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► **To cite this version:**

Natalia Zapata-Linares, Florent Eymard, Francis Berenbaum, Xavier Houard. Role of adipose tissues in osteoarthritis. *Current Opinion in Rheumatology*, 2021, 33 (1), pp.84-93. 10.1097/BOR.0000000000000763 . hal-03263622

**HAL Id: hal-03263622**

**<https://hal.sorbonne-universite.fr/hal-03263622v1>**

Submitted on 17 Jun 2021

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# Role of adipose tissues in osteoarthritis

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**Word count:** 2506

## Abstract

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**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

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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

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

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## **Methodology**

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

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## Role of systemic adipose tissues

### 83 *Description and physiology*

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

89 SCAT is situated beneath the skin whereas VAT fills the peritoneal cavity and the space  
90 between internal organs. Augmentation on either of them implies an increase on body weight and  
91 on joint loading. Mechanical stress is an important factor on OA initiation and development [11-  
92 13]. Exercise produces a loss of AT weight which alleviates pain symptoms in OA patients.  
93 Regarding the metabolic component, SCAT explants from OA patients stimulated with IL1 $\beta$   
94 have been reported to increase pro- and anti-inflammatory signals [14]. Visceral adipocytes seem  
95 to be more active in terms of lipolysis and lipogenesis and a major source of adipokines and  
96 cytokines in comparison to other types of adipocytes. Adipocytes are also found in the middle of  
97 skeletal muscles and their accumulation on females is correlated with OA progression [11, 15].  
98 Below we mention some of the most studied adipokines secreted by these different tissues and  
99 how they are related to OA.

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### 103 *Systemic adipokines and OA*

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

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

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

127

## 128 **Role of intra-articular adipose tissues**

### 129 *Description and physiology*

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

139 The physiological roles of IAAT are still not well characterized. IFP was initially supposed by  
140 Clopton Harvers at the end of 17<sup>th</sup> Century to secrete the synovial fluid and latter, by Jean  
141 Cruveilhier in the 19<sup>th</sup> Century, to fill gaps in the joint. By increasing the synovial surface, IFP  
142 facilitates the distribution of the synovial fluid. It may protect the patellar tendon and the anterior  
143 horns of the menisci and may supply nutriments to the patellar ligament [29]. IFP is also  
144 supposed to act as a shock absorber during joint movement. More recently, it was shown that IFP  
145 secrete factors [30, 31], especially prostaglandin F<sub>2α</sub> and prostaglandin E<sub>2</sub>, which induce a



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

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#### 149 *IAAT and OA*

150 A debate exists for several years on the protective or detrimental effect of IAAT on OA. The  
151 role of IFP as a shock absorber has been pointed out to explain its possible protective effect, as  
152 recently reviewed [11, 35]. A protective effect of IFP-secreted factors and IFP-derived MSCs  
153 have been also proposed [11, 35]. Nevertheless, meta-analyses showed little if any detrimental  
154 effect of IFP resection on clinical outcomes after total knee arthroplasty [36-38]. On the other  
155 side, alteration in magnetic resonance imaging signal intensity of IFP has been linked to OA  
156 progression [39] and may predict both accelerated knee OA [40, 41] and knee replacement [42\*].  
157 Interestingly, with the aim of an early detection of OA progressors, Bonakdari *et al.* developed a  
158 method to predict the volume of IFP [43]. Although the relationship between IFP volume and  
159 OA remains unclear, IFP volume is related to patello-femoral joint OA pain [44]. IFP contains  
160 numerous sensitive fibers [45] and is considered as a major source of knee pain [46, 47]. OA  
161 IAAT are characterized by inflammatory cell infiltration, fibrosis and increased vascularization  
162 [23\*, 48, 49]. Fibrosis and inflammation of IFP are known features of anterior knee pain. They  
163 are associated with an increased vascularization and calcitonin-positive nerve fibers in the  
164 fibrotic areas of IFP [50]. Similar observations were obtained with the monoiodoacetic acid  
165 (MIA) model of OA, in which IFP changes occurred before cartilage degradation [51, 52].

166 IAAT secrete factors with proinflammatory and tissue remodeling activities [23\*, 30, 31, 33,  
167 49] (Figure 1). Interestingly, IFP from patients with OA and rheumatoid arthritis display distinct  
168 fatty acid signatures [53], suggesting disease-specific phenotypes for IFP. The OA-specific

169 secretory phenotype of IAAT may be directly involved in synovial inflammation and fibrosis  
170 [23, 32, 33] since IFP remodeling precedes synovitis [52].

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

181

## 182 **Role of bone marrow adipose tissue**

### 183 *Description and physiology*

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

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

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

207 Aside of its paracrine role, BMAT could regulate systemic metabolism. Moreover, patients  
208 with BMAT alteration frequently develop ectopic storage of fat resulting on insulin resistance  
209 [71]. BMAT lipogenesis is triggered by short-term cold exposure and is less dependent on  
210 insulin than WAT [66]. Little is known about the lipolysis mechanisms on BMAT, but it could  
211 be either cytoplasmic lipase-mediated or by lipophagy [68\*\*, 72\*]. Specifically, the uptake and  
212 esterification of fatty acids is greater in BMAT than in WAT and those fatty acids fuel

213 hematopoietic tumors and their oxidation is crucial for hematopoietic stem cell maintenance [73,  
214 74]. Suchacki *et al.* have shown that BMAds have high basal glucose uptake that is greater in the  
215 axial skeleton than in long bones [66], suggesting that BMAT may influence systemic glucose  
216 homeostasis and that this characteristic is needed to support normal metabolic function and *de*  
217 *novo* lipogenesis.

