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Abstract

Purpose of the review. Epidemiologic studies reveal that the link between obesity and osteoarthritis (OA) cannot be uniquely explained by overweight-associated mechanical overload. For this reason, much attention focuses on the endocrine activity of adipose tissues. In addition to the systemic role of visceral and subcutaneous adipose tissues, many arguments highlight the involvement of local adipose tissues in OA.

Recent findings. Alteration in magnetic resonance imaging signal intensity of the infrapatellar fat pad may predict both accelerated knee OA and joint replacement. In this context, recent studies show that mesenchymal stromal cells could play a pivotal role in the pathological remodeling of intra-articular adipose tissues in OA. In parallel, recent findings underline bone marrow adipose tissue as a major player in the control of the bone microenvironment, suggesting its possible role in OA.

Summary. The recent description of AT of various phenotypes within an osteoarthritic joint allows us to evoke their direct involvement in the initiation and progression of the osteoarthritic process. We can expect in the near future the discovery of novel molecules targeting these tissues.

Keywords: osteoarthritis, adipose tissue, adipokines, intra-articular adipose tissues, bone marrow adipose tissue

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease and is one of the leading causes of disability worldwide. The disability-adjusted life years (DALYs) index for OA rose by 34.8% between 2005 and 2015 [1]. The increase in the number of OA patients cannot be explained solely by the ageing of the world population, highlighting the importance of other risk factors. Obesity is the main modifiable risk factor for OA [2]. The World Health Organization estimates that the worldwide prevalence of obesity nearly tripled since 1975 with more than 1.9 billion adults overweight in 2016, among them 650 million were obese.

The role of overweight-associated mechanical overload has long been pointed out to explain the link between OA and obesity. Clinical studies indeed described positive correlations between body mass index (BMI) and both the incidence and the progression of knee OA [3, 4]. However, obesity also impacts non-weight bearing joints [5], suggesting that factors other than mechanical overload also contribute to joint damage in obese patients.

In addition to their role in energetic metabolism, adipose tissues (AT) are endocrine organs releasing factors acting on distant organs. These factors, of which the prototype and the better known is leptin, are defined as adipokines [6]. Blood levels of leptin increase with BMI as they are in OA patients [7, 8]. Evidence argue for a role of leptin in OA [9]. Numerous other adipokines are produced by AT and their secretion pattern is also affected by obesity [10]. This altered secretion pattern of AT related to obesity reflects modifications in their tissue composition as well as modifications in the phenotype of cells present within AT.

AT do not constitute a unique entity. White and brown AT have been described, differing by their developmental origin, the phenotype of their adipocytes and their function in energetic

metabolism and thermogenesis. Moreover, multiple white AT (WAT) exist, present in the whole body as separate fat pads with specific features. In this review, we will describe the known features of different AT, including subcutaneous, visceral, intra-articular and bone marrow AT, and will focus on their potential roles in OA.

Methodology

A search for original articles published between January 2017 and October 2020 was performed on PubMed. The search terms used were “Adipose tissue AND Osteoarthritis” for reviews, “Adipokines AND Osteoarthritis”, “Lipodistrophy AND joint health”, “Leptin”, “Adiponectin”, “Visfatin”, “Resistin”, “Chemerin-1”, “Progranulin”, “Omentin”, “Lipocalin-2”, “infapatellar fat pad”, “intra-articular fat pad” and “Bone marrow adipose tissue AND lipids”. All articles identified were English-language papers. In addition relevant references from selected publications and relevant references were identified.

Role of systemic adipose tissues

Description and physiology

AT can be related to OA progression by biomechanical and metabolic mechanisms (Figure 1). The biomechanical ones refer to an increase in body weight due to AT gain leading to abnormal loading on the joints. The metabolic ones include abnormal lipid profile and secretion of adipokines by adipocytes. Herein we summarize the implication of Subcutaneous (SCAT) and Visceral AT (VAT) on those mechanisms.

SCAT is situated beneath the skin whereas VAT fills the peritoneal cavity and the space between internal organs. Augmentation on either of them implies an increase on body weight and on joint loading. Mechanical stress is an important factor on OA initiation and development [11-13]. Exercise produces a loss of AT weight which alleviates pain symptoms in OA patients. Regarding the metabolic component, SCAT explants from OA patients stimulated with IL1β have been reported to increase pro- and anti-inflammatory signals [14]. Visceral adipocytes seem to be more active in terms of lipolysis and lipogenesis and a major source of adipokines and cytokines in comparison to other types of adipocytes. Adipocytes are also found in the middle of skeletal muscles and their accumulation on females is correlated with OA progression [11, 15]. Below we mention some of the most studied adipokines secreted by these different tissues and how they are related to OA.

