Osteoarthritis and Cartilage Open 6 (2024) 100511

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131

Review

# Obesity-induced fibrosis in osteoarthritis: Pathogenesis, consequences and novel therapeutic opportunities

João Henriques [a], Francis Berenbaum [b,c,d], Ali Mobasheri [a,e,f,g,*]

[a] Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland
[b] Sorbonne University, Paris, France
[c] Department of Rheumatology, Saint-Antoine Hospital, Assistance Publique-Hopitaux de Paris, Paris, France
[d] INSERM CRSA, Paris, France
[e] State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania
[f] Department of Joint Surgery, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[g] World Health Organization Collaborating Center for Public Health Aspects of Musculoskeletal Health and Aging, Université de Liège, Liège, Belgium

ARTICLE INFO

Handling Editor: Professor H Madry

*Keywords:*
Osteoarthritis
Obesity
Fibrosis
Adiposity
Immunometabolic alterations
Therapeutic
Weight management

ABSTRACT

Osteoarthritis (OA) is a significant global burden, affecting more than half a billion people across the world. It is characterized by degeneration and loss of articular cartilage, synovial inflammation, and subchondral bone sclerosis, leading to pain and functional impairment. After age, obesity is a major modifiable risk factor for OA, and it has recently been identified as a chronic disease by the World Health Organization (WHO). Obesity is associated with high morbidity and mortality, imposing a significant cost on individuals and society. Obesity increases the risk of knee OA through increased joint loading, altered body composition, and elevated pro-inflammatory adipokines in the systemic circulation. Moreover, obesity triggers fibrotic processes in different organs and tissues, including those involved in OA. Fibrosis in OA refers to the abnormal accumulation of fibrous tissue within and around the joints. It can be driven by increased adiposity, low-grade inflammation, oxidative stress, and metabolic alterations. However, the clinical outcomes of fibrosis in OA are unclear. This review focuses on the link between obesity and OA, explores the mechanism of obesity-driven fibrosis, and examines potential therapeutic opportunities for targeting fibrotic processes in OA.

## 1. Introduction

Osteoarthritis (OA) is the most common form of arthritis affecting millions of people worldwide, negatively impacting their quality of life.[1] By 2020, over 595 million people were affected by OA, with 41 million new cases reported, an increase of 132.2% since 1990 [1]. The most common risk factors for OA include age, obesity, gender, previous joint injury, genetic predisposition, and anatomical variables such as malalignment and atypical joint shape [2,3]. Disease progression in the general population is slow, taking several decades to develop before significant symptoms become noticeable. Progression is faster in people with previous joint injuries, and those who are overweight and obese. As the disease progresses, it goes through different stages, with inflammatory and painful episodes and continued structural degeneration, contributing to exacerbated symptoms. This can lead to increased pain, stiffness, swelling, reduced joint function, and overall deterioration in the affected joint's condition [4].

The Osteoarthritis Research Society International (OARSI) defines OA as a joint disorder caused by cell stress and extracellular matrix (ECM) degradation, triggered by micro- and macro-injury. It triggers maladaptive repair responses within the innate immunity's pro-inflammatory pathways. The first manifestations may include abnormal metabolism, which is followed by anatomical and physiological abnormalities such as osteophyte formation, cartilage degradation, bone restructuring, joint inflammation, and loss of joint function [5] (see Fig. 1). The development of OA is a complex process involving genetic predisposition, epigenetic influences, biomechanical factors, diet, and lifestyle, all impacting molecular and metabolic variables [4,6]. Advancing age is the most significant risk factor for OA, as the natural structural changes in joint tissues occurring over time contribute to degeneration [7]. Additionally, joint

* Corresponding author.
*E-mail addresses:* Joao.Henriques@oulu.fi (J. Henriques), francis.berenbaum@aphp.fr (F. Berenbaum), ali.mobasheri@oulu.fi (A. Mobasheri).

[1] https://www.thelancet.com/gbd.

https://doi.org/10.1016/j.ocarto.2024.100511
Received 6 February 2024; Received in revised form 26 July 2024; Accepted 12 August 2024

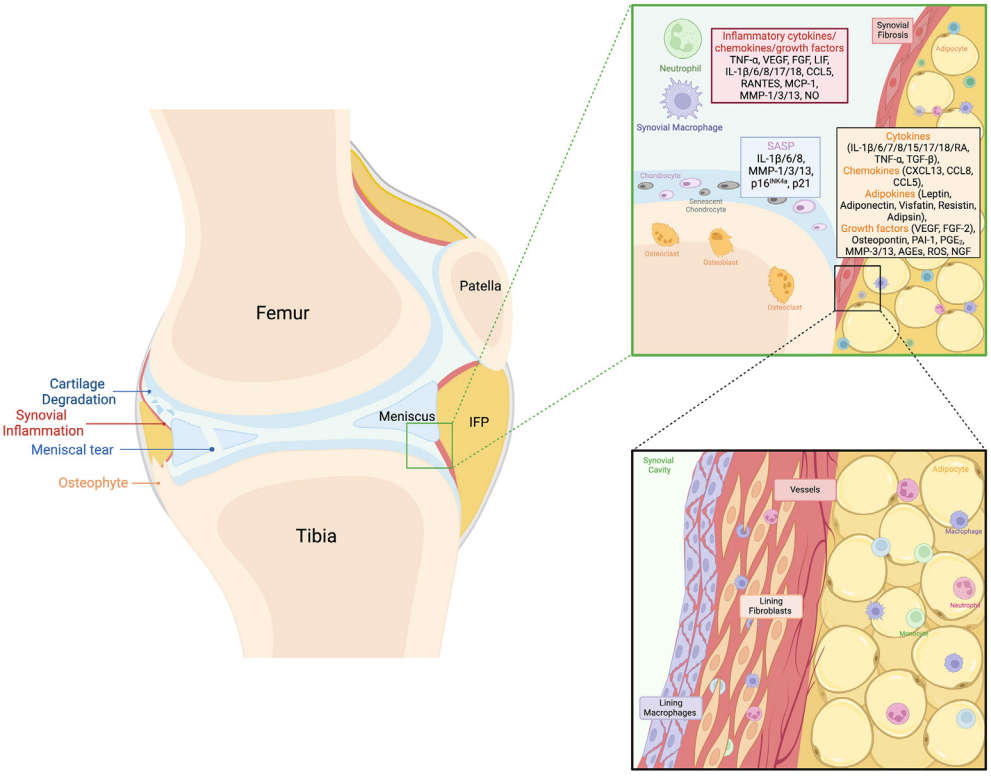


**Fig. 1.** Schematic illustration of an obesity derived OA knee (left) and its main features of OA progression including synovial inflammation and fibrosis, cartilage degradation, meniscus tear, adipocyte build-up, and osteophyte formation. In the adipose tissue (right top), multiple molecules contribute to OA pathology including inflammatory cytokines: IL-1β, IL-6, and TNF-α; along with chemokines (CXCL13, CCL8, CCL5), adipokines (leptin, adiponectin), and growth factors (VEGF, FGF-2). Additionally, factors like osteopontin, PAI-1, $PGE_2$, MMP-3/13, AGEs, ROS, and NGF contribute to the complex environment. Within the cartilage, due to cellular aging influence on OA progression, senescent cells release a senescence-associated secretory phenotype (SASP) including IL-1β, IL-6, IL-8, MMP-1, MMP-3, MMP-13, and express senescence associated proteins $p16^{INK4a}$, and p21. In the joint cavity, can also be found inflammatory cytokines, chemokines, and growth factors (TNF-α, VEGF, FGF, LIF, IL-1β, IL-6, IL-8, IL-17, IL-18, CCL5, RANTES, MCP-1, MMP-1, MMP-3, MMP-13, and NO). In the Inflamed Synovium (right bottom), macrophage and fibroblast disruption lead to an increased cell number, increased vascularization, and macrophage infiltration, emphasizing the structural alterations in the synovial tissue associated with inflammation in OA. Image created in Biorender.com.

injuries, repetitive stress, and structural abnormalities can predispose individuals to the development of OA earlier in the life course [7].

OA is a serious disease [8] and it is challenging to treat because there are no effective drugs that have been approved by regulatory agencies. Basic, translational and clinical research on causes, risk factors, and pathophysiology is ongoing [9]. Current diagnostic procedures are ineffective for detecting OA in its earliest stages, and current symptomatic treatments fail to control progression in all stages of the disease [10]. Exercise, weight loss, and education are now recommended in all the recent treatment guidelines [11–14]. Non-steroidal anti-inflammatory drugs are prescribed to decrease pain and inflammation, but they do not target the pathogenic mechanisms in OA. Furthermore, they can have significant side effects on the cardiovascular, renal, and gastrointestinal systems if used for extended periods of time [15]. In OA there are no treatments and the surgical procedures that are available for severe late-stage cases, such as knee arthroplasty or high tibial osteotomy are associated with the risk of failure [16,17].

## 2. Obesity

Obesity is a major global health crisis, with over 1.9 billion adult individuals overweight and 650 million obese worldwide [18]. Rates have more than doubled in the past three decades, leading to numerous chronic illnesses and high morbidity and high mortality rates, imposing significant costs on individuals and society [19]. According to the World Health Organization (WHO) ICD-11 for Mortality and Morbidity Statistics, obesity is a chronic and complex disease, defined by excessive adiposity that can impair health.[2] It is in most cases a multifactorial disease due to obesogenic environments, psycho-social factors, and genetic variants. In a subgroup of patients, single major etiological factors can be identified (medications, diseases, immobilization, iatrogenic procedures, monogenic disease/genetic syndrome). Body mass index (BMI) is a surrogate marker of adiposity calculated as weight (kg)/height$^2$ ($m^2$). The BMI categories for defining obesity vary by age and gender in infants, children and adolescents. The WHO uses BMI to categorize individuals as overweight (BMI ≥25), obese class I (BMI 30 to 35), obese class II (BMI 35 to 40), and obese class III (BMI ≥40) [20,21].