218

### 219 ***BMAT and OA***

220 Pathophysiological conditions where bone homeostasis is lost have been directly related to an  
221 increase in BMAT. Surprisingly, they all constitute OA risk factors. In addition, OA entails sub-  
222 chondral bone remodeling and BM is the only tissue where adipocytes and bone cells are in close  
223 association. All of these argue for a possible role of BMAT on OA (Figure 1). Moreover, the  
224 femoral heads from OA patients contained high amounts of fat and of *n-6* fatty acids, especially  
225 arachidonic acid [75] (Figure 3). Early this year, Collins *et al.* proposed that knee joints of  
226 lipodystrophic mice were protected from spontaneous or post-traumatic OA, independently from  
227 diet [76]. Susceptibility to post-traumatic OA was reintroduced using implantation of AT derived  
228 from wild type animals, probably due to the paracrine signalling from fat [76]. Nevertheless,  
229 lipodystrophic patients have multiple bone abnormalities such as subchondral bone sclerosis,  
230 similar to OA patients [77]. Interestingly, osteoblasts and osteocytes can also accumulate lipids  
231 [68]. The cross-talk between BMAT and joint tissues is far from being unveiled and more studies  
232 are needed to describe the mechanisms involved on OA pathogenesis.

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

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

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

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245

## Conclusion

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

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### **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.

### **Acknowledgments**

This work was supported by a grant from the Société Française de Rhumatologie. Natalia Zapata-Linares was supported by a grant from the Fondation pour la Recherche Médicale: SPF20160936284.

### **Author Contributions**

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

### **Conflict of interest**

None.

## References

- 275  
276 [1] Collaborators GDaH. Global, regional, and national disability-adjusted life-years (DALYs)  
277 for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic  
278 analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388:1603-1658.
- 279 [2] Felson DT, Anderson JJ, Naimark A *et al.* Obesity and knee osteoarthritis. The Framingham  
280 Study. *Ann Intern Med* 1988; 109:18-24.
- 281 [3] Reijman M, Pols HA, Bergink AP *et al.* Body mass index associated with onset and  
282 progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. *Ann Rheum*  
283 *Dis* 2007; 66:158-62.
- 284 [4] Lohmander LS, Gerhardsson de Verdier M, Rollof J *et al.* Incidence of severe knee and hip  
285 osteoarthritis in relation to different measures of body mass: a population-based prospective  
286 cohort study. *Ann Rheum Dis* 2009; 68:490-6.
- 287 [5] Yusuf E, Nelissen RG, Ioan-Facsinay A *et al.* Association between weight or body mass  
288 index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* 2010; 69:761-5.
- 289 [6] Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose  
290 tissue. *Br J Nutr* 2004; 92:347-55.
- 291 [7] Matsubara M, Maruoka S, Katayose S. Inverse relationship between plasma adiponectin and  
292 leptin concentrations in normal-weight and obese women. *Eur J Endocrinol* 2002; 147:173-  
293 80.
- 294 [8] de Boer TN, van Spil WE, Huisman AM *et al.* Serum adipokines in osteoarthritis;  
295 comparison with controls and relationship with local parameters of synovial inflammation and  
296 cartilage damage. *Osteoarthritis Cartilage* 2012; 20:846-53.

- 297 [9] Gao YH, Zhao CW, Liu B *et al.* An update on the association between metabolic syndrome  
298 and osteoarthritis and on the potential role of leptin in osteoarthritis. *Cytokine* 2020;  
299 129:155043.
- 300 [10] Iannone F, Lapadula G. Obesity and inflammation--targets for OA therapy. *Curr Drug*  
301 *Targets* 2010; 11:586-98.
- 302 [11] Chang J, Liao Z, Lu M *et al.* Systemic and local adipose tissue in knee osteoarthritis.  
303 *Osteoarthritis Cartilage* 2018; 26:864-871.
- 304 [12] Ramage L, Nuki G, Salter DM. Signalling cascades in mechanotransduction: cell-matrix  
305 interactions and mechanical loading. *Scand J Med Sci Sports* 2009; 19:457-69.
- 306 [13] Visser AW, de Mutsert R, le Cessie S *et al.* The relative contribution of mechanical stress  
307 and systemic processes in different types of osteoarthritis: the NEO study. *Ann Rheum Dis*  
308 2015; 74:1842-7.
- 309 [14] Kontny E, Zielinska A, Ksiezopolska-Orlowska K, Gluszko P. Secretory activity of  
310 subcutaneous abdominal adipose tissue in male patients with rheumatoid arthritis and  
311 osteoarthritis - association with clinical and laboratory data. *Reumatologia* 2016; 54:227-235.
- 312 [15] Li S, Schwartz AV, LaValley MP *et al.* Association of Visceral Adiposity With Pain but  
313 Not Structural Osteoarthritis. *Arthritis Rheumatol* 2020; 72:1103-1110.
- 314 [16] Carrion M, Frommer KW, Perez-Garcia S *et al.* The Adipokine Network in Rheumatic Joint  
315 Diseases. *Int J Mol Sci* 2019; 20.
- 316 \* [17] Tu C, He J, Wu B *et al.* An extensive review regarding the adipokines in the pathogenesis  
317 and progression of osteoarthritis. *Cytokine* 2019; 113:1-12.
- 318 *A detailed review on the different cytokines with a role on OA pathogenesis.*



319 [18] Xie C, Chen Q. Adipokines: New Therapeutic Target for Osteoarthritis? Curr Rheumatol  
320 Rep 2019; 21:71.