Systemic adipokines and OA

Adipokines may play a role in early diagnosis and management of OA symptoms due to their role on cartilage degradation, synovial inflammation and bone remodeling (Table). The evaluation of adipokine content in clinical and experimental models is obtained from serum, plasma or synovial fluid. Asides of AT, joint tissues participate in adipokines secretion. A great amount of adipokines have been correlated to OA onset, development and progression, being leptin the most studied one, followed by adiponectin, resistin and visfatin. Table summarizes recently published data on adipokines, whereas the text below focuses on the best described adipokines. These adipokines in OA drive pathways directly related to inflammation, cartilage degradation, infiltration of joint tissues by immune cells, mesenchymal stem cell (MSCs) differentiation, chondrocytes de-differentiation or osteoclast activation [16-18]. In addition, resistin and visfatin have been described as markers of knee function while leptin and adiponectin as pain markers in OA [19, 20], but further studies need to be performed.

Omentin-1 and vaspin have been reported to be secreted exclusively by VAT but their role seems to be opposed to the rest of other adipokines. *In vitro*, they display chondro-protective activity and are negatively related to OA severity [17*]. Leptin, adiponectin and visfatin could also act under specific conditions as anti-inflammatory and anti-catabolic agents, avoiding tissue degradation. Chemerin for instance could be a marker for obesity-associated OA and with a possible role on innate immune system-associated inflammation on those patients, while lipocalin-2 has been suggested to be a mechano-responsive adipokine [17*, 18]. Interestingly, apelin is the only adipokine described so far to be directly involved with synovium angiogenesis, a known marker of severity in OA [21]. Many other adipokines have been shown to have a

possible role on OA [17*, 22]. Researchers keep testing if those interesting molecules could serve on the early diagnosis of OA as well as targets for future therapeutic strategies.

Role of intra-articular adipose tissues

Description and physiology

Intra-articular adipose tissues (IAAT) are fat pads found between the synovium and the joint capsule. The best characterized and the largest IAAT is the infrapatellar fat pad (IFP). IAAT are white AT (WAT) as SCAT and VAT. Although their characteristics are close to those of VAT, IAAT share common features with SCAT that distinguish them from VAT [23*]. There is no clear consequence of high fat diet on adipocyte size or inflammation of IFP in mice, with contradictory published results [24-26]. Recent data on human OA patients reported an absence of link between obesity and IFP volume [27] or between BMI of OA patients and either adipocyte or inflammatory features of IFP [28], suggesting that IAAT may be different to SCAT and VAT and display specific functions.

The physiological roles of IAAT are still not well characterized. IFP was initially supposed by Clopton Harvers at the end of 17^{th} Century to secrete the synovial fluid and latter, by Jean Cruveilhier in the 19^{th} Century, to fill gaps in the joint. By increasing the synovial surface, IFP facilitates the distribution of the synovial fluid. It may protect the patellar tendon and the anterior horns of the menisci and may supply nutriments to the patellar ligament [29]. IFP is also supposed to act as a shock absorber during joint movement. More recently, it was shown that IFP secrete factors [30, 31], especially prostaglandin $F_{2\alpha}$ and prostaglandin E_2, which induce a

fibrotic and inflammatory response in fibroblast-like synoviocytes [32, 33], suggesting that IAAT and synovium are partners of a same functional unit [23*, 34].

IAAT and OA

A debate exists for several years on the protective or detrimental effect of IAAT on OA. The role of IFP as a shock absorber has been pointed out to explain its possible protective effect, as recently reviewed [11, 35]. A protective effect of IFP-secreted factors and IFP-derived MSCs have been also proposed [11, 35]. Nevertheless, meta-analyses showed little if any detrimental effect of IFP resection on clinical outcomes after total knee arthroplasty [36-38]. On the other side, alteration in magnetic resonance imaging signal intensity of IFP has been linked to OA progression [39] and may predict both accelerated knee OA [40, 41] and knee replacement [42*]. Interestingly, with the aim of an early detection of OA progressors, Bonakdari *et al.* developed a method to predict the volume of IFP [43]. Although the relationship between IFP volume and OA remains unclear, IFP volume is related to patello-femoral joint OA pain [44]. IFP contains numerous sensitive fibers [45] and is considered as a major source of knee pain [46, 47]. OA IAAT are characterized by inflammatory cell infiltration, fibrosis and increased vascularization [23*, 48, 49]. Fibrosis and inflammation of IFP are known features of anterior knee pain. They are associated with an increased vascularization and calcitonin-positive nerve fibers in the fibrotic areas of IFP [50]. Similar observations were obtained with the monoiodoacetic acid (MIA) model of OA, in which IFP changes occurred before cartilage degradation [51, 52].