## 3. Obesity-induced low-grade inflammation

Obesity-related OA is a recognized subtype of the disease characterized by ongoing low-grade inflammation [20] and metabolic alteration. It is significantly influenced by adipose deposition, insulin resistance, and immune dysregulation [21]. Obese individuals have increased knee adduction moments due to their larger stature and unique gait patterns, altering loading on articular cartilage [22,23], which increases the production of pro-inflammatory adipo-cytokines (adipokines) [24,25].

The accelerated progression of obesity-related OA is associated with higher frequency and severity of synovial inflammation [26]. Inflammatory and catabolic processes in the synovial joint induce metabolic alterations in ECM macromolecule biosynthesis and degradation, further deteriorating cartilage integrity [27]. Weight gain worsens OA by affecting the subchondral bone and cartilage, leading to pathological alterations such as horizontal fissuring at the osteochondral junction, cartilage degradation, persistent low-grade inflammation, microvessel dysfunction, and microcapillary break [28]. Targeting metabolic processes may offer effective treatment approaches to address the dysregulation of proinflammatory adipokine production [29].

Persistent low-grade inflammation in white adipose tissue (WAT), disrupts its normal function and promotes insulin resistance [30]. The primary purpose of WAT is to store energy and secrete adipokines. In obesity, WAT secretes signalling molecules that attract immune cells such as macrophages, fueling pro-inflammatory processes and immunometabolic alterations [19,31]. Obesity increases WAT mass and biological activity, leading to fibrosis [19,32] and reduced elasticity, thus preventing

[2] https://icd.who.int/browse11/l-m/en.

fat mobilization. This abnormal lipid accumulation in WAT affects multiple organs, exacerbating metabolic dysfunction [33]. An organ impacted by obesity-related inflammation is the liver, potentially causing non-alcoholic fatty liver disease (NAFLD), and progressing to liver fibrosis [34,35]. Additionally, lipid accumulation increases the risk of cardiovascular diseases by promoting atherosclerosis and hypertension [36].

## 4. Role of inflammatory cells in adipose tissue

Adipose tissue, primarily composed of adipocytes, hosts various cell types that contribute to its function and growth. Obesity induces significant changes in the cellular composition of adipose tissue, including the recruitment of macrophages, which are closely linked to systemic inflammation and insulin resistance, representing a complex interplay between adipose tissue, macrophages, and metabolic changes in obesity [37].

Inflammation of the synovium causes thickening and stiffening of the synovial membrane, disrupting the physiological balance of synovial fluid [38,39]. This reduction in flexibility impairs daily tasks such as walking, bending, or climbing stairs [29]. Additionally, excessive body fat is linked to higher concentrations of pro-inflammatory mediators such as C-reactive protein (CRP) and interleukin-6 (IL-6), predictors for type 2 diabetes [40,41]. Notably, interventions focused on decreasing these factors may lead to improvements in pain, physical function, and reduced systemic inflammation, impacting cartilage structure [42]. Macrophage recruitment into adipose tissue and synovium leads to a pro-inflammatory state in OA, through CCL2 and CCR2 signaling [43]. Higher concentrations of these molecules in synovial fluid are correlated with the severity of OA symptoms, including pain and stiffness [43]. Active macrophages release signalling molecules such as S100A8 and S100A9, which promote inflammation and tissue restructuring in OA [44,45]. Maintaining the balance between pro-inflammatory M1 and anti-inflammatory M2 macrophage activity is crucial for the regulation of synovial joint inflammation [41,46,47].

## 5. Adipocytokines in obesity-induced inflammation

WAT in obesity is a source of inflammatory adipokines, such as leptin and adiponectin, contributing to low-grade inflammation [41,48], and in turn increases catabolic activity in the joint [49–53].

Leptin is linked to an increased risk of obese individuals developing OA, correlating with cartilage degeneration and OA-related symptoms [41,48]. A high-fat diet significantly raises leptin levels, correlated with osteophyte formation, cartilage damage, and increased infrapatellar fat pad (IFP) size [54]. Leptin directly promotes inflammation and catabolism in cartilage and other joint tissues due to elevated levels of interleukin-1β, matrix metalloproteinases (MMP)-9, and MMP-13, responsible for cartilage degradation [55]. Leptin can also stimulate the expression of ADAMTS-4, -5, and -9 in healthy chondrocytes via activating NF-*K*B and mitogen-activated protein kinase (MAPK) signalling pathways [56].

Adiponectin plays a complex role in OA [57]. Plasma adiponectin levels are associated with clinical and radiographic severity in knee OA, suggesting its potential as a biomarker [58]. Higher synovial fluid adiponectin levels in nonobese women with knee OA have been linked to increased clinical severity and local inflammation markers [59]. Adiponectin levels in synovial fluid are positively correlated with IL-6 and TGF-β, implicating its involvement in metabolic alterations in OA [59]. Serum adiponectin levels in knee OA patients are greater than in healthy controls, and they are associated with knee pain and physical function. Conversely, studies have found adiponectin levels are negatively correlated with BMI and decrease as joint deterioration progresses [60]. In obese knee OA patients, adiponectin levels decline, which correlates with increased pain and more severe structural damage [61].

## 6. Fibrosis and fibrotic events in the skin and vital organs

Fibrosis is an extension of wound-healing responses [62], characterized by excessive ECM deposition that usually follows tissue damage or inflammation during the healing phase of a lesion [63]. Dysfunctional fibrosis is linked to several diseases, including cirrhosis, chronic kidney disease, hepatitis, nonalcoholic steatohepatitis (NASH), myocardial infarction, idiopathic pulmonary fibrosis (IPF), heart failure, diabetes, and scleroderma [64].

Scleroderma research has highlighted an important role for myofibroblasts in fibrosis [65]. These cells transform from fibroblasts and other mesenchymal cells through the overexpression of pro-fibrotic cytokines like fibroblast growth factors (FGFs) and platelet-derived growth factors (PDGFs) [66]. During normal healing processes, active myofibroblasts (contractile, α-smooth muscle actin-positive cells) are removed from the wound site in the skin and other internal organs by apoptosis [67]. However, throughout the fibrotic process, myofibroblasts persist, leading to an excessive buildup of ECM [68]. This buildup hampers oxygen delivery, driving hypoxia and further stiffening of the scar tissue, which impairs tissue homeostasis and cell function [38]. Additionally, parenchymal cell dysfunction, dysregulated cell-cell interaction and abnormal vascular endothelial cell function, contribute to fibrosis [69]. Also, a known factor that contributes to fibrosis is adiposity which contributes to increased production of profibrotic factors that stimulate collagen production by fibroblasts [70]. Studies on liver fibrosis have consistently shown that weight loss significantly improves hepatic function and reduces fibrosis in patients with NASH [71]. Visceral fat is metabolically active, and is linked to a high risk of developing cardiometabolic complications and inducing fibrosis compared to subcutaneous fat [72]. Furthermore, a 10% weight loss has been associated with significant histological improvements in NASH and NAFLD, including fibrosis regression [73], and even reduce liver fat and inflammation [74]. Additionally, following gastric bypass surgery for weight loss has been associated with fibrosis reduction within adipose tissue [75], and has been associated with improvements in liver fibrosis for patients post-surgery [76].

## 7. Hypoxia, immunometabolic stress and oxidative stress in cartilage and fibrotic events

Articular cartilage, an avascular connective tissue, relies on oxygen and nutrient diffusion from synovial fluid [69]. In healthy conditions, chondrocytes maintain metabolic homeostasis primarily through glycolysis, with only 25% reliance on oxidative phosphorylation [77]. However, if injured, or if the loading is abnormal, this balance is disrupted causing an immunometabolic shift [78], resulting in dysregulation of the glycolytic cascade, lactate buildup, and acidification of the local microenvironment. Consequently, ECM production is disrupted, ATP synthesis impaired, limiting cell activity and survival, playing a role in triggering or exacerbating fibrotic processes [79]. When cartilage is injured or stressed, chondrocytes undergo a metabolic shift increasing reactive oxygen species (ROS) and oxidative stress [80]. AMPK activation has been shown to inhibit pulmonary fibrosis by promoting catabolic pathways and reducing inflammatory responses [81], whereas mTOR signalling dysregulation is closely associated with pulmonary fibrosis by stimulating anabolic pathways, including protein synthesis and cell proliferation, which may contribute to tissue remodelling, fibrosis and cell survival [82]. Interestingly, these protective pathways not only aid in cellular survival, but also have implications for fibrosis. While chondrocytes can resist and recover from temporal metabolic changes, persistent disruption may lead to cellular dysfunction. By protecting cartilage, reducing symptoms, and fostering repair and regeneration, these molecular pathways could provide potential therapeutic targets for treating joint diseases involving cartilage [83].

## 8. Fibrosis in obesity-related OA

In obesity, fibrosis may disrupt ECM remodelling, hindering the joint's ability to repair and regenerate. It is well known that fibrotic changes occur in OA, which involve decreased type II collagen and

increased type I collagen, weakening the structural integrity of cartilage [84,85]. Peri-articular ligaments also undergo fibrotic changes in OA induced by obesity, leading to reduced elasticity and stability in joints [86]. Subchondral bone fibrosis, caused by microfractures and increased bone density, disrupts the cross-talk between subchondral bone and cartilage, worsening joint pain, and stiffness [87]. Additionally, the synovium and joint capsule in obese individuals with OA often exhibit fibrosis. This synovial fibrosis contributes to synovitis, characterized by synovial thickening and inflammation, consequently, joint pain and dysfunction [88]. Similarly, capsular fibrosis reduces the range of motion and joint flexibility, compounding the functional limitations experienced by individuals with obesity-related OA [89].