321 [19] Calvet J, Orellana C, Albinana Gimenez N *et al.* Differential involvement of synovial  
322 adipokines in pain and physical function in female patients with knee osteoarthritis. A cross-  
323 sectional study. Osteoarthritis Cartilage 2018; 26:276-284.

324 [20] Askari A, Arasteh P, Homayounfar R *et al.* The role of adipose tissue secretion in the  
325 creation and pain level in osteoarthritis. Endocr Regul 2020; 54:6-13.

326 [21] Wang YH, Kuo SJ, Liu SC *et al.* Apelin Affects the Progression of Osteoarthritis by  
327 Regulating VEGF-Dependent Angiogenesis and miR-150-5p Expression in Human Synovial  
328 Fibroblasts. Cells 2020; 9.

329 [22] Scotece M, Koskinen-Kolasa A, Pemmari A *et al.* Novel adipokine associated with OA:  
330 retinol binding protein 4 (RBP4) is produced by cartilage and is correlated with MMPs in  
331 osteoarthritis patients. Inflamm Res 2020; 69:415-421.

332 \*[23] Eymard F, Pigenet A, Citadelle D *et al.* Knee and hip intra-articular adipose tissues  
333 (IAATs) compared with autologous subcutaneous adipose tissue: a specific phenotype for a  
334 central player in osteoarthritis. Ann Rheum Dis 2017; 76:1142-1148.

335 *An interesting study showing that IAAT from knee and hip of OA patients share similar*  
336 *charecteristics that differ from those of SCAT but also from VAT. This study defines IAAT and*  
337 *synovium as a same functional unit.*

338 [24] Iwata M, Ochi H, Hara Y *et al.* Initial responses of articular tissues in a murine high-fat  
339 diet-induced osteoarthritis model: pivotal role of the IPFP as a cytokine fountain. PLoS One  
340 2013; 8:e60706.

341 [25] Barboza E, Hudson J, Chang WP *et al.* Profibrotic Infrapatellar Fat Pad Remodeling  
342 Without M1 Macrophage Polarization Precedes Knee Osteoarthritis in Mice With Diet-  
343 Induced Obesity. *Arthritis Rheumatol* 2017; 69:1221-1232.

344 [26] Warmink K, Kozijn AE, Bobeldijk I *et al.* High-fat feeding primes the mouse knee joint to  
345 develop osteoarthritis and pathologic infrapatellar fat pad changes after surgically induced  
346 injury. *Osteoarthritis Cartilage* 2020; 28:593-602.

347 [27] Masaki T, Takahashi K, Hashimoto S *et al.* Volume change in infrapatellar fat pad is  
348 associated not with obesity but with cartilage degeneration. *J Orthop Res* 2019; 37:593-600.

349 [28] de Jong AJ, Klein-Wieringa IR, Andersen SN *et al.* Lack of high BMI-related features in  
350 adipocytes and inflammatory cells in the infrapatellar fat pad (IFP). *Arthritis Res Ther* 2017;  
351 19:186.

352 [29] Eymard F, Chevalier X. Inflammation of the infrapatellar fat pad. *Joint Bone Spine* 2016;  
353 83:389-93.

354 [30] Distel E, Cadoudal T, Durant S *et al.* The infrapatellar fat pad in knee osteoarthritis: an  
355 important source of interleukin-6 and its soluble receptor. *Arthritis Rheum* 2009; 60:3374-7.

356 [31] Ushiyama T, Chano T, Inoue K, Matsusue Y. Cytokine production in the infrapatellar fat  
357 pad: another source of cytokines in knee synovial fluids. *Ann Rheum Dis* 2003; 62:108-12.

358 [32] Bastiaansen-Jenniskens YM, Wei W, Feijt C *et al.* Stimulation of fibrotic processes by the  
359 infrapatellar fat pad in cultured synoviocytes from patients with osteoarthritis: a possible role  
360 for prostaglandin f2alpha. *Arthritis Rheum* 2013; 65:2070-80.

361 [33] Eymard F, Pigenet A, Citadelle D *et al.* Induction of an inflammatory and prodegradative  
362 phenotype in autologous fibroblast-like synoviocytes by the infrapatellar fat pad from patients  
363 with knee osteoarthritis. *Arthritis Rheumatol* 2014; 66:2165-74.