IAAT secrete factors with proinflammatory and tissue remodeling activities [23*, 30, 31, 33, 49] (Figure 1). Interestingly, IFP from patients with OA and rheumatoid arthritis display distinct fatty acid signatures [53], suggesting disease-specific phenotypes for IFP. The OA-specific

secretory phenotype of IAAT may be directly involved in synovial inflammation and fibrosis [23, 32, 33] since IFP remodeling precedes synovitis [52].

IAAT cellular composition comprises adipocytes, leukocytes, endothelial and mesenchymal cells, all participating in the OA-specific secretory phenotype of IAAT [49, 54, 55]. Although the specific roles of IAAT macrophages remains unknown [56, 57], those of MSCs are more understood. Initially, an anti-inflammatory activity of IFP-derived MSCs from OA patients has been reported [58]. It has been recently proposed that IFP-derived MSCs may be deleterious in OA via their secretion of inflammatory factors, their ability to recruit monocytes and their exacerbated response to an inflammatory stimulus [54, 55]. In addition, cell lineage tracing experiments identified IFP perivascular MSCs as able to transdifferentiate into myofibroblasts and induce IFP fibrosis in posttraumatic OA model [59, 60*]. Moreover, fibroblasts isolated from fibrotic IFP have been involved in inflammatory cell recruitment and pain [61*].

Role of bone marrow adipose tissue

Description and physiology

Bone marrow adipose tissue (BMAT) constitutes over 10% of total adipose mass and 70% of the bone marrow (BM) volume in young lean healthy human adults. The initial concept of BMAT as a passive fat storage depot has been challenged in the recent years although little is known about its physiological roles. It is now well accepted that BMAT has a unique development, molecular profile, regulation and modulation of the anatomical context that make it different from the other types of AT.

BMAT volume changes upon the pathophysiological conditions; it increases with ageing, obesity, type 2 diabetes, osteoporosis or skeletal unloading [62], whereas it decreases with exercise [63], mechanical loading and hormonal changes (Figure 2). BMAT can be classified into constitutive (cBMAT) and regulated BMAT (rBMAT). Both of them differ by the time of their development, their localization in the skeleton, their gene expression pattern and their content in saturated/unsatured lipids [64**]. These differences could indicate different functions and even different progenitors. Nevertheless, rBMAT could also change to a cBMAT phenotype under specific conditions [62].

BM adipocytes (BMAds) have one unilocular lipid droplet with abundant mitochondria [65] and their gene expression pattern is similar to white adipocytes [62]. It is believed that BMAds arise from BM MSCs, probably the same progenitors as osteoblasts. A recent study has proved the progenitors to be more white-like [66] even though it is possible multiple populations within the BMAds could exist [67]. BMAds secrete extracellular vesicles and numerous soluble factors, which may control bone microenvironment [62, 68**]. Zou *et al.* indeed recently showed that BMAds ablation provokes massive bone formation due to the activation of bone morphogenetic protein receptor signaling pathway in MSCs [69**]. In addition, lack of adipo-progenitors on mice produces bone loss and abnormal vasculature [70**].

Aside of its paracrine role, BMAT could regulate systemic metabolism. Moreover, patients with BMAT alteration frequently develop ectopic storage of fat resulting on insulin resistance [71]. BMAT lipogenesis is triggered by short-term cold exposure and is less dependent on insulin than WAT [66]. Little is known about the lipolysis mechanisms on BMAT, but it could be either cytoplasmic lipase-mediated or by lipophagy [68**, 72*]. Specifically, the uptake and esterification of fatty acids is greater in BMAT than in WAT and those fatty acids fuel

hematopoietic tumors and their oxidation is crucial for hematopoietic stem cell maintenance [73, 74]. Suchacki *et al.* have shown that BMAds have high basal glucose uptake that is greater in the axial skeleton than in long bones [66], suggesting that BMAT may influence systemic glucose homeostasis and that this characteristic is needed to support normal metabolic function and *de novo* lipogenesis.