Subgroups within the OA population with specific metabolic conditions, such as insulin resistance or dyslipidemia, may potentially be more susceptible to developing obesity-related fibrosis. Although there is no published evidence for this in OA, there is a link between metabolic conditions and the development of fibrosis in NASH [81,84]. Although the severity varies, fibrosis is a typical characteristic in most OA patients. It is not yet associated with a particular identified grouping, although several conditions may make it more prevalent. The degree of fibrosis and the severity of OA appear to be correlated, and this relationship may be particularly pronounced in joints like the knee. Patients with higher levels of synovial fibrosis tend to have reduced range of motion, before undergoing total knee arthroplasty (TKA) [90]. Currently, there is no definitive diagnostic for fibrosis. MRI scans and sonography can also assist detect synovial thickness, which may be an indicator of fibrosis [91]. Additionally, inflammation causes swelling, and discomfort in the joint, and the result from the scar-like tissue formation, leads to stiffness, and diminished flexibility [92]. Also, joint lining thickening can irritate surrounding nerves, leading to pain [89].

## 9. Mechanisms and cellular mediators of fibrosis

Obesity-related OA leads to a series of molecular and cellular mechanisms that accelerate joint tissue deterioration [29]. Key factors include altered gene expression, disrupted cell interaction, and dysregulated signalling pathways. Excessive fibrosis in this context leads to altered ECM architecture, specifically collagens, proteoglycans, and other collagenous and non-collagenous macromolecules [21]. Accumulated and crosslinked collagens reduce ECM flexibility, impeding joint mobility, while disturbed proteoglycans affect water retention and shock absorption [93]. Matricellular proteins, although less common, aid in signalling and cell-matrix interactions during fibrosis [94].

Pro-inflammatory mediators (i.e. interleukins, TNF-α), adipokines (i.e. adiponectin) and fibroblast growth factors (i.e. basic FGF) are found to be highly expressed in OA patients with obesity, increasing immune cell and fibroblast-like cell activity, and ECM remodelling leading to excessive fibrosis and compromised joint function [95,96]. Weight reduction strategies are well-established for OA management. Even though weight loss strategies have not been proven to reverse fibrosis they create a more favorable environment for the joint by reducing inflammation and stress, offering significant benefits in terms of pain reduction, improved mobility, and potentially slowing down the overall disease process.

## 10. Molecular crosstalk between inflammation and fibrosis

Obesity-related OA and fibrosis share a complex and closely related mechanistic interaction between inflammatory and fibrotic pathways. Inflammatory mediators, such as TNF-α, IL-1β, and IL-6, play a crucial role in the activation of fibroblasts, which produce collagen and other ECM components [97]. MMPs are produced in response to the inflammatory microenvironment, while inflammatory mediators block tissue inhibitors of metalloproteinases (TIMPs), which regulate ECM remodelling. This imbalance favors fibrosis and feeds tissue alterations caused by inflammation [98]. Inflammation produces reactive oxygen species (ROS), which activate pathways that promote fibroblast activation and differentiation, accelerating fibrotic processes [99]. Inflammatory signals can induce epigenetic modifications in fibroblasts and promote fibrotic responses [100]. The thickening ECM and enhanced collagen deposition in fibrotic tissues provide a hypoxic microenvironment, increasing inflammation and fibrotic tissue alterations in OA caused by obesity [88].

## 11. Single cell profiling

Single-cell profiling has revealed the presence of distinct synovial fibroblast subgroups, indicating variations in pain incidence and disease phases. Early OA displayed diverse fibroblast subsets, while end-stage OA showed a shift toward a more concise fibroblast pathotype associated with OA. These fibroblasts in end-stage OA expressed genes linked to cartilage breakdown, stress response, and inflammatory pain, highlighting the complexity of synovial changes in OA progression [101].

In a murine study investigating progenitor fibroblast responses in the synovium following joint damage, growth/differentiation factor 5 (GDF5)-lineage cells linked to inflammatory arthritis, were identified. The study distinguished synovial lining cells expressing proteoglycan 4 (PRG4) (lubricin) and fibroblast-like synoviocytes (FLS) as distinct groups, revealing FLS expansion driven by proliferating PRG4-expressing progenitors. Transcription factors SOX5, FOXO1, and CREB5 were identified as critical for maintaining the FLS phenotype. Additionally, fibroblasts near blood vessels exhibited phenotypic plasticity, assuming a facultative progenitor role under joint degeneration stress [102].

Using an anterior cruciate ligament rupture-based post-traumatic OA (PTOA) preclinical model, distinct synovial fibroblast subpopulations were identified in both healthy and injured joints. Subpopulations included osteochondral progenitors, αSMA+ myofibroblast-like cells, IL-6+ immune-interacting synovial fibroblasts, and DPP4+ mesenchymal progenitors. The Wnt/β-catenin agonist R-spondin 2 (RSPO2) released by lining synovial fibroblasts was linked to PTOA promotion, emphasizing the significance of canonical Wnt/β-catenin signalling and cell speciation in PTOA. The study also unveiled a DPP4+ progenitor pool contributing to RSPO2-expressing lining synovial fibroblasts, offering insights into the regulation of synovial hyperplasia in PTOA [103].

Tyrosine 814 (Y814) in GP130 was identified as a key cellular stress sensor influencing disease progression. Mice with constitutively inactivated Y814 showed resistance to surgically induced OA, reduced synovitis, and fibrosis. Targeting Y814 upstream of SRC and MAPK pathways with R805, a small chemical, protected injured tissues. Single-cell sequencing data indicated that genetic and pharmacological regulation of Y814 reduced inflammatory gene signatures in skin and joint tissues. Targeting Y814 may enhance wound repair processes, reduce chronic inflammation, and boost intrinsic regeneration capacity in various tissues [104].

Comparative analysis of synovial tissue from individuals with obesity and normal weight revealed significant effects on the inflammatory environment of synovial fibroblasts. Four molecular endotypes with functional roles were identified, with obesity influencing immune cell control, fibroblast activation, and inflammatory signalling. Specific patterns in the OA synovium of obese patients, including overexpression of markers such as CXCL12, CFD, and CHI3L1, has implicated obesity as a major factor determining synovial fibroblast behavior. The study proposed MYC and FOS as driving factors for different endotypes, highlighting CHI3L1 and INBHA as potential indicators for patient stratification in targeted treatments [105].

Single-cell RNA sequencing was also applied to analyze IFPs and synovium in healthy and OA-affected joints. A recent study identified a distinct mesenchymal progenitor cell population leading to mature adipocytes in IFPs and fibroblasts in the synovium. Specific localization of subpopulations was observed, with DPP4+ MPCs residing predominantly in the synovial sublining layer. The study highlighted the involvement of intermediate fibroblasts and synovial lining layer fibroblasts in driving fibrosis in OA and addressed the inflammatory component, revealing an

**Table 1**
Repurposing drugs for the treatment of obesity induce fibrosis in the context of AO.

| Target | Drug Name | Health Condition | Mechanism of Action |
|---|---|---|---|
| TGF-β | Pirfenidone | IPF, Myelofibrosis | Inhibits the synthesis and activation of TGF-βs, reducing fibroblast activation, collagen synthesis, and ECM deposition. Clinical trials have shown that it reduces lung function decline, decreases mortality, and improves overall survival of IPF patients and is FDA-approved. |
| | Luspatercept | Myelofibrosis-associated Anemia | A recombinant fusion protein that binds TGF-β ligands to reduce Smad2/3 signaling. Clinical studies in myelofibrosis-associated anemia patients have shown increases in hemoglobin levels. |
| | Hydronidone | Potential therapeutic efficacy for hepatic fibrosis | Clinical studies have demonstrated that in Chinese participants in good health, it is readily absorbed and well tolerated. Its effectiveness for HBV-induced liver fibrosis is being investigated in a phase III trial. |
| β-catenin | PRI-724: | Liver Diseases, HCV-induced cirrhosis | Modulates β-catenin/CBP transcription, reducing ECM deposition and hepatic inflammation; studied in liver diseases. |
| ASK-1 | Selonsertib | NASH with bridging fibrosis or compensated cirrhosis | ASK1 inhibitor, with demonstrated efficacy in reducing collagen deposition, fibrosis stage, steatosis, and inflammation in a phase 2 study, but its phase III clinical trial was terminated, due to the lack of significant effects on fibrosis. |
| PPARs | Pemafibrate | NAFLD | PPARα modulator regulating lipid and glucose metabolism, shown to improve insulin resistance, inhibit hepatocyte ballooning degeneration, decrease NAFLD score, and reduce myeloid cell recruitment in high-risk NAFLD patients. |
| FXR | Obeticholic acid | NASH | PPARα modulator regulating lipid and glucose metabolism; reduced liver stiffness and ALT levels in patients. In phase 3 trials, there was no difference in NASH. Patients usually stop or reduce their dosage due to severe pruritus. |
| | Cilofexor | hepatic steatosis | Non-steroidal FXR agonist; improved bile acid metabolism and hepatic steatosis but had no significant effect on fibrosis. |
| | EDP-305 | NASH | Effective FXR agonist with minimal cross-reaction with other nuclear receptors, effectively inhibiting HSCs activation, reducing MCD-induced steatohepatitis and liver fibrosis, and reducing liver fat and ALT levels in NASH patients. |
| | Tropifexor | NASH | Non-steroidal FXR agonist, significantly reduced steatohepatitis and fibrosis in a pre-clinical NASH model. |
| GIP and GLP-1 | Tirzepatide | NASH | Dual GIP and GLP-1 receptor agonist; reduced NASH-related biomarkers in patients with type 2 diabetes; phase III trials for NASH in progress. |
| | Cotadutide | NASH | Dual receptor agonist of GIP and GLP-1 has shown safety and tolerability in reducing hepatic lipid content, inflammation, steatosis, and NAS score in a mouse model of NASH. |
| | Semaglutide | NASH | GLP-1 receptor agonist; improved NASH-related biomarkers in NASH patients without worsening fibrosis. |
| TLR4 | JKB-121: | NAFLD | Nonselective opioid TLR4 antagonist that effectively reduces liver inflammation and inhibits hepatic stellate cell activation in models of NAFLD. |
| RTKs | Nintedanib | IPF | Inhibitor of receptor tyrosine kinases that target growth factor pathways including FGFRs, VEGFRs, and PDGFRs. Acts by reducing lung inflammation and fibrosis in IPF by decreasing collagen, chemokines, and pro-fibrotic factors. |

IPF - Idiopathic pulmonary fibrosis; NAFLD - Non-alcoholic fatty liver disease; NASH - nonalcoholic fatty liver disease. Adapted from Zhao, M. et al. Targeting fibrosis: mechanisms and clinical trials. Signal Transduction and Targeted Therapy 2022 7:1 7, 1–21 (2022).

increase in inflammatory macrophages. The study also explored the role of apolipoprotein E (APOE) in OA, indicating its potential as a therapeutic target for OA therapy [106].