- 364 [34] Macchi V, Stocco E, Stecco C *et al.* The infrapatellar fat pad and the synovial membrane: an  
365 anatomo-functional unit. *J Anat* 2018; 233:146-154.
- 366 [35] Jiang LF, Fang JH, Wu LD. Role of infrapatellar fat pad in pathological process of knee  
367 osteoarthritis: Future applications in treatment. *World J Clin Cases* 2019; 7:2134-2142.
- 368 [36] Sun C, Zhang X, Lee WG *et al.* Infrapatellar fat pad resection or preservation during total  
369 knee arthroplasty: a meta-analysis of randomized controlled trials. *J Orthop Surg Res* 2020;  
370 15:297.
- 371 [37] White L, Holyoak R, Sant J *et al.* The effect of infrapatellar fat pad resection on outcomes  
372 post-total knee arthroplasty: a systematic review. *Arch Orthop Trauma Surg* 2016; 136:701-8.
- 373 [38] Ye C, Zhang W, Wu W *et al.* Influence of the Infrapatellar Fat Pad Resection during Total  
374 Knee Arthroplasty: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11:e0163515.
- 375 [39] Ruhdorfer A, Haniel F, Petersohn T *et al.* Between-group differences in infra-patellar fat  
376 pad size and signal in symptomatic and radiographic progression of knee osteoarthritis vs  
377 non-progressive controls and healthy knees - data from the FNIH Biomarkers Consortium  
378 Study and the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2017; 25:1114-1121.
- 379 [40] Davis JE, Ward RJ, MacKay JW *et al.* Effusion-synovitis and infrapatellar fat pad signal  
380 intensity alteration differentiate accelerated knee osteoarthritis. *Rheumatology (Oxford)* 2019;  
381 58:418-426.
- 382 [41] Harkey MS, Davis JE, Lu B *et al.* Early pre-radiographic structural pathology precedes the  
383 onset of accelerated knee osteoarthritis. *BMC Musculoskelet Disord* 2019; 20:241.
- 384 \*[42] Wang K, Ding C, Hannon MJ *et al.* Signal intensity alteration within infrapatellar fat pad  
385 predicts knee replacement within 5 years: data from the Osteoarthritis Initiative. *Osteoarthritis*  
386 *Cartilage* 2018; 26:1345-1350.

387 *A clinical study showing that IFP alterations revealed by MRI predicts knee replacement within*  
388 *5 years.*

389 [43] Bonakdari H, Tardif G, Abram F *et al.* Serum adipokines/related inflammatory factors and  
390 ratios as predictors of infrapatellar fat pad volume in osteoarthritis: Applying comprehensive  
391 machine learning approaches. *Sci Rep* 2020; 10:9993.

392 [44] Cowan SM, Hart HF, Warden SJ, Crossley KM. Infrapatellar fat pad volume is greater in  
393 individuals with patellofemoral joint osteoarthritis and associated with pain. *Rheumatol Int*  
394 2015; 35:1439-42.

395 [45] Bohnsack M, Meier F, Walter GF *et al.* Distribution of substance-P nerves inside the  
396 infrapatellar fat pad and the adjacent synovial tissue: a neurohistological approach to anterior  
397 knee pain syndrome. *Arch Orthop Trauma Surg* 2005; 125:592-7.

398 [46] Belluzzi E, Stocco E, Pozzuoli A *et al.* Contribution of Infrapatellar Fat Pad and Synovial  
399 Membrane to Knee Osteoarthritis Pain. *Biomed Res Int* 2019; 2019:6390182.

400 [47] Draghi F, Ferrozzi G, Urciuoli L *et al.* Hoffa's fat pad abnormalities, knee pain and  
401 magnetic resonance imaging in daily practice. *Insights Imaging* 2016; 7:373-83.

402 [48] Favero M, El-Hadi H, Belluzzi E *et al.* Infrapatellar fat pad features in osteoarthritis: a  
403 histopathological and molecular study. *Rheumatology (Oxford)* 2017; 56:1784-1793.

404 [49] Klein-Wieringa IR, Kloppenburg M, Bastiaansen-Jenniskens YM *et al.* The infrapatellar fat  
405 pad of patients with osteoarthritis has an inflammatory phenotype. *Ann Rheum Dis* 2011;  
406 70:851-7.

407 [50] Onuma H, Tsuji K, Hoshino T *et al.* Fibrotic changes in the infrapatellar fat pad induce new  
408 vessel formation and sensory nerve fiber endings that associate prolonged pain. *J Orthop Res*  
409 2020; 38:1296-1306.

- 410 [51] Clements KM, Ball AD, Jones HB *et al.* Cellular and histopathological changes in the  
411 infrapatellar fat pad in the monoiodoacetate model of osteoarthritis pain. *Osteoarthritis*  
412 *Cartilage* 2009; 17:805-12.
- 413 [52] Inomata K, Tsuji K, Onuma H *et al.* Time course analyses of structural changes in the  
414 infrapatellar fat pad and synovial membrane during inflammation-induced persistent pain  
415 development in rat knee joint. *BMC Musculoskelet Disord* 2019; 20:8.
- 416 [53] Mustonen AM, Kakela R, Lehenkari P *et al.* Distinct fatty acid signatures in infrapatellar fat  
417 pad and synovial fluid of patients with osteoarthritis versus rheumatoid arthritis. *Arthritis Res*  
418 *Ther* 2019; 21:124.
- 419 [54] Bravo B, Guisasola MC, Vaquero J *et al.* Gene expression, protein profiling, and  
420 chemotactic activity of infrapatellar fat pad mesenchymal stem cells in pathologies of the  
421 knee joint. *J Cell Physiol* 2019; 234:18917-18927.
- 422 [55] Eymard F, Pigenet A, Rose C *et al.* Contribution of adipocyte precursors in the phenotypic  
423 specificity of intra-articular adipose tissues in knee osteoarthritis patients. *Arthritis Res Ther*  
424 2019; 21:252.
- 425 [56] Wu CL, Harasymowicz NS, Klimak MA *et al.* The role of macrophages in osteoarthritis and  
426 cartilage repair. *Osteoarthritis Cartilage* 2020; 28:544-554.
- 427 [57] Xie J, Huang Z, Yu X *et al.* Clinical implications of macrophage dysfunction in the  
428 development of osteoarthritis of the knee. *Cytokine Growth Factor Rev* 2019; 46:36-44.
- 429 [58] Manferdini C, Maumus M, Gabusi E *et al.* Adipose-derived mesenchymal stem cells exert  
430 antiinflammatory effects on chondrocytes and synoviocytes from osteoarthritis patients  
431 through prostaglandin E2. *Arthritis Rheum* 2013; 65:1271-81.

