

OA is a progressive degenerative disease involving the entire joint structure in a vicious circle that includes the capsule-bursa tissue inflammation, synovial fluid modifications, cartilage breakdown and erosions, osteochondral inflammatory damage leading to bone erosion and distortion.

Research has identified the initial inflammatory-immunologic process that starts this vicious cycle leading to so-called *early OA*. Research has also identified the role played in the disease advancement by synoviocytes *type A* and *B*, chondrocytes, extracellular matrix, local immune-inflammatory mediators and proteases.

This article investigates the joint-resident *MSCs* that play an essential local homeostatic role and regulate cell turn over and tissue repair. Resident *MSCs* establish and maintain a local *regenerative microenvironment*.

The understanding of *OA* physiopathology clarifies the core mechanisms by which minimally invasive interventions might be able to halt and reverse the course of early stage *OA*. Interventions employing *PRP*, *MSCs* and *exosomes* are considered in this article.

Contents

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1. Introduction

Degenerative osteoarthritis (*OA*) is the most common chronic musculoskeletal disorder.

Whilst *OA* can affect all joints, the knee, spine, hip, hands, feet, and shoulder are most frequently affected.

Chronic pain leading to disability is the most common direct consequence.

OA is the single most common cause of disability in older adults.

OA risk factors include obesity, sedentary lifestyle, chronic postural defects, bone density, occupational injury, trauma and genetic predisposition.

The 2010 Global Burden of Disease Study estimated that 10%–15% of all adults aged over 60 had some degree of symptomatic *OA*, with prevalence higher among females than males [1,2].

This millennium has seen significantly deeper understanding of the physiopathology and cellular-molecular biology processes that underlie degenerative *OA*. This deeper understanding has unveiled new opportunities first for *OA* management and now for reversal.

Understanding the early biological processes that trigger *OA* challenges the view of OA as a chronic disease centred on cartilage degeneration.

It is now well recognised that the progression of the disease involves the entire joint structure in a cycle that includes inflammation of the capsule-bursa tissue, changes to the synovial fluid, erosion of the cartilage, osteochondral inflammatory damage and bone distortion.

Initial inflammation and local homeostatic imbalance between the cartilage and the synovial membrane play key roles in *early OA*.

The ability of *resident joint MSCs* to modulate local inflammatory and immunologic responses is important to our understanding of how to break the cycle of biological events that lead to *OA*.

Suitable persistent stimulation of *MSCs* is the foundation of a promising treatment to halt and reverse both early stage OA and more advanced joint degeneration.

This article examines how the above knowledge may be applied to therapeutic opportunities for tissue regeneration in *OA* cases.

2. Synovial membrane (SM)

The joint capsule is a connective envelope around a synovial joint or diarthrosis.

The capsule has two main layers:

- The external *fibrous membrane* is mainly composed of connective fibrous tissue. It is highly innervated by nerves that cross the adjacent muscles and tendons and connect to the joint.
- The internal *synovial membrane* (*SM*) is the synovial fluid secreting layer [3].

The synovial membrane or synovium refers to the special mesenchymal tissue lining the joint cavity, tendon sheaths and bursa tissues [4].

The internal surface of synovium may appear flat or folded as “finger-like projections” or villi. This loose structure adapts the membrane to change its form as the joint surfaces move one on another.

The synovium has a dense net of capillary vessels that provide nutrients for synovium and for the avascular cartilage. *SM* contains vessels that provide cartilage nutrition through synovial fluid production and diffusion [5].

These membranes, like an inner tube, seal the synovial fluid in the joint space and effectively provide a hydropneumatic cushion to sustain the body weight and soften the traumatic impact during movements.

The *fibrous membrane* structure can vary in different joints: from fibrous dense collagenous in the hip to loose connective tissue (rich of elastin) in the shoulder. In some joints connective adipose tissue is well represented such as Hoffa's fat pad in knee joints [5].

SM consists of a thin sheet of loose connective tissue that forms an Extracellular Matrix (ECM). This hosts different cell types, many of which have multiple functions. A primary function of the synovial membrane is production of synovial fluid [5,6].

The principal roles of the *synovial fluid* are to reduce friction between the articular cartilages, to nourish the cartilage and remove debrides.

Synovial fluid belongs to the family of transcellular fluids which can be isolated by blood plasma filtration. The fluid is a transudate and viscous in nature. It facilitates the continuous exchange of oxygen, carbon dioxide and metabolites between the intima permeable blood vessels, the synovial cells and the cartilage [6].

Synovial fluid and its nutrients are essential to metabolically support the superficial and middle zones of the cartilage layers. Under normal conditions the synovial fluid contains hyaluronan, lubricin, proteinase, collagenases, prostaglandins and rare <200 to 2000 WBC/mm^3.

The external cartilage ring directly in contact with the synovial membrane can receive nutrition directly from the synovium. However, most of the cartilage obtain nutrients through the diffusion of synovial fluid [7].

2.1. Synovial cells

SM consists of two anatomically distinct cell layers: the internal layer named *intima* and, the underlying supporting tissue *subintima*. The main *intima* cell components are macrophages and fibroblasts while the *subintima* includes blood vessels, adipose cells and fibroblasts with a few lymphocytes and macrophages [4] (Fig. 1).

The *intima* cells are mainly of two types:

Macrophage-like synovial cells known as *type A* synoviocytes and fibroblast-like synoviocytes (*FLS*) known as *type B* synoviocytes.

1) Type A synoviocytes keep the synovial fluid clean by removing wear debris and degraded substances. They account for approximately 25% of cells lining the synovium [3].