BMAT and OA

Pathophysiological conditions where bone homeostasis is lost have been directly related to an increase in BMAT. Surprisingly, they all constitute OA risk factors. In addition, OA entails sub-chondral bone remodeling and BM is the only tissue where adipocytes and bone cells are in close association. All of these argue for a possible role of BMAT on OA (Figure 1). Moreover, the femoral heads from OA patients contained high amounts of fat and of *n*-6 fatty acids, especially arachidonic acid [75] (Figure 3). Early this year, Collins *et al*. proposed that knee joints of lipodystrophic mice were protected from spontaneous or post-traumatic OA, independently from diet [76]. Susceptibility to post-traumatic OA was reintroduced using implantation of AT derived from wild type animals, probably due to the paracrine signalling from fat [76]. Nevertheless, lipodystrophic patients have multiple bone abnormalities such as subchondral bone sclerosis, similar to OA patients [77]. Interestingly, osteoblasts and osteocytes can also accumulate lipids [68]. The cross-talk between BMAT and joint tissues is far from being unveiled and more studies are needed to describe the mechanisms involved on OA pathogenesis.

Since all joint tissues are of mesenchymal origin and OA is a whole joint disease, it is possible that OA affects MSC features. Both the synthesis of a poorly mineralised matrix and

high content of fat characterize OA bone. This may result from a defect on the differentiation capacity of MSCs favouring preferentially adipogenic over osteogenic lineage. Moreover, a direct role of sclerostin in inducing BM adipogenesis through inhibiting Wnt signaling has recently been reported [78]. The inhibition of Wnt signaling increased expression of adipogenic transcription factors Pparγ and Cebpα and stimulated adipogenesis [79]. However, lack of adiponectin-positive progenitors in mice leads to both bone and angiogenic defects [70].

The role of BMAT in OA still remains speculative but numerous arguments indicate that it could be involved in the dysregulation of joint tissues in OA. Future studies are needed to explore in detail the role of BMAT in OA.

Conclusion

The discovery of the role of low-grade inflammation in certain phenotypes of OA has opened up new physiopathological hypotheses involving AT. The recent description of AT of various phenotypes within an osteoarthritic joint allows us to evoke their direct involvement in the initiation and progression of the osteoarthritic process (Figure 1). We can expect in the near future the discovery of novel molecules targeting these tissues.

Key points

- Visceral and subcutaneous adipose tissues secrete adipokines, which differentially affect joint tissue homeostasis.
- Intra-articular adipose tissue fibrosis and inflammation are early events in osteoarthritis and alteration in magnetic resonance imaging signal intensity of infrapatellar fat pad may predict both accelerated knee osteoarthritis and replacement.
- Inflammatory and remodeling factors secreted by intra-articular adipose tissue may be responsible for cell and tissue damages of both intra-articular adipose tissue and synovium, as components of a same functional unit.
- Bone marrow adipose tissue is a newly studied adipose tissue and a known regulator of bone microenvironment. Its volume changes in pathophysiological conditions associated with osteoarthritis and its composition is enriched in *n*-6 fatty acids, especially arachidonic acid, in osteoarthritic patients, suggesting that it may be a new adipose tissue playing role in osteoarthritis.

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Author Contributions

- Drafting of the article: NZL, FE, FB, XH
- Final approval of the article: NZL, FE, FB, XH

Conflict of interest

None.

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Table. Adipokine in osteoarthritis

Adipokine	Source of detection	Described action	References 2018-2020
Leptin	Plasma	Synovial fluid human knee OA biomarker	[80, 81]
	Serum	Remarkable diagnostic value in the incidence of human knee OA	[82]
	Synovial Fluid	Leptin and its receptor may be an emerging target for intervention in human metabolic-associated OA.	[9, 83]
Adiponectin	Serum	Promising biomarker on human OA pathogenesis	[84]
	Synovial Fluid	Low levels observed in synovial fluids patients of lower OA grades.	[81]
		Gene polymorphism intensifies the risk of human knee OA	[85]
Visfatin	Synovial fluid	Oxidative stress induction human in OA Synoviocytes	[86, 87]
		Human cartilage catabolic effects (Apoptosis, matrix degradation, oxidative stress)	[88]
		Bone remodeling on pig OA model	[89]
Resistin	Plasma	Modulates OA miRs with Visfatin	[86]
	Serum	Progression and pathogenesis of human knee OA	[90]
	Synovial Fluid	Novel and reliable biomarker for human OA severity	
		Pro-inflammatory effects in human OA	[91]