432 [59] Sono T, Hsu CY, Negri S *et al.* Platelet-derived growth factor receptor-beta (PDGFRbeta)  
433 lineage tracing highlights perivascular cell to myofibroblast transdifferentiation during post-  
434 traumatic osteoarthritis. *J Orthop Res* 2020.

435 \*[60] Sono T, Hsu CY, Wang Y *et al.* Perivascular Fibro-Adipogenic Progenitor Tracing during  
436 Post-Traumatic Osteoarthritis. *Am J Pathol* 2020; 190:1909-1920.

437 *Using cell lineage tracing, this study reveals the importance of perivascular MSC in IFP*  
438 *fibrosis.*

439 \*[61] Paish HL, Kalson NS, Smith GR *et al.* Fibroblasts Promote Inflammation and Pain via IL-  
440 1alpha Induction of the Monocyte Chemoattractant Chemokine (C-C Motif) Ligand 2. *Am J*  
441 *Pathol* 2018; 188:696-714.

442 *An interesting study that highlights the role of fibrosis and fibroblasts in IFP inflammation and*  
443 *pain.*

444 [62] Li Y, Meng Y, Yu X. The Unique Metabolic Characteristics of Bone Marrow Adipose  
445 Tissue. *Front Endocrinol (Lausanne)* 2019; 10:69.

446 [63] Patel VS, Ete Chan M, Rubin J, Rubin CT. Marrow Adiposity and Hematopoiesis in Aging  
447 and Obesity: Exercise as an Intervention. *Curr Osteoporos Rep* 2018; 16:105-115.

448 \*\*[64] Scheller EL, Doucette CR, Learman BS *et al.* Region-specific variation in the properties  
449 of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. *Nat*  
450 *Commun* 2015; 6:7808.

451 *One of the first studies focused on the molecular characterization of BMAT. Notably, this study*  
452 *evidences the existence of several subtypes of BMAT with different behaviors.*

453 [65] Li Z, Hardij J, Bagchi DP *et al.* Development, regulation, metabolism and function of bone  
454 marrow adipose tissues. *Bone* 2018; 110:134-140.

455 [66] Suchacki KJ, Tavares AAS, Mattiucci D *et al.* Bone marrow adipose tissue is a unique  
456 adipose subtype with distinct roles in glucose homeostasis. *Nat Commun* 2020; 11:3097.

457 [67] Horowitz MC, Berry R, Holtrup B *et al.* Bone marrow adipocytes. *Adipocyte* 2017; 6:193-  
458 204.

459 \*\*[68] Rendina-Ruedy E, Rosen CJ. Lipids in the Bone Marrow: An Evolving Perspective. *Cell*  
460 *Metab* 2020; 31:219-231.

461 *A detailed review specific on the lipid content of bone marrow adipose tissue that could help to*  
462 *bring some light on the still unknown functions of this tissue.*

463 \*\*[69] Zou W, Rohatgi N, Brestoff JR *et al.* Ablation of Fat Cells in Adult Mice Induces  
464 Massive Bone Gain. *Cell Metab* 2020.

465 *An interesting study showing that BMADs display a negative control on bone mass via the*  
466 *secretion of inhibitors of bone morphogenetic protein receptor signaling pathway in MSCs.*

467 \*\*[70] Zhong L, Yao L, Tower RJ *et al.* Single cell transcriptomics identifies a unique adipose  
468 lineage cell population that regulates bone marrow environment. *Elife* 2020; 9.

469 *An original article revealing a progenitor population for bone marrow adipocytes and showing*  
470 *finally the need to find a balance between adipogenesis and bone remodeling.*

471 [71] Yamamoto A, Kusakabe T, Sato K *et al.* Seipin-linked congenital generalized lipodystrophy  
472 type 2: a rare case with multiple lytic and pseudo-osteopoikilosis lesions. *Acta Radiol Open*  
473 2019; 8:2058460119892407.

474 \* [72] Sebo ZL, Rendina-Ruedy E, Ables GP *et al.* Bone Marrow Adiposity: Basic and Clinical  
475 Implications. *Endocr Rev* 2019; 40:1187-1206.

476 *A Review on the bone marrow adipocyte characteristics in comparison to other adipose tissues.*

477 [73] Diedrich JD, Herroon MK, Rajagurubandara E, Podgorski I. The Lipid Side of Bone  
478 Marrow Adipocytes: How Tumor Cells Adapt and Survive in Bone. *Curr Osteoporos Rep*  
479 2018; 16:443-457.