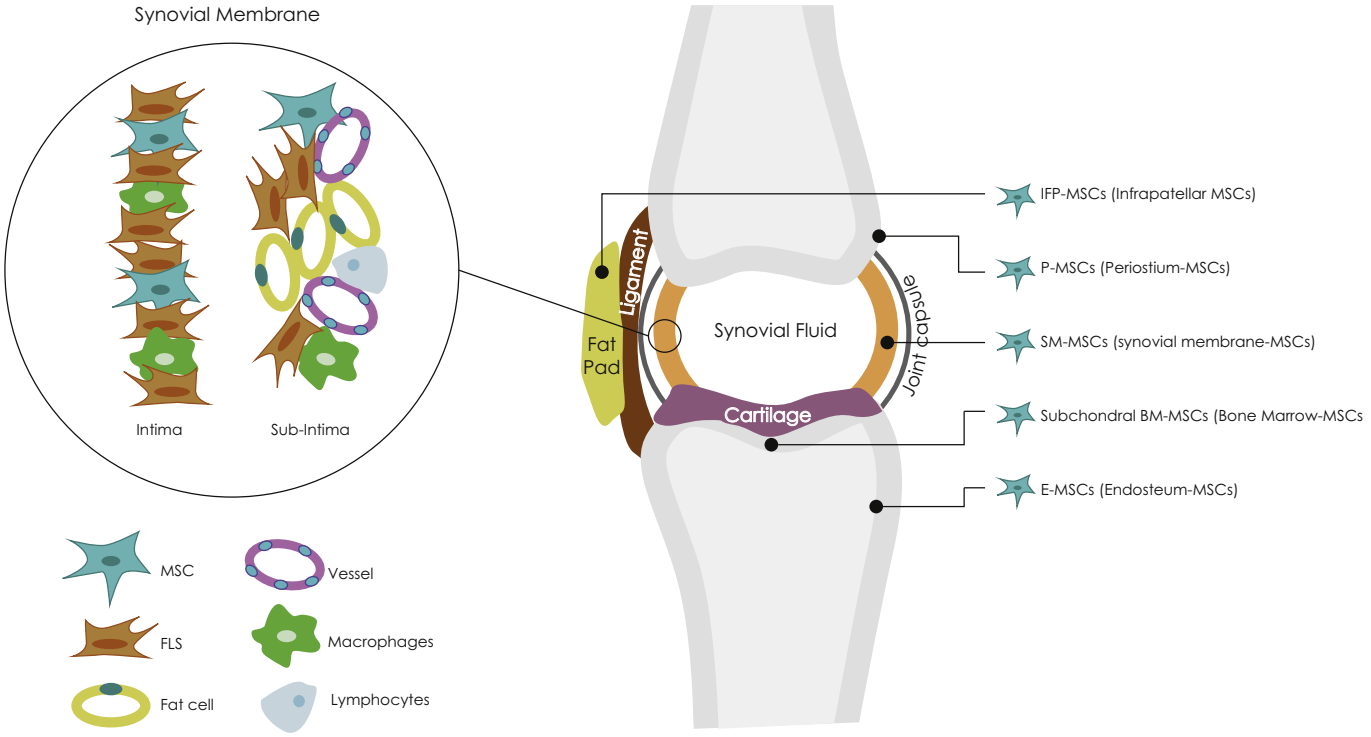

Fig. 1. Distribution of various cells in the synovium and joint tissues. FLS = fibroblast-like synoviocytes only represent *intima* fibroblasts. Joint location of different resident MSCs.

Type A synoviocytes have the cell surface markers CD163 and CD68; these identify them as deriving from the macrophage lineage [4].

Smith et al. suggested that macrophage-like synovial cells derive from blood monocytes [8].

2) The fibroblast-like synoviocytes (*FLS*) or *Type B* synoviocytes produce a long-chain polymer called hyaluronan which gives the synovial fluid a viscous character, similar to egg-white. Hyaluronan, together with a molecule called lubricin, lubricates the joint surfaces. Water, the main component of synovial fluid, is effectively trapped in the joint space by the strong hydrophilic property of hyaluronan [3].

Type B synoviocytes are typified by surface markers such as CD44 and intercellular adhesion molecule-1 (ICAM-1). These markers classify them as locally derived fibroblasts [4].

The *type B* synoviocytes possess the morphologic appearence of fibroblasts and have been shown to be capable to generate a large group of molecules including hyaluronic acid, lubricin, proteoglycans, cytokines, arachidonic acid metabolites, and metalloproteinases [9,10].

Recent studies have shown that there is a great difference between synovial *intimal* fibroblasts and *subintimal* fibroblasts. *Synovial intimal fibroblasts* express high levels of UDPGD (Uridine diphosphoglucose dehydrogenase), which is related to the production of hyaluronan. *Subintimal fibroblasts* do not have this capacity [4,10,11].

Other findings suggested that *synovial intimal fibroblasts* express several adhesion markers such as VCAM1, ICAM-1, CD44, and β1 integrins, while *subintimal fibroblasts* and fibroblasts from other sources express lower levels of CD44 and β1 integrins and do not express VCAM-1 [4,8,12].

In 2001, *De Bari* et al. first isolated *MSCs* from human synovial membrane (*SM*) both intima and subintima. He called them *Synovium-derived MSCs* (*SM-MSCs*) [13].

SM-MSCs were reported to possess high self-renewal capacity; they can be expanded *in vitro* over at least ten passages with limited cell senescence.

Furthermore, *SM-MSCs* often express various markers of synovial fibroblasts in different phases of their differentiation process. This finding suggests that synovial fibroblasts are likely derived from *SM-MSCs* which are involved in the various stages of fibroblasts maturation and differentiation [13,14].

Li et al. in 2019, confirmed that *SM-MSCs* have stem cell-like characteristics, immunomodulatory abilities, self-renewal and differentiation properties which lead to the fibroblast lines. Further, they are directly involved in the process of *type B* synoviocytes turn over and joint connective tissue regeneration [4].

Moreover, other *MSC-like* cells have been found in other connective tissue of the musculoskeletal system [15].

2.2. MSCs general properties

MSCs were first isolated in bone marrow (*BM*) and then identified as *residential* stem-cells in almost all connective tissue. They regulate local homeostasis, turn over of cells and *ECM*, immune-modulation and tissue regeneration [16].

A well-known *in vitro* capacity of *MSCs* is to differentiate in all mesenchymal lineages: fibroblasts, chondroblasts, adipocytes, muscle-cells, osteoblasts and other mesenchymal lineages [17,18].

This stem-cell property might be expressed *in vivo directly* through the proliferation and differentiation in various mesenchymal cells lineages or by *indirectly* activating a regenerative microenvironment that facilitates local immune-modulation and trophic changes through the stimulation of local progenitor cells.

These *MSCs* capabilities operate through autocrine and paracrine effects that play an essential role in tissue repair [16,19].

Caplan AI was the first to locate and identify *MSCs* as *pericytes* wrapping the connective tissue microvasculature [20]. While

Sacchetti et al. was the first to recognise that CD146+ cells enveloping the micro-vessels in bone marrow are *MSCs* [21].

Caplan AI and other authors documented that *MSCs-pericytes* are identified in the perivascular cells. This position is regulated by several factors however, the *PDGF* receptor is currently considered the main component. Its activation promotes chemotactic and mitogen stimulus for *MSCs* and facilitates interactions between endothelial cells and *MSCs* [21,22].