## 12. Therapeutic approaches

Current OA therapies that are in clinical development lack the required safety and efficacy profiles for regulatory approval. Total knee arthroplasty (TKA) is the last option, revealing a gap in joint-preserving treatments [20]. Cartilage tissue engineering shows promising for OA treatment, but obesity-induced OA presents unique challenges, due to coexisting health conditions such as diabetes and cardiovascular diseases, low-grade inflammation, compromised wound healing, altered joint stability, and even accelerated wear and tear of the prosthetic components, making it more prone to intraoperative and postoperative complications [107].

Obesity-related fibrosis in OA worsens patient outcomes. Repurposing existing anti-fibrotic drugs or developing novel interventions, targeting PI3/AKT/mTOR pathway, TGF-β signalling, epidermal growth factor receptors (EGFR), Toll-like receptors (TLRs), and proinflammatory cytokines could slow disease progression and enhance patient quality of life. Targeting immune dysregulation with immunosuppressants or immunomodulators may prevent tissue damage and reduce scarring. Emerging therapies focused on restoring normal cell function by targeting epigenetic modifications or genetic mutations associated with fibrosis offer potential opportunities for intervention. Synovial fibrosis is closely associated with joint pain, hyperalgesia, and stiffness in OA [108], highlighting the benefits of therapies targeting fibrosis. Small molecule inhibitors targeting for example MMPs, ADAMTS, IL-1β, TNF-$\alpha$, WNT, and NF-$\kappa$B, have shown positive effects on OA [109]. Repurposing drugs provides an efficient approach for expediting fibrosis treatment development, potentially delivering effective therapies to patients more swiftly than traditional methods.

Multiple anti-fibrotic drugs have been tested for treating fibrotic diseases, targeting different molecular pathways implicated in fibrogenesis, including TGF-β, apoptosis signal-regulating kinase 1 (ASK-1), angiotensin receptor blockers (ARBs), peroxisome proliferator-activated receptors (PPARs), toll-like receptor 4 (TLR4), and receptor tyrosine kinases (RTKs), offering potential alternative therapeutic intervention for obesity-related fibrosis. Pirfenidone and nintedanib, in preclinical and clinical studies, have demonstrated efficacy in conditions such as IPF [110]. Additionally, GLP-1 receptor agonists like semaglutide and dual GIP/GLP-1 receptor agonists such as tirzepatide and cotadutide have shown potential in mitigating fibrosis and inflammation in conditions like NASH (Table 1) [111].

## 13. GLP-1 analogs

GLP-1 receptor agonists (GLP-1RAs) are recognized for treating type 2 diabetes [112], and weight management [113], with exenatide, semaglutide, liraglutide, and dulaglutide being designated biological drugs [114]. GLP-1 exhibits beneficial activities in different organs (see Fig. 2), including the heart, brain, and lung, promoting metabolic control and exerting anti-inflammatory actions [115]. GLP-1 agonism demonstrates anti-apoptotic, anti-autophagic, and anti-senescence effects, influencing subchondral bone remodelling and adipokine synthesis. In the context of OA, GLP-1 agonism exhibits anti-inflammatory, anti-catabolic, anabolic, and anti-oxidative stress properties. It hinders catabolic processes, promoting cell proliferation, differentiation, maturation, migration, and autophagy, impacting even the adipogenic processes [116]. Given the documented anti-inflammatory properties of GLP-1 and the presence of GLP-1R in joint tissues, GLP-1 analogs emerge as promising therapeutic

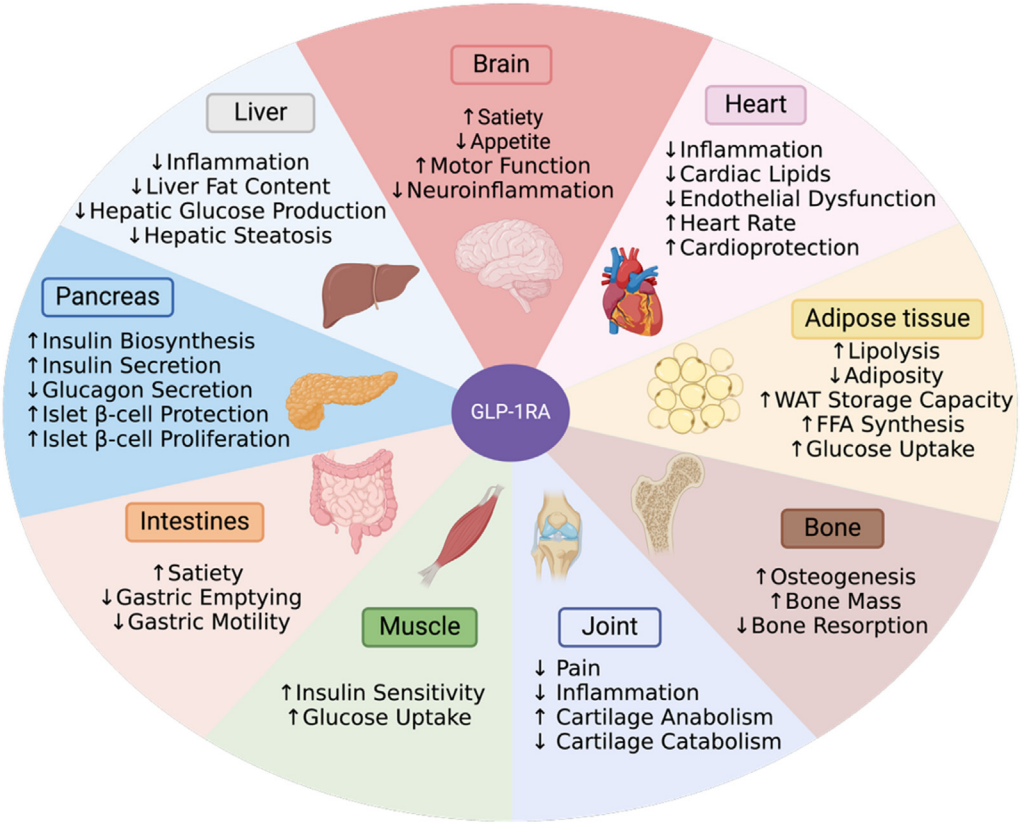


**Fig. 2.** GLP-1 and GLP-1R Agonists impact on multiple organs such as the brain, heart, muscle, bone, adipose tissue, intestines, pancreas and liver. Image created in Biorender.com.

candidates for treating OA. Beyond addressing cartilage loss [116], GLP-1RAs may contribute to OA management by leveraging their anti-inflammatory activities, making them versatile options for multi-faceted OA treatments [117].

GLP-1R signaling in chondrocytes prevents apoptosis, exhibits anti-inflammatory activity, and protects ECM [118,119]. GLP-1R activation diminishes NF-*K*B pathway activity, reducing the secretion of inflammatory mediators, including IL-6, CCL2, and TNF-$\alpha$ [120]. Primary mouse chondrocytes treated with liraglutide showed reduced mRNA expression of iNOS, MMP-13, and ADAMTS5, and decreased release of inflammatory markers such as prostaglandin E2, IL-6, and nitric oxide (NO), through the PKA/CREB signaling pathway in the mono-iodoacetate (MIA) rat model. Intra-articular injection of liraglutide alleviated pain-related behavior in the *in vivo* MIA OA mouse model, which was probably driven by the GLP-1R-mediated anti-inflammatory activity [121]. The anti-catabolic activity of GLP-1 analogs is evident in their ability to reduce MMP-3, MMP-13, ADAMTS4, and ADAMTS5 mRNA expression in TNF-$\alpha$-stimulated human chondrocytes, associated with increased levels of aggrecan and type II collagen proteins [122]. In the ACL transection (ACLT) rat model, subcutaneous administration of liraglutide for 3 or 6 weeks significantly lowered the OARSI score [121,122].

GLP-1-based therapies influence macrophage activity, promoting a shift from pro-inflammatory M1 to anti-inflammatory M2 in inflamed synovium [123]. GLP-1 effects on adipogenesis vary: stimulation enhances pre-adipocyte differentiation while suppressing GLP-1R expression in pre-adipocytes reduces proliferation, induces apoptosis and modulates by PKC signalling pathway [124]. From human-derived mesenchymal stem cells, GLP-1 inhibits early adipocyte differentiation and promotes the proliferation of differentiated cells [125]. The dual pro- and anti-adipogenic activities of GLP-1 depend on the tissue milieu, cell type, and differentiation stage [116]. While studies have explored GLP-1/GLP-1R expression in adipose tissues, notably in white or brown adipose tissue, there remains a knowledge gap concerning their presence in IFP, in which further studies should be considered.