480 [74] Zhang Z, Huang Z, Ong B *et al.* Bone marrow adipose tissue-derived stem cell factor  
481 mediates metabolic regulation of hematopoiesis. *Haematologica* 2019; 104:1731-1743.

482 [75] Plumb MS, Aspden RM. High levels of fat and (n-6) fatty acids in cancellous bone in  
483 osteoarthritis. *Lipids Health Dis* 2004; 3:12.

484 [76] Collins KH, Lenz KL, Pollitt EN *et al.* Adipose Tissue is a Critical Regulator of  
485 Osteoarthritis. *bioRxiv* 2020; doi: 10.1101/2020.06.04.134601.

486 [77] Teboul-Core S, Rey-Jouvin C, Miquel A *et al.* Bone imaging findings in genetic and  
487 acquired lipodystrophic syndromes: an imaging study of 24 cases. *Skeletal Radiol* 2016;  
488 45:1495-506.

489 [78] Lories RJ, Monteagudo S. Review Article: Is Wnt Signaling an Attractive Target for the  
490 Treatment of Osteoarthritis? *Rheumatol Ther* 2020; 7:259-270.

491 [79] Fairfield H, Falank C, Harris E *et al.* The skeletal cell-derived molecule sclerostin drives  
492 bone marrow adipogenesis. *J Cell Physiol* 2018; 233:1156-1167.

493 [80] Boffa A, Merli G, Andriolo L *et al.* Synovial Fluid Biomarkers in Knee Osteoarthritis: A  
494 Systematic Review and Quantitative Evaluation Using BIPEDs Criteria. *Cartilage*  
495 2020:1947603520942941.

496 [81] Sachdeva M, Aggarwal A, Sharma R *et al.* Chronic inflammation during osteoarthritis is  
497 associated with an increased expression of CD161 during advanced stage. *Scand J Immunol*  
498 2019; 90:e12770.



- 499 [82] Min S, Shi T, Han X *et al.* Serum levels of leptin, osteopontin, and sclerostin in patients  
500 with and without knee osteoarthritis. *Clin Rheumatol* 2020.
- 501 [83] Yan M, Zhang J, Yang H, Sun Y. The role of leptin in osteoarthritis. *Medicine (Baltimore)*  
502 2018; 97:e0257.
- 503 [84] Xiao K, Yu L, Zhu L *et al.* Urine Proteomics Profiling and Functional Characterization of  
504 Knee Osteoarthritis Using iTRAQ Technology. *Horm Metab Res* 2019; 51:735-740.
- 505 [85] Shang H, Hao Y, Hu W *et al.* Association between ADIPOQ gene variants and knee  
506 osteoarthritis in a Chinese population. *Biosci Rep* 2019; 39.
- 507 [86] Cheleschi S, Gallo I, Barbarino M *et al.* MicroRNA Mediate Visfatin and Resistin Induction  
508 of Oxidative Stress in Human Osteoarthritic Synovial Fibroblasts Via NF-kappaB Pathway.  
509 *Int J Mol Sci* 2019; 20.
- 510 [87] Yapici Yavuz G, Simsek Kaya G, Kiziltunc A. Analysis of synovial fluid visfatin level in  
511 temporomandibular joint disorders. *Cranio* 2019; 37:296-303.
- 512 [88] Cheleschi S, Tenti S, Mondanelli N *et al.* MicroRNA-34a and MicroRNA-181a Mediate  
513 Visfatin-Induced Apoptosis and Oxidative Stress via NF-kappaB Pathway in Human  
514 Osteoarthritic Chondrocytes. *Cells* 2019; 8.
- 515 [89] Macfadyen MA, Daniel Z, Kelly S *et al.* The commercial pig as a model of spontaneously-  
516 occurring osteoarthritis. *BMC Musculoskelet Disord* 2019; 20:70.
- 517 [90] Alissa EM, Alzughairi LS, Marzouki ZM. Relationship between serum resistin, body fat  
518 and inflammatory markers in females with clinical knee osteoarthritis. *Knee* 2020; 27:45-50.
- 519 [91] Chen WC, Lin CY, Kuo SJ *et al.* Resistin Enhances VCAM-1 Expression and Monocyte  
520 Adhesion in Human Osteoarthritis Synovial Fibroblasts by Inhibiting MiR-381 Expression  
521 through the PKC, p38, and JNK Signaling Pathways. *Cells* 2020; 9.