Tissue injury and inflammation activate the *resident MSCs* which show several local healing and regenerative effects:

- *Local immune modulation. MSCs* inhibit immune cells surveillance of the injured tissue through the *MSCs* secretion of *HGF* (*Epatocyte growth factor*), *TGF-beta* (*Transforming growth factor-beta*) and *PGE2* (*Prostaglandin E2*) and other local mediators. These factors induce lymphocytes to produce IL-10 that balance type 1 T-helper/type 2 T-helper and suppress T-cells activation. The *MSCs* immunomodulatory effects are so evident that *allogenic hMSCs* (*human-MSCs*) infused in the bloodstream for different clinical purposes do not trigger any *GVHD* (*graft versus host disease*) and can even protect against xenogeneic rejection when grafts are from different species [23–27].
- *Trophic effects.* The secretion of an array of bioactive molecules inhibit apoptosis, prevent scar formation and stimulate angiogenesis through *VEGF* (*Vascular Endothelial growth factor*) and other mediators. The secretion of mitogenic factors induces the *local progenitor cells* to promote tissue regeneration [28,29].

For the above reasons, *Caplan AI* suggested it is more accurate to consider *MSCs* like “medicinal signalling cells” as *MSCs* do not directly function in the body as stem-cells for tissues renewal, rather promoting a *regenerative microenvironment* [19].

2.3. MSCs tissue-specific properties

MSCs are a heterogeneous stem cells population that varies in diverse tissues because they reside in the tissue-specific microenvironment. The tissue-specific *MSCs* population would include both multipotent and progenitor cells with exclusive capabilities of tissue regeneration and immune response modulation [28].

For example *in vitro*, dexamethasone stimulates *BM-hMSCs* to differentiate into osteoblasts but to generate cartilage *BM-hMSCs* require TGF-beta and a specific medium. Instead, *ASCs (Adipose derived-MSCs)* requires TGF-beta and BMP-6 (Bone Morphogenetic Protein-6) to differentiate in chondroblasts [30,31].

Therefore, *MSCs* are not completely the same because they are conditioned by the tissue-specific microenvironment to accomplish their biological role.

2.4. MSCs exosomes

In the last decade, in several experimental models and clinical applications, *MSCs* have shown local and systemic beneficial effects promoting healing and tissue regeneration.

However, it was very difficult to verify the *MSCs* survival rate and the specific effects of transplanted cells on the host tissue [32].

Various molecular and biological findings supported the hypothesis that transplanted *MSCs* did not proliferate and differentiate into tissue-specific mature cells but instead their immune-regenerative actions were supported by the paracrine function [20].

The paracrine action is currently understood to be mostly related to exosomes secretion. *Exosomes* consist of membrane-enclosed vesicles *(EVs)* which are generally classified for morphology and size: lipid nanospheres *liposome* (40–100 nm), *MVs* or *ectosomes* which are fragments of plasma membranes (100–1000 nm) and *apoptotic bodies* (1–5 μm) released by the cell's membrane during apoptosis [20]. *Exosomes* contain fragments of nucleic acids and various peptides transcription factors, lipids, a large pool of HSPs (the HSP 70 is the most studied) several microRNAs and GFs (VEGF, TGF-beta 1, IL-8, HGF, TCF4) [33].

This vast range of complex molecules locally regulates tissue homeostasis, cell turn over and performance, and tissue regeneration [34].

The *exosomes* transport and deliver a range of small molecules which mediate the *MSCs* immunomodulatory effect on local tissue and generate a favourable regenerative microenvironment.

Injured tissue exhibits local hypoxia and lower pH which are optimal conditions for exosome best performance. miRNAs, HSPs and GFs have definitive antiapoptotic and anti-inflammatory effects and promote neovascularization [33,35].

Rani et al. recently reported exosomes not only networking with the local cells; via the blood stream they can reach distant targets [35].

Exosomes, in experimental models, showed significant ability to induce bone regeneration and cartilage repair [36,37].

2.5. Hoffa's MSCs

Adipose tissue is a minor joint tissue component that becomes clinically significant in some conditions such as in the Hoffa's syndrome. The infrapatellar fat pad (Hoffa's fat pad) is an intracapsular but extra-synovial structure and only its deepest portion is covered by the synovial layer.

The infrapatellar fat pad (*IFP*) with adjacent synovium plays key roles in knee inflammation and *OA* onset, including the down-regulation of *Substance P (SP)* which implements the local inflammatory response and nociceptive signal transmission [38].

IFP has a reservoir of tissue-specific *MSCs*. The isolated *IFP-MSCs* exhibit increased clonogenicity and *in vitro* chondrogenic potential compared with *BM-MSCs* [39].

IFP-MSCs demonstrated plastic-adherence and a fibroblast-like morphology. They also demontrate comparable growth rates to *BM-MSCs* under basal conditions.

IFP-MSCs sustain high *CFU-F* (fibroblast colony-forming units) generation through passaging; they express increased chondrogenic differentiation and show a rise in extracellular matrix production compared to *BM-MSCs* [38,39].

IFP activity is emphasised by the close relationship with intra-articular structures and its essential role played in joint homeostasis and *early OA* process [38].

The strong immunomodulatory features of *IFP-MSCs* is confirmed by the high expression of immune suppressive molecule CD10, CD200 and CXCR4, IL-10, and other key immunomodulatory molecules such as IDO, HLA-G and cytokine inhibitors IL6sR and sTNF-RII [38,39].

Moreover, the *IFP-MSCs* facilitate the degradation of *SP* which, plays a basic role in the local immune response including T cell proliferation via IL-2 and, stimulation of inflammatory cytokine production [40].

2.6. Joint resident MSCs location

Joint resident *MSCs* mostly reside in pericytes position spreading together with the microvasculature.

It is currently recognised that there are several types of *MSCs* contained in the joint structure: *SM-MSCs*, *IFP-MSCs*, *P-MSCs (Periostium-MSCs)*, *E-MSCs (Endosteum-MSCs)* and *Subchondral BM-MSCs* [13,38,44] (Fig. 1).

Furthermore, stem-cells have been found in other joint structures, for example intervertebral disc stem-cells *IVDSCs*. These

show the capacity to differentiate in adipogenic, osteogenic, and chondrogenic tissues [41].

SM-MSCs lie in niches in the *SM* intima and subintima. They are mostly packed in the proximity of entheses such as the synovium and the capsule insertion to the periosteum. Similarly, *SM-MSCs-like* are in tendons and ligaments close to the bone junctions [42,43].

IFP-MSCs are located in the Hoffa's pad and it has been supposed they may reside in adipose tissue other joints, probably in niches close to the bursa-capsule [38].

Periosteum *P-MSCs* and endosteum *E-MSCs* play an essential role during fracture repair by becoming bone-forming osteoblasts and chondrocytes that undertake endochondral ossification [44].

Subchondral BM-MSCs exist in a variety of bone medullary cavities, including the mineralized bone matrix and the adipose marrow [44].

Subchondral bone is a highly vascularized tissue allowing the recruitment of *MSCs* and progenitor cells. It may support cartilage regeneration in particular conditions [45].

Specifically, Subchondral bone consists of the subchondral bone plate (*SBP*) to which the subchondral trabecular bone *(STB)* is attached.