In a recent clinical study, the Shanghai Osteoarthritis Cohort suggested that with adequate treatment duration, GLP-1RA therapies could potentially modify the disease course for knee OA patients with type 2 diabetes, potentially influenced in part by weight reduction. Also, in November 2023, Novo Nordisk's STEP 9 trial demonstrated the effectiveness of semaglutide 2.4 mg in reducing WOMAC pain scores and body weight in knee osteoarthritis patients with obesity. Compared to placebo, semaglutide exhibited superior results, with a significant treatment difference in both pain scores and body weight [126]. These findings show a promising impact of semaglutide and highlight its potential role in managing knee OA symptoms since they also seem to be safe and well-tolerated [127]. Nevertheless, additional research is necessary to comprehensively comprehend the impact of GLP-1RA on the disease progression, integrity of joints, and outcomes reported by patients in OA [128].

## 14. Conclusions

The increasing incidence of obesity and the progression of OA are global concerns, and it is increased by a growing aged and obese population. While fibrosis in OA may initially appear as a secondary consequence, it is imperative to recognize its substantial impact beyond being merely an epiphenomenon. Fibrosis, in joints and in other tissues, adds another layer of complexity at the cellular and molecular level and increases the burden of patients to perform daily tasks. Obesity-related fibrosis also presents itself as an opportunity for therapeutic intervention and drug repositioning using candidate anti-fibrotic agents. By targeting fibrotic pathways, there is potential to not only alleviate symptoms but also modify disease progression, offering hope for improved patient outcomes. It is important to recognize fibrosis as a significant contributor to the pathogenesis of OA and therefore continue

further research. It is essential to understand the biological mechanisms involved in fibrosis and identify upstream regulators of the process and thus develop novel therapeutic approaches for the treatment of an important facet of OA in an increasingly elderly population.

## Author contributions

All authors made substantial contributions to discussion of the content, writing of the original outline, and reviewing/editing of the manuscript before submission. All authors approve the final version for publication and agree to be accountable for the accuracy and integrity of the work.

## Declaration of competing interest

FB is the co-founder and Chief Medical Officer of 4Moving Biotech, a company involved in the development of intraarticular GLP1RAs for OA treatment.

## Acknowledgments

This research was supported by the Research Council of Finland through the Profi6 336449 grant awarded to AM at the University of Oulu. AM acknowledges financial support from the European Structural and Social Funds through the Research Council of Lithuania (Lietuvos Mokslo Taryba), according to the Program Attracting Foreign Researchers for Research Implementation (Grant No. 01.2.2-LMT-K-718-02-0022). AM also acknowledges consortium funding from Horizon Europe (PROTO - Advanced PeRsOnalized Therapies for Osteoarthritis – TACKLING INFLAMMATION TO IMPROVE PATIENT OUTCOMES, Grant agreement ID: 101095635, https://cordis.europa.eu/project/id/101095635 and ENgineered CArtilage from Nose for the Treatment of Osteoarthritis (ENCANTO), Grant agreement ID: 101137315, https://cordis.europa.eu/project/id/101137315). JH, FB and AM acknowledge networking support from the European Cooperation in Science and Technology (COST) Association, Action CA21110 – Building an open European Network on OsteoArthritis research (NetwOArk; https://www.cost.eu/actions/CA21110/).

The comments expressed in this article represent those of the authors and do not reflect those of any official scientific role or institution that the authors may hold or be affiliated with.

## References

[1] M.L. Ferreira, K. de Luca, L.M. Haile, J.D. Steinmetz, G.T. Culbreth, M. Cross, et al., Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021, Lancet Rheumatol 5 (6) (2023) e316–e329, https://doi.org/10.1016/S2665-9913(23)00098-X.

[2] M. Blagojevic, C. Jinks, A. Jeffery, K.P. Jordan, Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis, Osteoarthritis Cartilage 18 (1) (2010) 24–33, https://doi.org/10.1016/j.joca.2009.08.010.

[3] D.T. Felson, R.C. Lawrence, P.A. Dieppe, R. Hirsch, C.G. Helmick, J.M. Jordan, et al., Osteoarthritis: new insights - Part 1: the disease and its risk factors, Ann. Intern. Med. 133 (8) (2000) 635–646, https://doi.org/10.7326/0003-4819-133-8-200010170-00016.

[4] Y.A. Rim, J.H. Ju, The role of fibrosis in osteoarthritis progression, Life 11 (1) (2021) 1–13, https://doi.org/10.3390/life11010003.

[5] V.B. Kraus, F.J. Blanco, M. Englund, M.A. Karsdal, L.S. Lohmander, Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use, Osteoarthritis Cartilage 23 (8) (2015) 1233–1241, https://doi.org/10.1016/j.joca.2015.03.036.

[6] U.T. Timur, H. Jahr, J. Anderson, D.C. Green, P.J. Emans, A. Smagul, et al., Identification of tissue-dependent proteins in knee OA synovial fluid, Osteoarthritis Cartilage 29 (1) (2021) 124–133, https://doi.org/10.1016/j.joca.2020.09.005.

[7] M. Iwata, H. Ochi, Y. Hara, M. Tagawa, D. Koga, A. Okawa, et al., Initial responses of articular tissues in a murine high-fat diet-induced osteoarthritis model: pivotal role of the IPFP as a cytokine fountain, PLoS One 8 (4) (2013), https://doi.org/10.1371/journal.pone.0060706.

[8] F. Berenbaum, C. Walker, Osteoarthritis and inflammation: a serious disease with overlapping phenotypic patterns, Postgrad. Med. 132 (4) (2020) 377–384, https://doi.org/10.1080/00325481.2020.1730669.

[9] S. Muthu, J.V. Korpershoek, E.J. Novais, G.F. Tawy, A.P. Hollander, I. Martin, Failure of cartilage regeneration: emerging hypotheses and related therapeutic strategies, Nat. Rev. Rheumatol. 19 (7) (2023) 403–416, https://doi.org/10.1038/s41584-023-00979-5.

[10] S. Glyn-Jones, A.J.R. Palmer, R. Agricola, A.J. Price, T.L. Vincent, H. Weinans, et al., Osteoarthritis, Lancet 386 (9991) (2015) 376–387, https://doi.org/10.1016/S0140-6736(14)60802-3.

[11] M. Sabha, M.C. Hochberg, Non-surgical management of hip and knee osteoarthritis; comparison of ACR/AF and OARSI 2019 and VA/DoD 2020 guidelines, Osteoarthr Cartil Open 4 (1) (2022) 100232, https://doi.org/10.1016/j.ocarto.2021.100232.

[12] N.K. Arden, T.A. Perry, R.R. Bannuru, O. Bruyère, C. Cooper, I.K. Haugen, et al., Non-surgical management of knee osteoarthritis: comparison of ESCEO and OARSI 2019 guidelines, Nat. Rev. Rheumatol. 17 (1) (2021) 59–66, https://doi.org/10.1038/s41584-020-00523-9.

[13] S.L. Kolasinski, T. Neogi, M.C. Hochberg, C. Oatis, G. Guyatt, J. Block, et al., 2019 American college of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee, Arthritis Rheumatol. 72 (2) (2020) 220–233, https://doi.org/10.1002/art.41142.

[14] R.R. Bannuru, M.C. Osani, E.E. Vaysbrot, N.K. Arden, K. Bennell, S.M.A. Bierma-Zeinstra, et al., OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis, Osteoarthritis Cartilage 27 (11) (2019) 1578–1589, https://doi.org/10.1016/j.joca.2019.06.011.

[15] D.J. Selig, A.T. Kress, I.M. Horton, J.R. Livezey, E.J. Sadik Bs, J.P. Deluca, et al., Pharmacokinetics, safety and efficacy of intra-articular non-steroidal anti-inflammatory drug injections for the treatment of osteoarthritis: a narrative review, J. Clin. Pharm. Therapeut. 47 (2022) 1122–1133, https://doi.org/10.1111/jcpt.13669.

[16] C.P. Hannon, S.M. Goodman, M.S. Austin, A. Yates, G. Guyatt, V.K. Aggarwal, et al., 2023 American college of rheumatology and American association of hip and knee surgeons clinical practice guideline for the optimal timing of elective hip or knee arthroplasty for patients with symptomatic <scp>Moderate-to-Severe</scp> osteoarthritis or advanced symptomatic osteonecrosis with secondary arthritis for whom nonoperative therapy is ineffective, Arthritis Rheumatol. 75 (11) (2023) 1877–1888, https://doi.org/10.1002/art.42630.

[17] H. Madry, Surgical therapy in osteoarthritis, Osteoarthritis Cartilage 30 (8) (2022) 1019–1034, https://doi.org/10.1016/j.joca.2022.01.012.

[18] Vaamonde JG, Álvarez-Món MA. Obesity and overweight. Medicine. doi:10.1016/j.med.2020.07.010.

[19] G. Marcelin, E.L. Gautier, K. Clement, Adipose tissue fibrosis in obesity: etiology and challenges, Annu. Rev. Physiol. 84 (2022) 135–155, https://doi.org/10.1146/annurev-physiol-060721-092930.

[20] A.R.J. Sun, A. Udduttula, J. Li, Y. Liu, P.G. Ren, P. Zhang, Cartilage tissue engineering for obesity-induced osteoarthritis: physiology, challenges, and future prospects, J Orthop Translat 26 (2021) 3–15, https://doi.org/10.1016/j.jot.2020.07.004.

[21] U. Nedunchezhiyan, I. Varughese, A.R.J. Sun, X. Wu, R. Crawford, I. Prasadam, Obesity, inflammation, and immune system in osteoarthritis, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.907750.

[22] T.P. Andriacchi, A. Mündermann, The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis, Curr. Opin. Rheumatol. 18 (5) (2006) 514–518, https://doi.org/10.1097/01.bor.0000240365.16842.4e.

[23] G.M. Brouwer, A.W. Van Tol, A.P. Bergink, J.N. Belo, R.M.D. Bernsen, M. Reijman, et al., Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee, Arthritis Rheum. 56 (4) (2007) 1204–1211, https://doi.org/10.1002/art.22515.