- 522 [92] Cajas Santana LJ, Rondon Herrera F, Rojas AP *et al.* Serum chemerin in a cohort of  
523 Colombian patients with primary osteoarthritis. *Reumatol Clin* 2020.
- 524 [93] Pirozzi C, Francisco V, Guida FD *et al.* Butyrate Modulates Inflammation in Chondrocytes  
525 via GPR43 Receptor. *Cell Physiol Biochem* 2018; 51:228-243.
- 526 [94] Feng D, Kang X, Wang R *et al.* Progranulin modulates cartilage-specific gene expression  
527 via sirtuin 1-mediated deacetylation of the transcription factors SOX9 and P65. *J Biol Chem*  
528 2020; 295:13640-13650.
- 529 [95] Zhi L, Zhao J, Zhao H *et al.* Downregulation of LncRNA OIP5-AS1 Induced by IL-1beta  
530 Aggravates Osteoarthritis via Regulating miR-29b-3p/PGRN. *Cartilage*  
531 2020:1947603519900801.
- 532 [96] Jiang L, Xu K, Li J *et al.* Nesfatin-1 suppresses interleukin-1beta-induced inflammation,  
533 apoptosis, and cartilage matrix destruction in chondrocytes and ameliorates osteoarthritis in  
534 rats. *Aging (Albany NY)* 2020; 12:1760-1777.
- 535 [97] Wang Q, Xu X, Kang Z *et al.* Paeonol prevents IL-1beta-induced inflammatory response  
536 and degradation of type II collagen in human primary chondrocytes. *Artif Cells Nanomed*  
537 *Biotechnol* 2019; 47:2139-2145.
- 538 [98] Conde J, Scotece M, Abella V *et al.* Identification of novel adipokines in the joint.  
539 Differential expression in healthy and osteoarthritis tissues. *PLoS One* 2015; 10:e0123601.
- 540 [99] Li H, Yang HH, Sun ZG *et al.* Whole-transcriptome sequencing of knee joint cartilage from  
541 osteoarthritis patients. *Bone Joint Res* 2019; 8:288-301.
- 542 [100] Sanchez C, Mazzucchelli G, Lambert C *et al.* Comparison of secretome from osteoblasts  
543 derived from sclerotic versus non-sclerotic subchondral bone in OA: A pilot study. *PLoS One*  
544 2018; 13:e0194591.

545 [101] Tang S, Deng S, Guo J *et al.* Deep Coverage Tissue and Cellular Proteomics Revealed IL-  
546 1beta Can Independently Induce the Secretion of TNF-Associated Proteins from Human  
547 Synoviocytes. *J Immunol* 2018; 200:821-833.

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**Table. Adipokine in osteoarthritis**

<b>Adipokine</b>	<b>Source of detection</b>	<b>Described action</b>	<b>References 2018-2020</b>
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	
		Pro-inflammatory effects in human OA	[91]

<b>Adipokine</b>	<b>Source of detection</b>	<b>Described action</b>	<b>References 2018-2020</b>
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	<i>In vitro</i>	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]

<b>Adipokine</b>	<b>Source of detection</b>	<b>Described action</b>	<b>References 2018-2020</b>
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-1 $\beta$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ) 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 aggrecan, 3. Immune response by the infiltration of joint tissues by monocytes and leucocytes which increases even more the inflammatory 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 proliferation 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 revealed. 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<sub>2</sub> 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).