Adipokine	Source of detection	Described action	References 2018-2020
Chemerin	Serum	Cartilage degradation	[92]
		Inflammation	
		Found on serums of patients with primary OA of the hand, knee or hip	
Omentin-1	Synovial Fluid Serum	Possible chondroprotective role in human cells	[16]
Vaspin	*In vitro*	Possible anti-catabolic effect in human cartilage	[16]
		Possible anti-inflammatory effect	
Lipocalin-2	Synovial Fluid	Pro-inflammatory effects in human OA	[93]
		Its downregulation reduces chondrocyte inflammation and cartilage degradation	
Apelin	In vitro human cells	Angiogenesis synovium	[21]
		Catabolic effects	
Progranulin	In vitro human cells	Triggers anabolic markers	[94, 95]
		Anti-inflammatory and anti-catabolic effects	
Nesfatin-1	In vitro human cells	Possible protective role in the development of OA	[96]
	Animal model	Upregulated in OA chondrocytes	[97]

Adipokine	Source of detection	Described action	References 2018-2020
RBP4	Synovial Fluid	Matrix degradation in human cartilage	[22]
	Blood samples	Positive correlation with other OA adipokines	
New Adipokines (SERPINE2, WISP2, GPBMB, ITIH5)	In vitro	Secreted by human OA chondrocytes, human OA sclerotic subchondral bone, human OA synovial tissues and human OA IAAT	[98-101]

Figure legend

Figure 1. Roles of the different adipose tissues on OA progression by biomechanical and metabolic mechanisms.

Increases on systemic AT like SCAT (Subcutaneous adipose tissue), VAT (Visceral adipose tissue) and intra-muscular adipose tissue contribute to abnormal loading of the joint, this mechanical stress have been shown to be part of OA onset and progression. Lipocalin adipokine family has emerged as sensors of mechanical load, inflammatory status and catabolic stimuli of the joint, suggesting its involvement in OA pathophysiology. On the other hand, the paracrine role of SCAT, VAT, intra-muscular AT and local AT BMAT (Bone marrow adipose tissue) and IAAT (intra-articular adipose tissue) affect joint health. The adipokines secreted by all those tissues have proven to promote directly: 1. Secretion of inflammatory cytokines like Interleukin-1beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) which are well-documented for their active involvement in the pathophysiology of OA, 2. Cartilage catabolism, including inhibition of proliferation in chondrocytes and degradation of the matrix components, collagen type 2 and agrecan, 3. Immune response by the infiltration of joint tissues by monocytes and leucocytes which increases even more the inflmmatory signals present on the joint affected, 4. Loss of balance between osteoclast and osteoblast affecting directly bone remodeling, changes on bone constitution are part of OA pathology and 5. Changes on stem cell principal characteristics like prolifereation and differentiation capacity.

Figure 2. General characteristics of bone marrow adipose tissue.

BMAT is currently considered as a tissue with significant paracrine and endocrine activities which make it a major player on different pathologies. BM adipocytes' gene expression pattern is similar to white-like adipocytes, they have one unilocular lipid droplet with abundant mitochondria and recent study has proved the progenitors to be more white-like. Their secretory profile includes extracellular vesicles and numerous molecules like inflammatory factors, adipokines or RANKL. BMAT is a unique adipose tissue which functions are still to be reveled. BMAT has a high intrinsic plasticity, increases with age as well as in other pathological contexts like: obesity, type 2 diabetes or osteoporosis. BMAT content can also decrease with exercise, mechanical loading or hormonal changes. In terms of development it can be classified into cBMAT or constitutive BMAT and rBMAT or regulated BMAT. cBMAT developed early in life, located in the distal skeleton, repository of unsaturated lipids and constituted by adipocytes larger in size with reduced expression of adipogenic markers. On the other hand, rBMAT increases with age, is located in the proximal skeleton where the adipocytes contain saturated lipids and express high levels of known adipogenic markers.

Figure 3. Possible role of bone marrow adiposity in joint health.

BMAT may play a role on inflammation, subchondral bone sclerosis, aberrant angiogenesis, adipogenic differentiation and bone remodeling all of them involved on joint health and OA development and progression. Femoral heads from OA patients contain high amounts of fat, especially arachidonic acid precursor of prostaglandin E_2 a known participant on OA inflammation [75]. Lipodystrophic mice were protected from spontaneous or post-traumatic OA,

this study proposes that adipose tissue is a critical antagonist of cartilage health and integrity due precisely to the paracrine signalling from fat [76]. Mice without adiponectin-positive progenitors had elevated trabecular bone mass and their vessels within the bone marrow were less in number and high in diameter; characteristics that were far from normal. Sclerostin produced by the bone-mechanosensing osteocytes inhibits Wnt signaling stimulated adipogenesis of mouse MSCs and human MSCs [79]. Nevertheless, the cross-talk between all joint tissues and BMAT is far from being unveiled and more studies are needed to describe the mechanisms, adipokines, pathways and signalling involved on OA pathogenesis. OA BMAd (bone marrow adipocytes from OA patients), Pre-BMAd (bone marrow adipocytes precursors).