Subchondral bone contains at least five different bone cell types – osteocytes, osteoprogenitor cells, bone lining cells, osteoblasts, and osteoclasts. Osteoblasts and osteoclasts form the "bone remodelling unit" that maintain the integrity of the bone and balance between deposited and resorbed bone.

The marrow in the trabecular bone maintains a heterogeneous population of various multipotent mesenchymal stromal cells *(BM-MSCs)* that provide progenitors for differentiation of osteochondral and other mesenchymal cell lineages [46].

3. Synovial inflammation and early osteoarthritis (EOA)

Historically, *OA* has been considered a degenerative chronic disease centred on cartilage degeneration. Only recently, research and clinical evidence have indicated that *OA* involves progressively the entire joint tissues on different timing [47,48].

Rheumatology traditionally defines *OA* as a condition marked by significant cartilage loss and joint space narrowing and *OA* classification criteria require the presence of radiographic bony changes or osteophyte formation in accordance with Kellgren and Lawrence standard [49].

These criteria are in agreement with the prevalent physiopathology interpretation that synovitis may be induced by a mechanical injury that generates micro-fissures and micro cartilage fragments. This initial cartilage degradation includes wearing particles, debrides and microcrystals that enter the synovial fluid and trigger the inflammation.

These components, released into the synovial fluid, are phagocyted by synovial macrophages (*Type A cells*). *Type A cells* fuel and maintain the inflammation of the synovial membrane through the synthesis of inflammatory mediators and protease which, in turn, diffuse through the synovial fluid into the cartilage generating a vicious circle. This results in progressive cartilage degradation, sustaining and accelerating the vicious circle by producing additional inflammation [48].

Normal articular cartilage is formed by extracellular matrix *ECM* (water, collagen, proteoglycans and a small amount of calcium salt) and chondrocytes [50]. The normal turnover of the *EMC* components is managed by the chondrocytes which synthetize these elements and by the proteolytic enzymes responsible for their breakdown.

Chondrocytes are in turn influenced by several factors including synovial fluid composition, GFs and cytokines, joint biomechanics and even by the constituents of the *EMC* itself [51].

Therefore, *EOA* results from the failure of chondrocytes and synovial membrane to maintain homeostasis between synthesis and degradation of the *ECM* components.

Breakdown of *ECM* collagen and proteoglycans cause the activation of synovial macrophages and the release of proinflammatory cytokines, like TNFα, IL-1 and IL-6. These cytokines push chondrocytes to further release metalloproteinases, inhibit type II collagen production and promote chondrocytes apoptosis; intensifying cartilage degradation [52,53].

In advanced *OA*, along with articular cartilage damage, chronic inflammation catalyses several changes in the joint capsule and synovium and in synovial fluid, ligaments and tendons.

As the disease progresses, inflammation elevates intra-articular pressure and extensive cartilage destruction allows the synovial fluid to infiltrate the subchondral bone marrow. This causes the production of bone marrow pseudocysts leading to bone erosion and remodelling and the formation of osteophytes [54,55].

Clinically, cartilage debris in the synovial fluid and micro-injuries in articular cartilage may be present for a long time before any degeneration can be noted using MRI or arthroscopy [49].

In 2012 Luyten et al. proposed classification criteria for early knee OA (*EKOA*), with the aim of identifying patients with signs of initial joint disease in order to initiate early therapeutic approaches [56,57].

A very recent review has focused on early knee *OA* (*EKOA*) classification and standardization.

Specifically, two proposals from the Italian Rheumatology Association International and from the First International Early OA Workshop have been recommended.

Various combinations of symptoms, risk factors and minimal X-ray Kellgren & Lawrence (0–1) deviations have been considered for *EKOA* classification.

International consensus is felt necessary to undertake the *OA* treatment at an early stage when the disease progression is still reversible.

Discussion about the MRI and USs role and standardisation is still open [58].

Nonetheless, it is still unclear whether the morphological changes that occur in the synovial membrane during *OA* are the consequence of cartilage degradation and joint inflammation or whether they are primary to these events [59].

Some *authors* indicated that synovial inflammation may be primary to other structural changes. Abnormalities in joints biomechanics and chronic postural defects certainly play a key role in *OA* induction.

It has been postulated that excessive or abnormal joint loading and motility disbalance may do more than simply initiate joint tissue damage by wear and tear. Additionally, loading and disbalance may stimulate joint tissue cells to produce pro-inflammatory factors and proteases which ultimately promote *OA* development [60].

Clinical findings showed that inflammation was present in *OA* well before the development of significant radiologic changes. Magnetic resonance imaging (*MRI*), as well as arthroscopy procedures suggested that even at the earliest stage before detectable cartilage degeneration has occurred, *OA* was already an inflammatory disease in progress [49].

Some studies based on MRI with or without contrast enhancement indicated the presence of synovitis at early stages of OA progression. MRI often showed that thickening of capsule bursa tissue precedes cartilage degradation in OA disease development [61–63].

Other data support the observation of synovial inflammation in the earliest phases of *OA*.

In 2005 *Ayral* et al., performed a longitudinal study on 422 patients using diagnostic arthroscopy on knees with symptomatic but no radiographic markers of *OA*. The research revealed the presence of synovitis well before the development of medial cartilage loss [64].

Scanzello et al. analised a group of patients affected by traumatic meniscal injury without evidence of radiographic *OA*. During the artrhroscopies performed to repair meniscus, synovial inflammation was noted in 43% of patients and was associated with more severe preoperative pain and poor knee function scores [65].

In one histopathology report based on 70 synovial specimens obtained from arthroscopy, synovial inflammation was present in many patients with the minimal radiographic disease and, in 31% specimens, synovitis was staged as severe [49,66].

Although the synovial membrane is not the only tissue involved in *OA*-related inflammation, it seems to be a major site of initial inflammatory changes [67].

For histology, cartilage degradation in *EOA* has been defined and measured by the OARSI (Osteoarthritis Research Society International) scoring system within a range of 1–3 OARSI takes into account the depth of degradation into the articular cartilage layer. These changes involve only the superficial and middle zones of the cartilage.

Therefore, grade 1 is characterised by swelling of the articular cartilage and mild fibrillation in the superficial zone; in grade 2 small areas of the cartilage surface have been lost and chondrocytes have begun to form clusters; in grade 3 vertical fissures have advanced into the middle zone and formation of chondrons may be seen [68,69].

For some authors, *Early OA* includes a maximal involvement of 50% of the cartilage thickness up to OARSI grade 4 [57].

3.1. Seeking the primum movens

Independent of any discussion whether the synovial or cartilage injury is the starting point of *OA*; inflammation is the first joint immune-reaction and the main cause of the *OA* chronic degeneration.