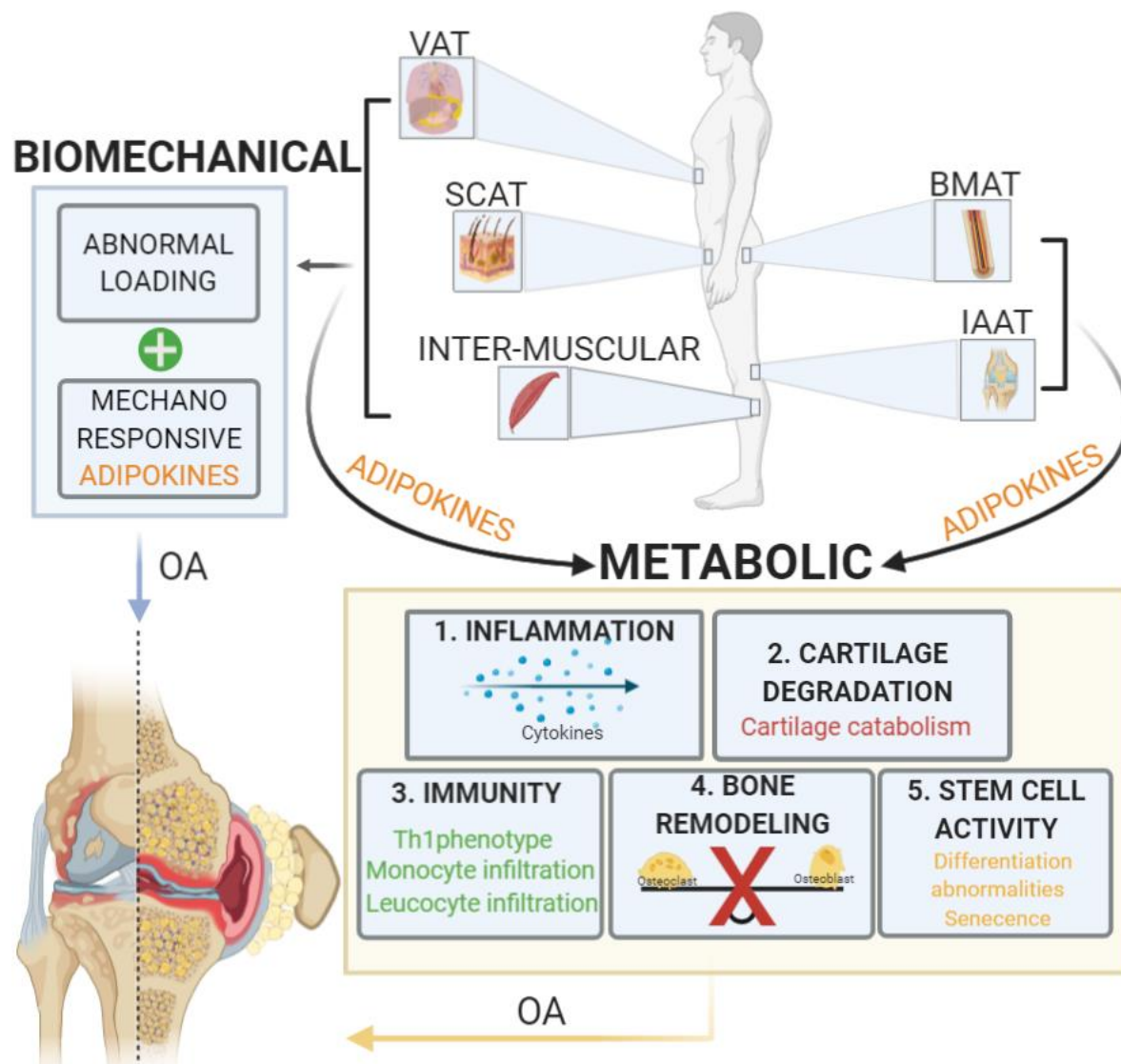


Figure 1

# BONE MARROW ADIPOSE TISSUE

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

Figure 2

# BONE MARROW ADIPOSITY AND JOINT HEALTH

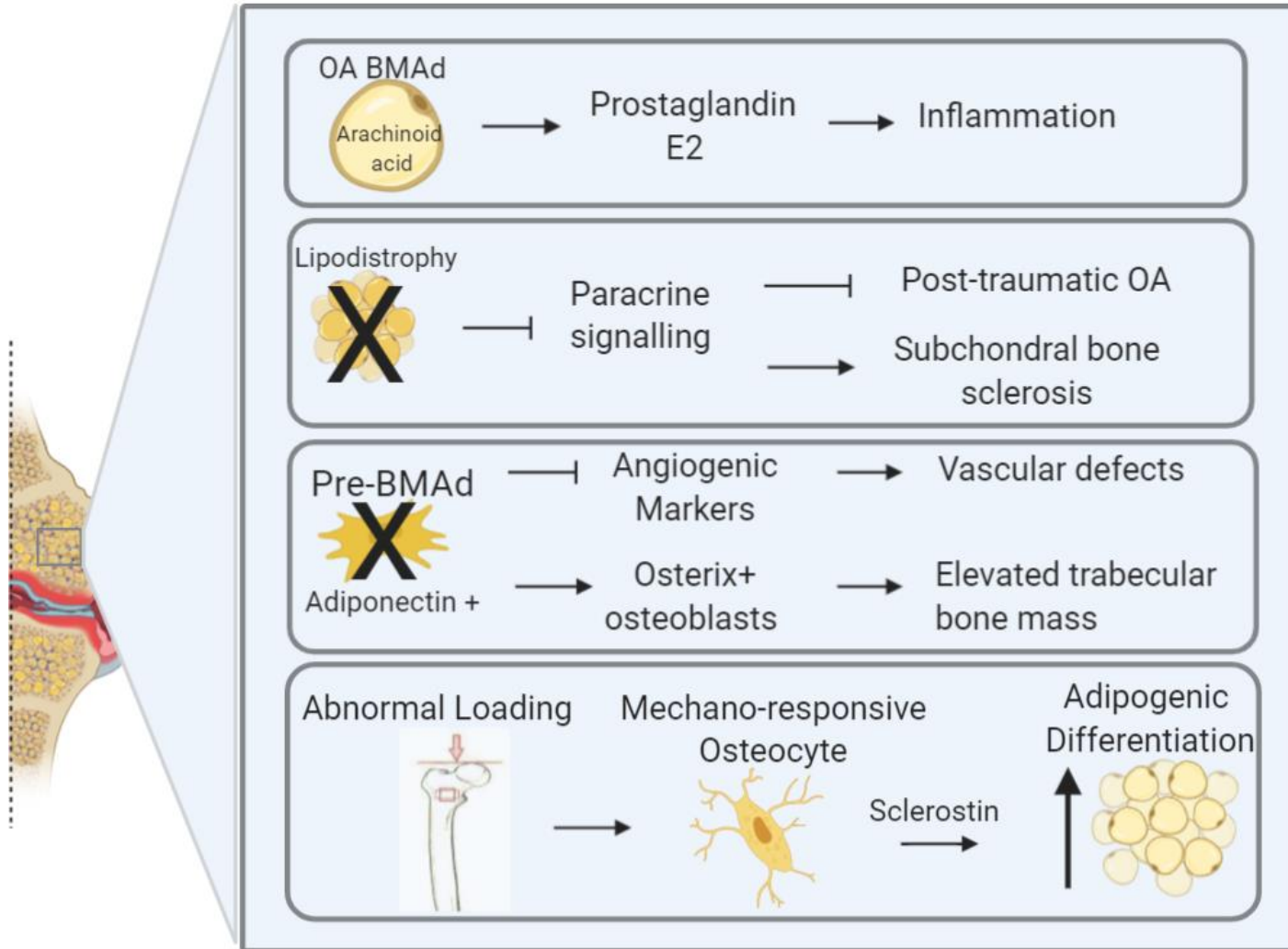


Figure 3