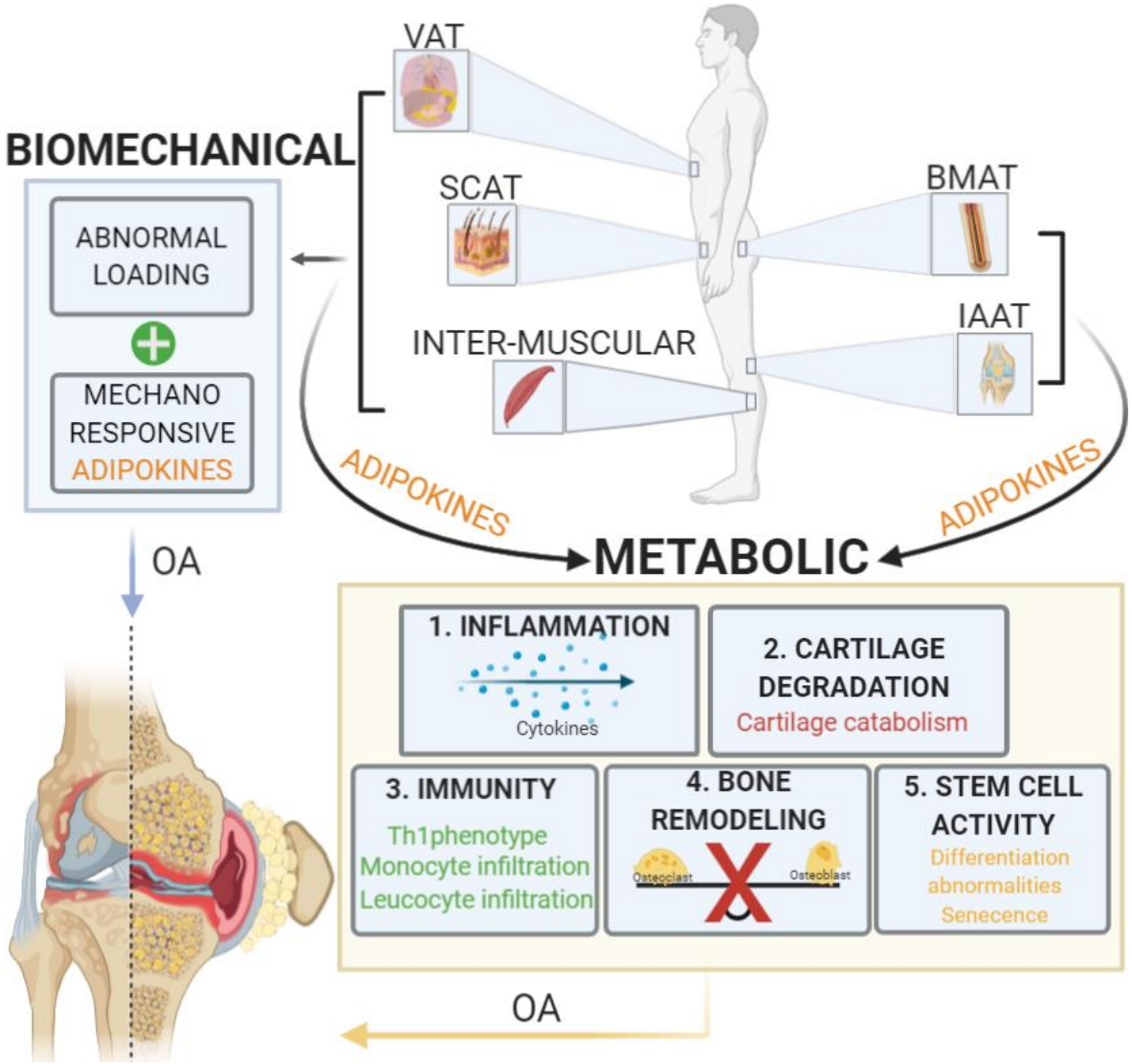
VAT
BIOMECHANICAL
SCAT
BMAT
ABNORMAL LOADING
IAAT
INTER-MUSCULAR
MECHANO RESPONSIVE ADIPOKINES
ADIPOKINES
ADIPOKINES
OA
METABOLIC
1. INFLAMMATION
Cytokines
2. CARTILAGE DEGRADATION
Cartilage catabolism
3. IMMUNITY
Th1phenotype
Monocyte infiltration
Leucocyte infiltration
4. BONE REMODELING
Osteoclast
Osteoblast
5. STEM CELL ACTIVITY
Differentiation abnormalities
Senecence
OA