[24] K. Honda, S. Ohno, K. Tanimoto, C. Ijuin, N. Tanaka, T. Doi, et al., The effects of high magnitude cyclic tensile load on cartilage matrix metabolism in cultured chondrocytes, Eur. J. Cell Biol. 79 (9) (2000) 601–609, https://doi.org/10.1078/0171-9335-00089.

[25] A. Schröder, U. Nazet, D. Muschter, S. Grässel, P. Proff, C. Kirschneck, Impact of mechanical load on the expression profile of synovial fibroblasts from patients with and without osteoarthritis, Int. J. Mol. Sci. 20 (3) (2019) 585, https://doi.org/10.3390/ijms20030585.

[26] T. Kanthawang, J. Bodden, G.B. Joseph, N.E. Lane, M. Nevitt, C.E. McCulloch, et al., Obese and overweight individuals have greater knee synovial inflammation and associated structural and cartilage compositional degeneration: data from the osteoarthritis initiative, Skeletal Radiol. 50 (1) (2021) 217–229, https://doi.org/10.1007/s00256-020-03550-5.

[27] R.F. Loeser, S.R. Goldring, C.R. Scanzello, M.B. Goldring, Osteoarthritis: a disease of the joint as an organ, Arthritis Rheum. 64 (6) (2012) 1697–1707, https://doi.org/10.1002/art.34453.

[28] L. Chen, F. Yao, T. Wang, G. Li, P. Chen, M. Bulsara, et al., Horizontal fissuring at the osteochondral interface: a novel and unique pathological feature in patients with obesity-related osteoarthritis, Ann. Rheum. Dis. 79 (6) (2020) 811–818, https://doi.org/10.1136/annrheumdis-2020-216942.

[29] L.K. King, L. March, A. Anandacoomarasamy, Obesity & osteoarthritis 63 (August) (2013) 185–193.

[30] T. Kawai, M.V. Autieri, R. Scalia, Adipose tissue inflammation and metabolic dysfunction in obesity, Am. J. Physiol. Cell Physiol. 320 (3) (2021) C375–C391, https://doi.org/10.1152/ajpcell.00379.2020.

[31] M. Reyes-Farias, J. Fos-Domenech, D. Serra, L. Herrero, D. Sánchez-Infantes, White adipose tissue dysfunction in obesity and aging, Biochem. Pharmacol. 192 (2021) 114723, https://doi.org/10.1016/j.bcp.2021.114723.

[32] Y.H. Lee, E.P. Mottillo, J.G. Granneman, Adipose tissue plasticity from WAT to BAT and in between, Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1842 (3) (2014) 358–369, https://doi.org/10.1016/j.bbadis.2013.05.011.
[33] E.E. Kershaw, J.S. Flier, Adipose tissue as an endocrine organ, J. Clin. Endocrinol. Metab. 89 (6) (2004) 2548–2556, https://doi.org/10.1210/jc.2004-0395.
[34] M.K. DeBari, R.D. Abbott, Adipose tissue fibrosis: mechanisms, models, and importance, Int. J. Mol. Sci. 21 (17) (2020) 6030, https://doi.org/10.3390/ijms21176030.
[35] B.M. Kim, A.M. Abdelfattah, R. Vasan, B.C. Fuchs, M.Y. Choi, Hepatic stellate cells secrete Ccl5 to induce hepatocyte steatosis, Sci. Rep. 8 (1) (2018) 7499, https://doi.org/10.1038/s41598-018-25699-9.
[36] C.F. Semenkovich, Insulin resistance and atherosclerosis, J. Clin. Invest. 116 (7) (2006) 1813–1822, https://doi.org/10.1172/JCI29024.
[37] A. Chait, L.J. den Hartigh, Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease, Front Cardiovasc Med 7 (2020) 22, https://doi.org/10.3389/fcvm.2020.00022.
[38] C.Y.J. Wenham, P.G. Conaghan, The role of synovitis in osteoarthritis, Ther Adv Musculoskelet Dis 2 (6) (2010) 349–359, https://doi.org/10.1177/1759720X10378373.
[39] T.M. Tamer, Hyaluronan and synovial joint: function, distribution and healing, Interdiscipl. Toxicol. 6 (3) (2013) 111, https://doi.org/10.2478/INTOX-2013-0019.
[40] K. Esposito, A. Pontillo, C. Di Palo, G. Giugliano, M. Masella, R. Marfella, et al., Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women, JAMA 289 (14) (2003) 1799, https://doi.org/10.1001/jama.289.14.1799.
[41] N. Ouchi, J.L. Parker, J.J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, Nat. Rev. Immunol. 11 (2) (2011) 85–97, https://doi.org/10.1038/NRI2921.
[42] P. Richette, C. Poitou, P. Garnero, E. Vicaut, J.L. Bouillot, J.M. Lacorte, et al., Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis, Ann. Rheum. Dis. 70 (1) (2011) 139–144, https://doi.org/10.1136/ard.2010.134015.
[43] S.P. Weisberg, D. Hunter, R. Huber, J. Lemieux, S. Slaymaker, K. Vaddi, et al., CCR2 modulates inflammatory and metabolic effects of high-fat feeding, J. Clin. Invest. 116 (1) (2006) 115–124, https://doi.org/10.1172/JCI24335.
[44] A. Larrañaga-Vera, A. Lamuedra, S. Pérez-Baos, I. Prieto-Potin, L. Peña, G. Herrero-Beaumont, et al., Increased synovial lipodystrophy induced by high fat diet aggravates synovitis in experimental osteoarthritis, Arthritis Res. Ther. 19 (1) (2017) 1–13, https://doi.org/10.1186/S13075-017-1473-Z/FIGURES/6.
[45] I. Prieto-Potín, J.A. Roman-Blas, M.J. Martínez-Calatrava, R. Gómez, R. Largo, G. Herrero-Beaumont, Hypercholesterolemia boosts joint destruction in chronic arthritis. An experimental model aggravated by foam macrophage infiltration, Arthritis Res. Ther. 15 (4) (2013) 1–14, https://doi.org/10.1186/AR4261/FIGURES/6.
[46] S. Nishimura, I. Manabe, M. Nagasaki, K. Eto, H. Yamashita, M. Ohsugi, et al., CD8 + effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity, Nat. Med. 15 (8) (2009) 914–920, https://doi.org/10.1038/nm.1964.
[47] S. Winer, Y. Chan, G. Paltser, D. Truong, H. Tsui, J. Bahrami, et al., Normalization of obesity-associated insulin resistance through immunotherapy, Nat. Med. 15 (8) (2009) 921–929, https://doi.org/10.1038/nm.2001.
[48] Y.E. Kang, J.M. Kim, K.H. Joung, J.H. Lee, B.R. You, M.J. Choi, et al., The roles of adipokines, proinflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction, in: G. López Lluch (Ed.), PLoS One 11 (4) (2016) e0154003, https://doi.org/10.1371/journal.pone.0154003.
[49] R. Gómez, J. Conde, M. Scotece, J.J. Gómez-Reino, F. Lago, O. Gualillo, What's new in our understanding of the role of adipokines in rheumatic diseases? Nat. Rev. Rheumatol. 7 (9) (2011) 528–536, https://doi.org/10.1038/nrrheum.2011.107.
[50] P. Garnero, J.C. Rousseau, P.D. Delmas, Molecular basis and clinical use of biochemical markers of bone, cartilage, and synovium in joint diseases, Arthritis Rheum. 43 (5) (2000) 953–968, https://doi.org/10.1002/1529-0131(200005)43:5<953. AID-ANR1>3.0.CO;2-Q.
[51] T. Simopoulou, K.N. Malizos, D. Iliopoulos, N. Stefanou, L. Papatheodorou, M. Ioannou, et al., Differential expression of leptin and leptin's receptor isoform (Ob-Rb) mRNA between advanced and minimally affected osteoarthritic cartilage; effect on cartilage metabolism, Osteoarthritis Cartilage 15 (8) (2007) 872–883, https://doi.org/10.1016/j.joca.2007.01.018.
[52] Y. Figenschau, G. Knutsen, S. Shahazeydi, O. Johansen, B. Sveinbjörnsson, Human articular chondrocytes express functional leptin receptors, Biochem. Biophys. Res. Commun. 287 (1) (2001) 190–197, https://doi.org/10.1006/bbrc.2001.5543.
[53] G. Karsenty, Convergence between bone and energy homeostases: leptin regulation of bone mass, Cell Metabol. 4 (5) (2006) 341–348, https://doi.org/10.1016/j.cmet.2006.10.008.
[54] T.M. Griffin, A. Batushansky, J. Hudson, E.B.P. Lopes, Correlation network analysis shows divergent effects of a long-term, high-fat diet and exercise on early stage osteoarthritis phenotypes in mice, J Sport Health Sci 9 (2) (2020) 119–131, https://doi.org/10.1016/j.jshs.2019.05.008.
[55] S. Pallu, P.J. Francin, C. Guillaume, P. Gegout-Pottie, P. Netter, D. Mainard, et al., Obesity affects the chondrocyte responsiveness to leptin in patients with osteoarthritis, Arthritis Res. Ther. 12 (3) (2010) R112, https://doi.org/10.1186/ar3048.
[56] K.O. Yaykasli, O.F. Hatipoglu, E. Yaykasli, K. Yildirim, E. Kaya, M. Ozsahin, et al., Leptin induces ADAMTS-4, ADAMTS-5, and ADAMTS-9 genes expression by mitogen-activated protein kinases and NF-κB signaling pathways in human chondrocytes, Cell Biol. Int. 39 (1) (2015) 104–112, https://doi.org/10.1002/cbin.10336.
[57] D. Azamar-Llamas, G. Hernández-Molina, B. Ramos-Ávalos, J. Furuzawa-Carballeda, Adipokine contribution to the pathogenesis of osteoarthritis, Mediat. Inflamm. 2017 (2017) 1–26, https://doi.org/10.1155/2017/5468023.
[58] N. Cuzdan Coskun, S. Ay, F.D. Evcik, D. Oztuna, Adiponectin: is it a biomarker for assessing the disease severity in knee osteoarthritis patients? Int J Rheum Dis 20 (12) (2017) 1942–1949, https://doi.org/10.1111/1756-185X.12790.
[59] C. Orellana, J. Calvet, A. Berenguer-Llergo, N. Albiñana, M. García Manrique, C. Galisteo Lencastre, et al., Synovial adiponectin was more associated with clinical severity than synovial leptin in women with knee osteoarthritis, Cartilage 13 (1_suppl) (2021) 1675S–1683S, https://doi.org/10.1177/1947603520904776.
[60] Q. Lai, Y. Liu, L. Huang, X. Liu, X. Yu, Q. Wang, et al., Expression of adiponectin in the subchondral bone of lumbar facet joints with different degrees of degeneration, BMC Muscoskel. Disord. 18 (1) (2017) 427, https://doi.org/10.1186/s12891-017-1786-8.
[61] W. Udomsinprasert, P. Manoy, P. Yuktanandana, A. Tanavalee, W. Anomasiri, S. Honsawek, Decreased serum adiponectin reflects low vitamin D, high interleukin 6, and poor physical performance in knee osteoarthritis, Arch. Immunol. Ther. Exp. 68 (3) (2020) 16, https://doi.org/10.1007/s00005-020-00580-8.
[62] C.L. Hill, D.J. Hunter, J. Niu, M. Clancy, A. Guermazi, H. Genant, et al., Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis, Ann. Rheum. Dis. 66 (12) (2007) 1599–1603, https://doi.org/10.1136/ARD.2006.067470.
[63] D.F.G. Remst, E.N. Blaney Davidson, P.M. van der Kraan, Unravelling osteoarthritis-related synovial fibrosis: a step closer to solving joint stiffness, Rheumatology 54 (11) (2015) 1954–1963, https://doi.org/10.1093/rheumatology/kev228.
[64] X. Zhao, J.Y.Y. Kwan, K. Yip, P.P. Liu, F.F. Liu, Targeting metabolic dysregulation for fibrosis therapy, Nat. Rev. Drug Discov. 19 (1) (2020) 57–75, https://doi.org/10.1038/s41573-019-0040-5.
[65] A. van Caam, M. Vonk, F. van den Hoogen, P. van Lent, P. van der Kraan, Unraveling SSc pathophysiology; the myofibroblast, Front. Immunol. 9 (NOV) (2018) 2452, https://doi.org/10.3389/fimmu.2018.02452.
[66] A.R. Phull, S.H. Eo, Q. Abbas, M. Ahmed, S.J. Kim, Applications of chondrocyte-based cartilage engineering: an overview, BioMed Res. Int. 2016 (2016), https://doi.org/10.1155/2016/1879837.
[67] R. Karuppal, Current concepts in the articular cartilage repair and regeneration, J. Orthop. 14 (2) (2017) A1–A3, https://doi.org/10.1016/J.JOR.2017.05.001.
[68] A.R. Armiento, M. Alini, M.J. Stoddart, Articular fibrocartilage - why does hyaline cartilage fail to repair? Adv. Drug Deliv. Rev. 146 (2019) 289–305, https://doi.org/10.1016/J.ADDR.2018.12.015.
[69] A.J. Sophia Fox, A. Bedi, S.A. Rodeo, The basic science of articular cartilage: structure, composition, and function, Sport Health: A Multidisciplinary Approach 1 (6) (2009) 461–468, https://doi.org/10.1177/1941738109350438.
[70] R.G. Marangoni, T.T. Lu, The roles of dermal white adipose tissue loss in scleroderma skin fibrosis, Curr. Opin. Rheumatol. 29 (6) (2017) 585–590, https://doi.org/10.1097/BOR.0000000000000437.
[71] E.B. Tapper, N. Krieger, R. Przybysz, N. Way, J. Cai, D. Zappe, et al., The burden of nonalcoholic steatohepatitis (NASH) in the United States, BMC Gastroenterol. 23 (1) (2023) 109, https://doi.org/10.1186/s12876-023-02726-2.
[72] T.W. Elffers, R. de Mutsert, H.J. Lamb, A. de Roos, K. Willems van Dijk, F.R. Rosendaal, et al., Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women, in: M. He (Ed.), PLoS One 12 (9) (2017) e0185403, https://doi.org/10.1371/journal.pone.0185403.
[73] S. Alam, M. Jahid Hasan, M.A.S. Khan, M. Alam, N. Hasan, Effect of weight reduction on histological activity and fibrosis of lean nonalcoholic steatohepatitis patient, J Transl Int Med 7 (3) (2019) 106, https://doi.org/10.2478/JTIM-2019-0023.
[74] K.T. Brunner, C.J. Henneberg, R.M. Wilechansky, M.T. Long, Nonalcoholic fatty liver disease and obesity treatment, Curr Obes Rep 8 (3) (2019) 220–228, https://doi.org/10.1007/s13679-019-00345-1.
[75] G. Kuziel, B.N. Moore, L.M. Arendt, Obesity and fibrosis: setting the stage for breast cancer, Cancers 15 (11) (2023) 2929, https://doi.org/10.3390/cancers15112929.
[76] A.T. Billeter, B. Reiners, S.E. Seide, P. Probst, E. Kalkum, C. Rupp, et al., Comparative effectiveness of medical treatment vs. metabolic surgery for histologically proven non-alcoholic steatohepatitis and fibrosis: a matched network meta-analysis, Hepatobiliary Surg. Nutr. 11 (5) (2022) 696–708, https://doi.org/10.21037/hbsn-21-5.
[77] L. Zheng, Z. Zhang, P. Sheng, A. Mobasheri, The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis, Ageing Res. Rev. 66 (2021) 101249, https://doi.org/10.1016/J.ARR.2020.101249.
[78] A. Mobasheri, M.P. Rayman, O. Gualillo, J. Sellam, P. van der Kraan, U. Fearon, The role of metabolism in the pathogenesis of osteoarthritis, Nat. Rev. Rheumatol. 13 (5) (2017) 302–311, https://doi.org/10.1038/nrrheum.2017.50.
[79] F.J. Blanco, I. Rego, C. Ruiz-Romero, The role of mitochondria in osteoarthritis, Nat. Rev. Rheumatol. 7 (3) (2011) 161–169, https://doi.org/10.1038/nrrheum.2010.213.
[80] J. Zuo, J. Tang, M. Lu, Z. Zhou, Y. Li, H. Tian, et al., Glycolysis rate-limiting enzymes: novel potential regulators of rheumatoid arthritis pathogenesis, Front. Immunol. 12 (November) (2021) 1–17, https://doi.org/10.3389/fimmu.2021.779787.