Recently, the *Substance P (SP)* has been proposed as a trigger factor for both joint pain and inflammatory response.

Substance P (SP) is an undecapeptide (a peptide composed of a chain of 11 amino acid) member of the tachykinin neuropeptide family. It is a *neuropeptide*, acting as a *neurotransmitter* and as a *neuromodulator*.

SP mediates interactions between neurons and immune cells thereby modulating immune cell proliferation and cytokine production. Interestingly, some immune cells have also been found to secrete *SP* which suggests a central role of *Substance P* in the local immune response [40].

SP has been found to be secreted by sensory nerve fibres in the synovium and even isolated in the infrapatellar fat pad *IFP* [40].

SP has been associated with nociceptive pathways promoting and exciting *pain*; it has also been considered a key modulator of acute local inflammation and chronic fibrotic degeneration.

Specifically, it has been found that *SP*-secreting sensory nerve fibres predominate over sympathetic ones in clinical presentation of knee pain and increased concentration of *SP* has been measured in synovial fluid during joint inflammation [70,71].

SP can modulate proliferation of immune cells and promote monocyte activation and migration to sites of inflammation [40].

SP receptor, neurokinin 1 *(NK1R)*, was found highly expressed within synoviocytes where it seems to modulate the expression of cartilage degrading matrix metalloproteinases *(MMPs)* and their tissue inhibitors *(TIMPs)* [40,72].

3.2. Cells and joint tissue inflammatory response

Normally, the synovial membrane is two or three cell layers thick and contains few inflammatory cells. However, during inflammation there is increasing hyperplasia of the *Type A* synovial cells (macrophages) followed by a rising number of T and B cells, natural killer and mast cells [73,74].

Typically, inflammatory arthritis was defined by the increased numbers of inflammatory cells, mostly leukocytes, which permeate the joint tissues and the synovial fluid. This turns into an inflammatory fluid and loses the main properties of lubrication and cartilage nutrition. This facilitates the degradation and erosion of cartilage. The inflammatory cellular reaction is not prominent in degenerative *OA*, where the number of leukocytes in the synovial fluid is normally low, and rarely exceeds 1000 to 2000 cells *per ml*. This is in contrast with inflammatory arthritis such as rheumatoid arthritis *(RA)*, where the number of synovial fluid leukocytes commonly exceed 2000 *per ml*. The severe leukocytes infiltration of the synovium and the synovial fibroblasts proliferation typical of the *RA* may result in “pannus” formation [75].

However, some range of synovial inflammation may be evident in *OA*; in some cases showing hyper immune-inflammatory reaction that can resemble *RA*.

Benito et al. demonstrated that the degree of leukocytes infiltration was highly heterogeneous in *OA*. In his study most of the patients exhibited minimally inflammatory and primarily degenerative histopathology while a minority, showed *RA*-like patterns [76].

In general, macrophages were found predominant in *OA* synovium, while in *RA* there were more *T cells* and *B cells* [77].

In *OA* the synovial membrane commonly thickens due to inflammation and leukocyte proliferation. Reports of changes in the synovium that occur at various stages of *OA* have shown that the amount of fibrin deposited in the synovial membrane and the degree of leukocyte infiltration are correlated with disease severity [78].

Activated *Type A* synoviocytes and chondrocytes generate large amounts of *matrix metalloproteinases* (MMPs) including MMP-1, MMP-3, MMP-9 and MMP-13 [79]. *Type A* synoviocytes are able to secrete not only proteolytic enzymes, but also proinflammatory *cytokines* (IL-1β, IL-6, TNF-α), which are deemed to be responsible for the inflammation progression and pain associated with the disease [67]. *Adipokines*, such as *resistin* are mainly released by the synovium during *OA* progression accelerating *in vitro* the *ECM* degradation [80]. *Osteopontin*, has been identified as a cytokine expressed by *A* synoviocytes which, has been correlated with *OA* prognosis marking the severity of the disease [81].

Therefore the vicious circle seems to be that synovium produces cytokines, chemokines and metalloproteinases which degrade cartilage that in turn catalyses release of the same destructive molecules [82].

The cartilage breakdown products and the exposure of the damaged *ECM* sustain the release of collagenase and proteolytic enzymes from synovial cells leading to the increased angiogenesis of the synovial membranes [83].

The initial synovial vasodilation is largely caused by *Type A* synovial cells that secrete inflammatory and pro-angiogenic factors. The latter increase blood vessel permeability and the up-regulation of adhesion molecules supporting the inflammatory response. Specifically, *Type A* synovial cells release local mediators that stimulate endothelial cells and fibroblasts to produce vascular endothelial growth factor *(VEGF)*, basic fibroblast growth factor *(bFGF)* and other GFs that support angiogenesis [83,84].

3.3. Role of the joint adipose tissue (Hoffa's fat-pad)

Adipose tissue is a minor joint tissue component that becomes clinically significant in some inflammatory conditions. The best studied joint adipose tissue is the *Hoffa's fat-pad* also called *infrapatellar fat pad (IFP).* It plays a key role in Hoffa's syndrome.

Synovium and *IFP* inflammation describe progressive knee Osteoarthritis, a chronic disease that induces articular cartilage loss and often ends up with a joint replacement.

Interplay between synovium and the adjacent *IFP* was demonstrated to be fundamental during the onset and progression of *OA* [38].

Both synovium and *IFP* host immune cells such as macrophages. When activated these produce pro-inflammatory and damaging molecules including tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin 1-beta (IL-1β) and IL-6 and various adipokines. These together promote cartilage damage [85,86].

4. From early OA to the chronic disease

Early OA features proinflammatory factors that lead to the activation of proteolytic enzymes responsible for the degradation of the extracellular matrix *(ECM)* resulting in joint tissue damage.

Although destruction and loss of the cartilage is a central component of *OA*, all joint tissues are progressively affected indicating that *OA* is a disease of the joint as an "organ" [87].

Current knowledge shows that chronic low-grade inflammation sets the stage for several chronic degenerative diseases. In *OA,* chronic inflammation is a major driver of the advancement of joint degeneration [49].

Literature indicates that atherosclerosis, chronic periodontitis, age-related macular degeneration, Alzheimer's disease and *OA* share chronic inflammation as a key factor of the progressive degeneration [88–90].

Joint injury and chronic biomechanical derangement induced by the injury (trauma, overuse, hypermobility, postural misalignments etc) are key factors to induce chronic inflammation in *OA*. They promote a vicious cycle comprising local tissue damage, inflammation and tissue repair failures resulting in chronic synovitis and fibrosis, cartilage loss and further joint degeneration. These *OA* events were intriguingly associated by *Scanzello* et al. to a chronic wound [91].

In the current view of *OA* progression, mechanical injury is the inducing factor for chronic inflammation.