Figure 1

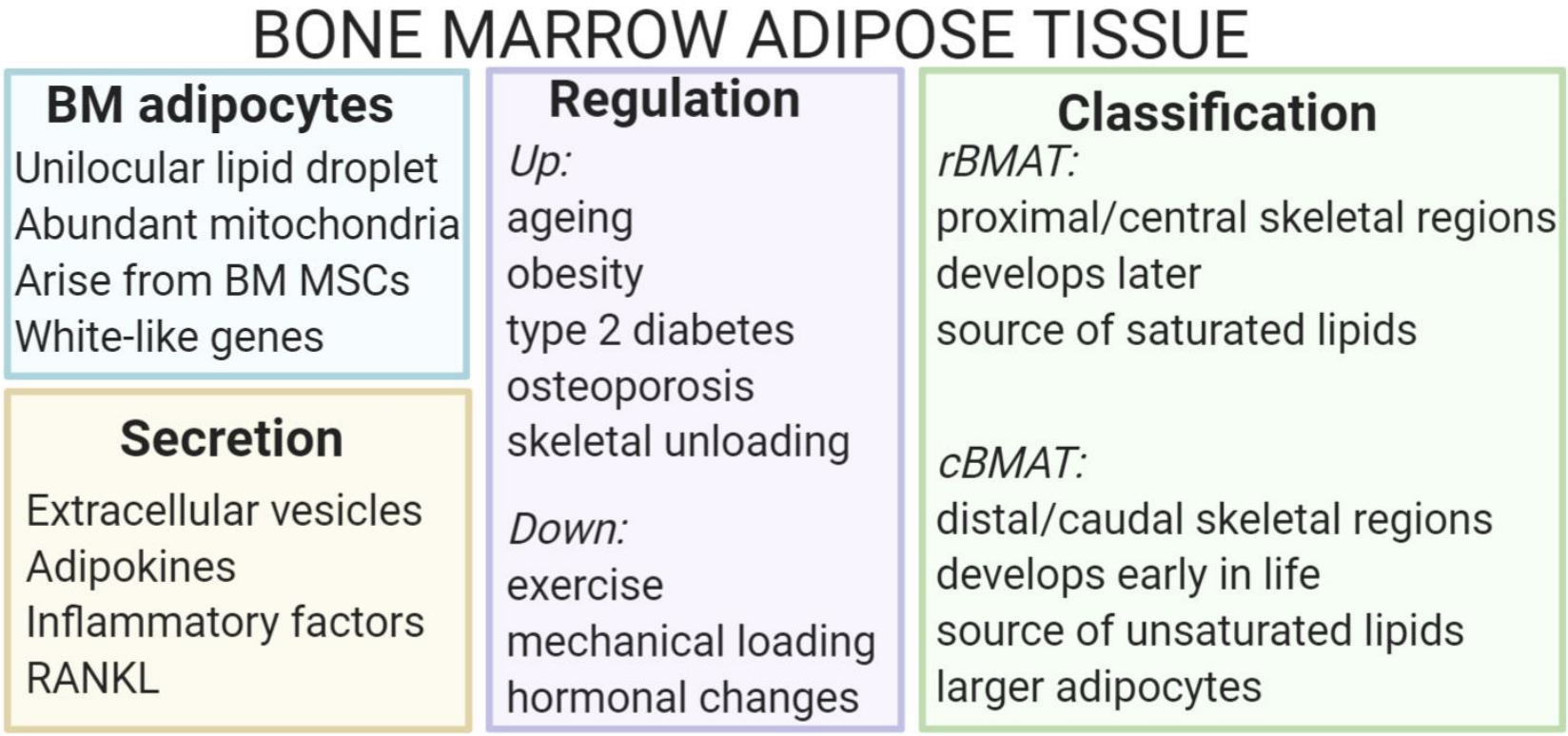
BONE MARROW ADIPOSE TISSUE
BM adipocytes
Unilocular lipid droplet
Abundant mitochondria
Arise from BM MSCs
White-like genes
Secretion
Extracellular vesicles
Adipokines
Inflammatory factors
RANKL
Regulation
Up:
ageing
obesity
type 2 diabetes
osteoporosis
skeletal unloading
Down:
exercise
mechanical loading
hormonal changes
Classification
rBMAT:
proximal/central skeletal regions
develops later
source of saturated lipids
cBMAT:
distal/caudal skeletal regions
develops early in life
source of unsaturated lipids
larger adipocytes