[81] M.M. Myerburg, J.D. King, N.M. Oyster, A.C. Fitch, A. Magill, C.J. Baty, et al., AMPK agonists ameliorate sodium and fluid transport and inflammation in cystic fibrosis airway epithelial cells, Am. J. Respir. Cell Mol. Biol. 42 (6) (2010) 676–684, https://doi.org/10.1165/2009-0147OC.

[82] J. Lawrence, R. Nho, The role of the mammalian target of rapamycin (mTOR) in pulmonary fibrosis, Int. J. Mol. Sci. 19 (3) (2018) 778, https://doi.org/10.3390/ijms19030778.

[83] S. Zhu, A. Batushansky, A. Jopkiewicz, D. Makosa, K.M. Humphries, H. Van Remmen, et al., Sirt5 deficiency causes posttranslational protein malonylation and dysregulated cellular metabolism in chondrocytes under obesity conditions, Cartilage 13 (2_suppl) (2021) 1185S–1199S, https://doi.org/10.1177/1947603521993209.

[84] X. Zhu, Y.T. Chan, P.S.H. Yung, R.S. Tuan, Y. Jiang, Subchondral bone remodeling: a therapeutic target for osteoarthritis, Front. Cell Dev. Biol. 8 (2020) 607764, https://doi.org/10.3389/FCELL.2020.607764.

[85] L. Zhang, J. Hu, K.A. Athanasiou, The role of tissue engineering in articular cartilage repair and regeneration, Crit. Rev. Biomed. Eng. 37 (1–2) (2009) 1, https://doi.org/10.1615/CRITREVBIOMEDENG.V37.I1-2.10.

[86] Y. He, Z. Li, P.G. Alexander, B.D. Ocasio-Nieves, L. Yocum, H. Lin, et al., Pathogenesis of osteoarthritis: risk factors, regulatory pathways in chondrocytes, and experimental models, Biology 9 (8) (2020) 1–32, https://doi.org/10.3390/BIOLOGY9080194.

[87] S.R. Goldring, Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis, Ther Adv Musculoskelet Dis 4 (4) (2012) 249, https://doi.org/10.1177/1759720X12437353.

[88] Y.A. Rim, J.H. Ju, The role of fibrosis in osteoarthritis progression, Life 11 (1) (2021) 1–13, https://doi.org/10.3390/LIFE11010003.

[89] D.J. Hunter, J.J. McDougall, F.J. Keefe, The symptoms of osteoarthritis and the genesis of pain, Rheum. Dis. Clin. N. Am. 34 (3) (2008) 623–643, https://doi.org/10.1016/j.rdc.2008.05.004.

[90] S. Hodgeson, S. O'brien, Jennifer Simkin |, E. Plakotaris, C. Mccarthy, V. Dasa, et al., Differences in synovial fibrosis relative to range of motion in knee osteoarthritis patients, J. Orthop. Res. 40 (2022) 584–594, https://doi.org/10.1002/jor.25061.