However, this process is fuelled by continuing disease factors that transform mechanical events into inflammatory signals.

4.1. Factors facilitating the chronic inflammation

Early OA is supported by pro-inflammatory mediators such as cytokines and chemokines that are in turn the consequence of the innate immune response to joint injury.

In advanced stages of *OA*, additional inflammatory and profibrotic modulators such as *connective tissue growth factor* (*CTGF*) together with *transforming growth factor-beta* (*TGF-β*) induce synovial and *IFP* fibrosis, further inducing articular cartilage destruction [49,92].

Innate immunity refers to the immune response induced by invariable *pattern-recognition receptors* (*PRRs*) that respond to preserved patterns in nature, including those introduced by invading pathogens such as bacteria, viruses, and fungi so-called *pathogen-associated molecular patterns* (*PAMPs*) [93].

Besides microbial patterns, *PRRs* also recognize multiple endogenous hazard molecules resulting from tissue damage. These group of molecules are known as *damage associated molecular patterns* (*DAMPs*). Both *PAMPs* and *DAMPs* signal to the immune system the presence of extraneous substances requiring a defensive response [49].

In the *OA* physiopathology *DAMPs* appear to be an essential component sustaining the inflammation pattern.

Unlike *RA*, *OA* does not appear to be associated with a significant acquired immune response. However, activation of the innate immune system is a common factor for both diseases.

Studies have reported several *DAMPs* contributing to the chronic inflammation in *OA*:

- *Extracellular matrix (ECM)* damage-associated molecules including fibronectin and hyaluronan [94].
- *Plasma protein* becomes elevated in the synovial fluid secondary to vascular leak and exudation of plasma proteins such as fibrin [95].
- *Intracellular alarmins* release from damaged and necrotic cells: *HMGB-1* (high-mobility group box 1 protein) and the *S100* proteins are the most studied [96,97].
- *Microscopic inorganic crystals,* including basic calcium phosphate (BCP) and calcium pyrophosphate dihydrate (CPPD) crystals, are frequently observed in osteoarthritic synovial fluids and synovial tissue [98].
- *Cellular mediators of innate immunity.* Besides macrophages, *Type B* synoviocytes and chondrocytes have a direct role in promoting local inflammation through molecular mediators such as cytokines TNFα, IL-1β, and proteolytic enzymes such as MMPs [81,92].
- *Complement activation.* This promotes *EMC* and cartilage damage which in turn, maintains the cycle of complement activation [99].
- *Mechanical stress-induced immune activation.* This refers to the capacity of mechanical forces to directly stimulate production of inflammatory mediators from cartilage and synovium [49].

5. Joint tissue regeneration

In recent years several *regenerative medicine* procedures have been introduced for *OA* treatment. These treatments have the common aim of improving symptoms through tissue regeneration and restoring homeostasis to local cells.

Unlike bone, articular cartilage is rather recalcitrant to regenerate.

Normal adult cartilage shows poor vascularization and innervation; it is prone to produce high concentrations of proteases but unable to make pro-inflammatory inhibitors. These biological features may partially account for the cartilage poor regenerative performance [100].

Furthermore, it is well known that cartilage tissue due to its lack of vasculature and innervation is not capable by itself of producing inflammation or pain at least in the early stages of degenerative *OA* [100].

5.1. Platelet-rich plasma (PRP)

Platelet-rich plasma (*PRP*), also known as autologous conditioned plasma, is a concentrate of platelet-rich plasma proteins derived from centrifuged whole blood.

PRP contains several growth factors including Platelet derived growth factor (*PDGF*); Vascular endothelial growth factor (*VEGF*); Transforming growth factor beta-1 (*TGF-b1*); Epidermal growth factor (*EGF*); Basic fibroblast growth factor (*FGF-ß*) and Insulin-like growth factor-1 (*IGF-1*) [101].

Preparations have been categorised by content into four main groups; *PPRP* (pure PRP), *L-PRP* (leukocyte and PRP), *P-PRF* (pure platelet-rich fibrin) and, *L-PRF* (leukocyte and platelet-rich fibrin) [101].

Depending on the centrifugation technique *PRP* may be manufactured with or without leukocytes. The role of leukocytes is controversial. Some authors advance hypothesis that leukocytes produce metalloproteinases and cytokines which may be detrimental for joint inflammation and pain. Other researchers believe that *PRP*-leukocytes release local inhibitor mediators that are crucial for the cartilage repair process [102].

The mechanism by which *PRP* can stimulate an antiinflammatory, proliferative and remodelling response in cartilage is unknown. It was suggested to be the result of cell stimulation, migration and proliferation from the adjacent bone marrow [103].

Literature showed *PRP* has chondrogenic differentiating properties found *in vitro* as well as *in vivo* in mice and rabbits indicating a major role in regeneration of osteoarthritic cartilage [104–107].

Further *in vitro* studies demonstrated that *PRP* was capable of inducing mesenchymal stem cells to proliferate and increasing chondrogenic differentiation. *PRP* increased gene expression for chondrogenic and osteogenic differentiation. The chondrogenic proliferation was associated with increased collagen synthesis [108–110].

PRP has been delivered usually through intraarticular injection with or without hyaluronic acid. Some orthopaedics combined microfracture arthroscopy injecting *PRP* into the cartilage defects to speed the cartilage re-growth [111].

Görmeli et al. compared the efficacy of *PRP* intra-articular injections against hyaluronic acid (HA) in the knee *OA*. Mostly in the *EKOA* (early knee *OA*) group, *PRP* showed a significant improvement of clinical outcomes (EQ-VAS and IKDC score) at six months after injections compared with HA [112].

As previously reported, the blood components and humoral factors of PRP vary significantly depending on the preparation method used.

The leucocyte content classifies PRPs as leucocyte-poor PRP (*LP-PRP*), or leucocyte-rich PRP (*LR-PRP*). Newly, autologous protein solution (*APS*), a version of *LR-PRP* with a higher concentration of humoral factors, has been examined [113].

A very recent study has investigated the differences of the humoral factors present in two types of PRP using the Autologous Protein Solution (*APS*) kit (*LR-PRP*) and the Cellaid Serum Collection Set P-type (*LP-PRP*).

The study was designed to establish a relationship between the levels of humoral factors in the preparations and clinical outcomes.

In the *APS* group, both anti-inflammatory and inflammatory cytokines were highly enhanced. Specifically, the concentrations of TNF-α, PDGF, FGF, sTNF-R2, sFas, TGF-β1 were higher than in *LP-PRP* group.

After treatment, there was no significant difference in the KOOS (knee injury and OA outcome score) score between *ASP* (*LR-PRP*) and *LP-PRP* groups.

However, after 3 months follow up KOOS total score and QOL (quality of life) score showed a significant improvement in the *ASP* group.