Figure 2

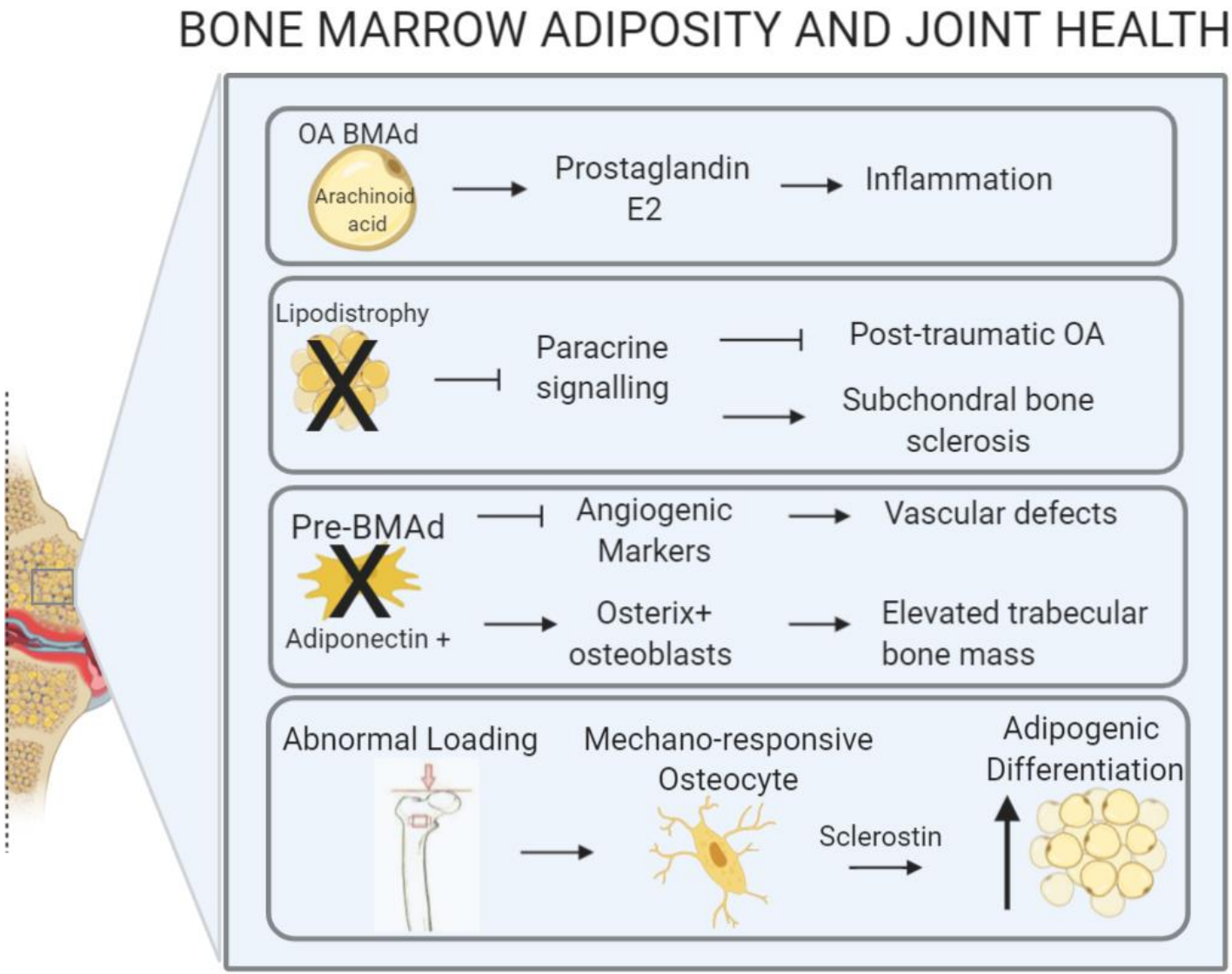
BONE MARROW ADIPOSITY AND JOINT HEALTH
OA BMAd
Arachinoid acid
Prostaglandin E2
Inflammation
Lipodistrophy
Paracrine signalling
Post-traumatic OA
Subchondral bone sclerosis
Pre-BMAd
Adiponectin +
Angiogenic Markers
Vascular defects
Osterix+ osteoblasts
Elevated trabecular bone mass
Abnormal Loading
Mechano-responsive Osteocyte
Sclerostin
Adipogenic Differentiation

Figure 3