The study emphasised the role of interleukin-1 receptor antagonist (IL-1RA) which was positively related to clinical outcome improvements [114].

The clinical effectiveness of *PRP* for osteoarthritis treatment is still under debate.

In recent systematic reviews and meta-analyses were examined the latest randomized controlled trials to test *PRP* products as intra-articular treatment for knee osteoarthritis and compared with control (mostly low and high molecular-weight hyaluronic acid). Results supported the *PRP* use over other intra-articular treatments. *PRP* quite often resulted to improve pain in short and medium-term (up to 6–12 months). However, the overall level of evidence is still low. The reasons may be found in the weak standardization of *PRP* products and, sometimes in poor trial design and unconsidered bias which significantly affect results [115,116].

5.2. MSCs therapy

In 2001 the FDA issued a set of regulations governing cellular and tissue-based therapies. The basic principle of these guidelines was that cellular and tissue therapies that require *minimal to no manipulation* of autologous tissue do not required FDA approval, whereas those that involve any significant modification or treatment, including genetic manipulation, require approval.

Allograft tissue containing allogenic cells are classified as transplant tissue and are subject to different regulations [117].

In general, Cell-based therapies include adult differentiated cells, progenitor cells, multipotent stem cells (e.g. MSCs) and pluripotent stem cells (e.g. ESCs; iPSCs). However, *MSCs* are the most frequently used in clinical practice.

In *OA* treatments, the *arthroscopy microfracture technique* was the first surgical technique used to stimulate the healing of small *hyaline-cartilage* defects. The aim was to induce bleeding from the osteochondral layer to activate migration of reparative stem cells from the bone marrow [118].

The result was the filling of the defect with a neo-generate *fibrocartilage* susceptible to deteriorate and fragment into the synovia. To improve the procedure *autologous chondrocyte implantation (ACI)* has been injected to fill the defect. *ACI* is a two-stage procedure encompassing chondrocyte isolation and *in vitro* expansion, followed by implantation. *ACI* is currently the only FDA approved cell-based treatment for local cartilage defect. Nonetheless, this technique did not show any obvious improvement against simple microfracture [117,119].

MSCs isolated from different sources such as bone marrow, adipose tissue, cord blood, amniotic fluid, omentum, peripheral blood etc, showed *in vitro* capacity to differentiate in all mesenchymal lineages: fibroblasts, chondroblasts, adipocytes, muscle-cells, osteoblasts and other mesenchymal lineages [17,120].

The process of proliferation and differentiation of *MSCs in vitro* is well defined. For example *BM-MSCs* are *in vitro* differentiated to chondrocites using TGF-β in define medium while adipose-derived stem cells *ASCs* requires TGF-β + BMP-6 to differentiate to chondrocites.

However, *in vivo* the local “disease environment” is completely different from *in vitro* studies. Animal models are generally not able to strictly replicate the human *OA*. *OA* is a long course chronic condition mostly affecting aged patients whereas most animal models have been applied to young, healthy animals in which iatrogenic damage is acutely induced and then the experimental intervention performed almost immediately [117].

The most common *MSCs* procedures in *OA* have been performed using *autologous* or *allogeneic* stem cells.

For *autologous MSCs treatments* in *OA* the use of adipose tissue-derived stem cells (*ASCs*) is the most common and the most studied. The use of peripheral blood stem cells (*PBSCs*) is becoming popular.

After liposuction collection, *ASCs* can be culture-expanded and then injected into the joint. However, ASCs are often abundant in fat samples hence they can be directly injected as *stromal vascular fraction SVF*. The procedure to make *SVF* is fairly simple: the fat sample is dispersed as a homogeneous slurry and incubated with collagenase to free the *MSCs* from the rest of tissue. Then after a saline wash the mixture is centrifuged. From the centrifuge is obtained the so called *stromal vascular fraction* (*SVF*) containing the

MSCs. *SVF* has been injected directly with well-reported therapeutic effects [28,121,122].

As with other *MSCs* it has been supposed that *ASCs* delivered into an injured tissue induce repair and regeneration via paracrine effects. The *ASCs* stimulate the resident stem cells and promote their differentiation along the required lineage pathway. Furthermore, *ASCs* similar to *BM-MSCs* can deliver new mitochondria to damaged cells, thereby rescuing aerobic metabolism [123].

MSCs has been used as mixed injections in combination with GFs, cytokines and scaffolds in order to improve their effectiveness. The most commune scaffolds used are hyaluronic acid and fibrin gel. PRP has been applied as a nutrient fluid containing chondrogenic and osteogenic growth factors (e.g., TGF-β and PDGF) to support the survival and differentiation of transplanted MSCs [124,125].

Several clinical trials are registered at Clinical Trials. gov using *MSCs* to treat cartilage defects. Some case-control studies reported significant improvement simply by injecting *MSCs* into the affected joint while others used *MSCs* in conjunction with arthroscopy subchondral drilling and hyaluronic acid [115]. Some authors have treated *OA* at various stages injecting MSCs/PRP suspensions into the articular cavity with encouraging results [126].

It is currently becoming more important to consider the potential use of both autologous and allogeneic *ASCs*. Autologous *ASCs* offer advantages from regulatory, histocompatibility, and infectious perspectives.

Recent studies support the immunologic safety of allogeneic *ASCs* transplantation. Three independent studies determined that human culture-expanded *ASCs* reduce their expression of surface histocompatibility antigens and no longer stimulate a mixed lymphocyte reaction when co-cultured with allogeneic peripheral blood monocytes. Like *BM-MSCs*, the *ASCs* actually suppress immunoreactions. This indicates that the *ASCs* may not cause any cytotoxic T-cell response *in vivo* [127].

Allogeneic MSCs from bone marrow, umbilical cord *UC-MSCs* and adipose tissue have been used in *OA* animal models. Some pharmaceutical laboratories are working to achieve FDA approval for allogeneic *MSCs* clinical use.

Allogeneic MSCs are quite well tolerated by the host due to their immune-modulatory properties. Different methods have been tried to isolate homogeneous *MSCs* colonies and to enable a sterile and purified expansion so that allogenic *MSCs* can be injected in the receiving bloodstream with no major complications.

In experimental models, *allogenic MSCs* when intraarticularly injected showed improvement in cartilage healing and regeneration. Specifically, *ASCs* demonstrated a definitive reparative potential in cartilage regeneration [128–130].

In a recent review, Wang et al. analysed last three years preclinical and clinical trials results of intra-articular *MSCs* injection for knee *OA*. They found that generally *MSCs* improve pain indexes, joint mobility and increase the volume of cartilage.

This systematic review suggested that *MSCs* are safe enough for both intravascular and intra-articular injection. Furthermore, allogenic *UC-MSCs* showed the capacity of tissue regeneration in the implanted site and can be used as an allogenic stem cell drug.

Despite these studies showed promising therapeutic effects in the short-mid-term *OA* treatment, the long-term results need to be further investigated. Moreover, larger randomized studies are needed to provide higher levels of evidence [131].

In conclusion, *MSCs* showed *in vitro* definitive capacity to generate chondrocytes and produce cartilage tissue. Although *in vivo*, there is substantial evidence that *MSCs* produce a wide range of secreted factors that induce a local regeneration through immune modulation and tissue repair. *MSCs* paracrine anti-inflammatory-immunosuppressive properties and tissue regeneration capacity are currently considered central by the most. Depending on the number of transplanted cells, the mode of administration and behaviour after implantation, *MSCs* can variously decrease local inflammation, prevent chondrocyte apoptosis as well as differentiate into cartilage-forming chondrocytes.

Modern therapeutic strategies rely on the combination of *MSCs* and tissue engineering so that *MSCs* suspensions combined with biodegradable materials may improve cells survival and tissue regeneration capacity [132].

Therefore, against the initial assumption that *MSCs* might *in vivo* reproduce the *in vitro* findings, evidence increasingly suggests that the main therapeutic function of *MSCs* could be the paracrine effect to induce a local regenerative microenvironment [19,133].

5.3. MSCs exosomes

In some experimental studies, *MSCs* exosomes promoted tissue repair and regeneration by restoring homeostasis after injury or induced heart disease. Specifically, it was reported that exosomes contain a large amount of ECM proteins and enzymes regulating and restoring the normal ECM turn-over [134].

In 2016 *Toh* et al. reported that exosomes micro-RNA fractions 22, 23b, 92a, 125b, 221,320 and 145, were involved in the regulation of chondrogenesis and cartilage homeostasis [135].

Afterwards, *Tao* et al. reported that exosomes derived from human synovial *MSCs* overexpressed with micro-RNA-140-5p can promote cartilage regeneration and reverse *OA* in rat models [136].

Human embryonic *MSCs derived exosomes* were tested in an animal model of cartilage repair. Osteochondral defects were made in adult rats on both distal femurs. The treatment consisted of intraarticular injections of exosomes in one side and phosphate-buffered saline (PBS) in, the other side. The *MSCs exosomes* and PBS were injected after surgery and afterwards weekly for 12 weeks. Histological findings showed that the exosome treated defects displayed greater improvements than the contralateral *PBS*-treated defects. In the exosome treated defects, cartilage and subchondral bone exhibited complete restoration and complete integration to adjacent cartilage as well as an *ECM* deposition resembling the healthy control [37].

However, additional studies are needed to define exosomes safety and effectiveness, as well as methods to standardize extraction and purification should be implemented.

5.4. Stimulation of resident MSCs

Most joint tissue regeneration treatments have targeted the cartilage tissue. The physiopathology of *early OA* has shown the essential role of articular cartilage together with the synovial membrane and synovial fluid modifications.

Joint pain is firstly triggered by changes to non-cartilaginous components such as the joint capsule, synovial membrane, tendons and ligaments where there is a significant innervation. In addition *Substance P* was found to be secreted by sensory nerve fibres and was identified in the synovium, synovial fluid and, even isolated in the infrapatellar fat pad *IFP* [40,137].

In 2012 the author published an article describing a new procedure based on stimulation of *joint resident MSCs*.

The aim of the study was to show long-term symptoms control through the recovery of local cell homeostasis and tissue repair.

The study examined an individual medication comprised of *polydeoxyribonucleotides* (*PDRN*), a specific set of *Heat Shock Proteins* (*HSPs*) and a *glycerol scaffold*. The *HSPs* were derived from the patient's own blood through a process of thermic stress.

This product named *Gel repair* (*GR*) was shown to be a biological activator able to stimulate the resident *MSCs* located in the capsule and synovial tissue.

An observational clinical trial with 3 years follow up showed a persistent improvement of symptoms together with a radiologic structural recovery of the joints involved in the degenerative osteoarthritis.

Lower pain level and increased joint mobility were observed in almost 80% treated patients and quite often imaging showed a downgrading of the degenerative *OA* [43,138].

6. Discussion and conclusion

Joint and back pain are often the result of degenerative *OA* and are one of the most frequent causes of patient visits for assessment.

Most of the current medical treatments are palliative and work on pain management and symptom control.

In advanced *OA*, total knee and hip replacement are the current standards to alleviate pain and improve function. However, the risks associated with the operation and the finite life span of joint prosthesis exclude this option for a significant group of patients.

Joint replacement cannot often be offered to frail, elderly patients (ASA III-IV) due to high risks of complications and increase mortality. Likewise, surgeons are reluctant to offer younger patients joint replacement due to the limited life span of a prosthesis and chronic postural imbalance induced by the new joint.

The result is the increasing consumption of chronic medications such as NSAIDs and opioids in so-called *pain management*. This palliation has a severe systemic backlash on patient care and health systems due to the complications related to chronic NSAIDs and opioids intake and addiction.

Dilemmas can arise when we seek to offer patients the greatest benefits along with minimal risks. The basic medical principles *primum non nocere, secundum cavere, tertium sanare* (first do not harm, second be careful, third cure) should always guide and inspire medical practice.

The latest knowledge about the biological processes involved in the *early OA*, has given general awareness that this process can be curbed and reversed if addressed at the early stage.

The development of regenerative medicine procedures has now enabled a major change in *OA* treatments.

Timely diagnostic investigations to tackle *early OA* such as MRI with or without contrast enhancement can give all the information about disease onset and progression and its impact on joint structure and tissues.

Moreover, US-scan has had an increasing interest because is a low-cost examination and can be performed by the same physician who will deliver the treatment. Specifically, USs can visualise synovium, ligaments and tendons and some cartilage modifications. The 3D USs increases the accuracy and improve the quality of information.

USs has shown to be reliable to detect progressive joint changes induced by *OA* including details of the articular cartilage damages and demonstration of the inflammation involving the synovial membrane and adjacent soft tissue. For this reason, is a sensible investigation tool to follow up *OA* progression [139].

USs guidance has been used to inject substances or therapeutic cells into joints and accurately infiltrate the injured site.

Further, USs has been proposed to follow up regenerative medicine procedures and test their effectiveness on joint structures.

Many advancements have been made for the treatment of *early OA* and even in more advanced stages of *OA* disease. The direct stimulation of joint resident *MSCs* is one of the most promising procedure together with the autologous or allogeneic *MSCs* transplant and *MSCs* exosomes application. These and other regenerative medicine treatments may become, in the near future, a new frontier for the care of *OA* using minimally invasive procedures.

Declaration of competing interest

The author declares that he does not have financial or nonfinancial competing interests.

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