[91] A. Turan, P. Celtikci, A. Tufan, M.A. Ozturk, Basic radiological assessment of synovial diseases: a pictorial essay, Eur J Rheumatol 4 (2) (2017) 166–174, https://doi.org/10.5152/eurjrheum.2015.0032.

[92] T. Wynn, Cellular and molecular mechanisms of fibrosis, J. Pathol. 214 (2) (2008) 199–210, https://doi.org/10.1002/path.2277.

[93] Y. Jia, H. Le, X. Wang, J. Zhang, Y. Liu, J. Ding, et al., Double-edged role of mechanical stimuli and underlying mechanisms in cartilage tissue engineering, Front. Bioeng. Biotechnol. 11 (2023), https://doi.org/10.3389/fbioe.2023.1271762.

[94] R.V. Iozzo, M.A. Gubbiotti, Extracellular matrix: the driving force of mammalian diseases, Matrix Biol. 71–72 (2018) 1–9, https://doi.org/10.1016/j.matbio.2018.03.023.

[95] K. Takata, K. Uchida, S. Takano, M. Mukai, G. Inoue, H. Sekiguchi, et al., Possible regulation of bFGF expression by mast cells in osteoarthritis patients with obesity: a cross-sectional study, Diabetes Metab Syndr Obes 14 (2021) 3291–3297, https://doi.org/10.2147/DMSO.S319537.

[96] K. Sun, X. Li, P.E. Scherer, Extracellular matrix (ECM) and fibrosis in adipose tissue: overview and perspectives, in: Comprehensive Physiology, Wiley, 2023, pp. 4387–4407, https://doi.org/10.1002/cphy.c220020.

[97] G. Landskron, M. De La Fuente, P. Thuwajit, C. Thuwajit, M.A. Hermoso, Chronic inflammation and cytokines in the tumor microenvironment, J Immunol Res 2014 (2014), https://doi.org/10.1155/2014/149185.

[98] G.A. Cabral-Pacheco, I. Garza-Veloz, CCD La Rosa, J.M. Ramirez-Acuña, B.A. Perez-Romero, J.F. Guerrero-Rodriguez, et al., The roles of matrix metalloproteinases and their inhibitors in human diseases, Int. J. Mol. Sci. 21 (24) (2020) 1–53, https://doi.org/10.3390/IJMS21249739.

[99] K. Richter, T. Kietzmann, Reactive oxygen species and fibrosis: further evidence of a significant liaison, Cell Tissue Res. 365 (3) (2016) 591–605, https://doi.org/10.1007/s00441-016-2445-3.

[100] S. Shrishrimal, E.A. Kosmacek, R.E. Oberley-Deegan, Reactive oxygen species drive epigenetic changes in radiation-induced fibrosis, Oxid. Med. Cell. Longev. 2019 (2019), https://doi.org/10.1155/2019/4278658.

[101] D.E. Nanus, A. Badoume, S.N. Wijesinghe, A.M. Halsey, P. Hurley, Z. Ahmed, et al., Synovial tissue from sites of joint pain in knee osteoarthritis patients exhibits a differential phenotype with distinct fibroblast subsets, EBioMedicine 72 (2021), https://doi.org/10.1016/j.ebiom.2021.103618.

[102] F.L. Collins, A.J. Roelofs, R.A. Symons, K. Kania, E. Campbell, E.S.R. Collie-duguid, et al., Taxonomy of fibroblasts and progenitors in the synovial joint at single-cell resolution, Ann. Rheum. Dis. 82 (3) (2023) 428–437, https://doi.org/10.1136/ard-2021-221682.

[103] A.J. Knights, E.C. Farrell, O.M. Ellis, L. Lammlin, L.M. Junginger, P.M. Rzeczycki, et al., Synovial fibroblasts assume distinct functional identities and secrete R-spondin 2 in osteoarthritis, Ann. Rheum. Dis. 82 (2023) 272–282, https://doi.org/10.1136/annrheumdis-2022-222773.

[104] R. Shkhyan, C. Flynn, E. Lamoure, A. Sarkar, B. Van Handel, J. Li, et al., Inhibition of a signaling modality within the gp130 receptor enhances tissue regeneration and mitigates osteoarthritis, Sci. Transl. Med. 15 (688) (2023), https://doi.org/10.1126/scitranslmed.abq2395.

[105] S.N. Wijesinghe, A. Badoume, D.E. Nanus, A. Sharma-Oates, H. Farah, M. Certo, et al., Obesity defined molecular endotypes in the synovium of patients with osteoarthritis provides a rationale for therapeutic targeting of fibroblast subsets, Clin. Transl. Med. 13 (4) (2023), https://doi.org/10.1002/ctm2.1232.

[106] S. Tang, L. Yao, J. Ruan, J. Kang, Y. Cao, X. Nie, et al., Single-cell atlas of human infrapatellar fat pad and synovium implicates APOE signaling in osteoarthritis pathology, Sci. Transl. Med. 16 (731) (2024), https://doi.org/10.1126/scitranslmed.adf4590.

[107] D.J. Hunter, D.T. Felson, Osteoarthritis, Br. Med. J. 332 (7542) (2006) 639–642, https://doi.org/10.1136/bmj.332.7542.639.

[108] L. Zhang, R. Xing, Z. Huang, L. Ding, L. Zhang, M. Li, et al., Synovial fibrosis involvement in osteoarthritis, Front. Med. 8 (2021) 684389, https://doi.org/10.3389/fmed.2021.684389.

[109] J. Lin, S. Jia, W. Zhang, M. Nian, P. Liu, L. Yang, et al., Recent advances in small molecule inhibitors for the treatment of osteoarthritis, J. Clin. Med. 12 (5) (2023) 1986, https://doi.org/10.3390/jcm12051986.

[110] M. Myllärniemi, R. Kaarteenaho, Pharmacological treatment of idiopathic pulmonary fibrosis – preclinical and clinical studies of pirfenidone, nintedanib, and N-acetylcysteine, Eur Clin Respir J 2 (1) (2015) 26385, https://doi.org/10.3402/ecrj.v2.26385.

[111] M. Zhao, L. Wang, M. Wang, S. Zhou, Y. Lu, H. Cui, et al., Targeting fibrosis: mechanisms and clinical trials, Signal Transduct. Targeted Ther. 7 (1) (2022) 1–21, https://doi.org/10.1038/s41392-022-01070-3, 2022 7:1.

[112] J.P. Frías, M.J. Davies, J. Rosenstock, F.C. Pérez Manghi, L. Fernández Landó, B.K. Bergman, et al., Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes, N. Engl. J. Med. 385 (6) (2021) 503–515, https://doi.org/10.1056/NEJMoa2107519.

[113] J.P.H. Wilding, R.L. Batterham, S. Calanna, M. Davies, L.F. Van Gaal, I. Lingvay, et al., Once-weekly semaglutide in adults with overweight or obesity, N. Engl. J. Med. 384 (11) (2021) 989–1002, https://doi.org/10.1056/NEJMOA2032183/SUPPL_FILE/NEJMOA2032183_DATA-SHARING.PDF.

[114] S. Kalra, S. Bhattacharya, N. Kapoor, Contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs), Diabetes Ther 12 (8) (2021) 2133–2147, https://doi.org/10.1007/S13300-021-01113-Y.

[115] T.D. Müller, B. Finan, S.R. Bloom, D. D'Alessio, D.J. Drucker, P.R. Flatt, et al., Glucagon-like peptide 1 (GLP-1), Mol. Metabol. 30 (2019) 72–130, https://doi.org/10.1016/j.molmet.2019.09.010.

[116] C. Meurot, C. Jacques, C. Martin, L. Sudre, J. Breton, R. Rattenbach, et al., Targeting the GLP-1/GLP-1R axis to treat osteoarthritis: a new opportunity? J Orthop Translat 32 (2022) 121–129, https://doi.org/10.1016/J.JOT.2022.02.001.

[117] S.R. Jafarzadeh, T. Neogi, J.J. Stefanik, J.S. Li, A. Guermazi, C.M. Apovian, et al., Mediating role of bone marrow lesions, synovitis, pain sensitization, and depressive symptoms on knee pain improvement following substantial weight loss, Arthritis Rheumatol. 72 (3) (2020) 420–427, https://doi.org/10.1002/ART.41125.

[118] M. Yao, J. Zhang, Z. Li, X. Bai, J. Ma, Y. Li, Liraglutide protects nucleus pulposus cells against high-glucose induced apoptosis by activating PI3K/Akt/mTOR/Caspase-3 and PI3K/Akt/GSK3β/Caspase-3 signaling pathways, Front. Med. 8 (2021), https://doi.org/10.3389/FMED.2021.630962/FULL.

[119] J. Chen, J.J. Xie, K.S. Shi, Y.T. Gu, C.C. Wu, J. Xuan, et al., Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat, Cell Death Dis. 9 (2) (2018), https://doi.org/10.1038/S41419-017-0217-Y.

[120] H. Gudbergsen, A. Overgaard, M. Henriksen, E.E. Wæhrens, H. Bliddal, R. Christensen, et al., Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial, Am. J. Clin. Nutr. 113 (2) (2021) 314–323, https://doi.org/10.1093/AJCN/NQAA328.

[121] C. Meurot, C. Martin, L. Sudre, J. Breton, C. Bougault, R. Rattenbach, et al., Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis, Sci. Rep. 12 (1) (2022), https://doi.org/10.1038/S41598-022-05323-7.

[122] J. Mei, J. Sun, J. Wu, X. Zheng, Liraglutide suppresses TNF-α-induced degradation of extracellular matrix in human chondrocytes: a therapeutic implication in osteoarthritis, Am J Transl Res 11 (8) (2019) 4800, pmc/articles/PMC6731440/. (Accessed 29 November 2023).

[123] S. Wan, H. Sun, Glucagon-like peptide-1 modulates RAW264.7 macrophage polarization by interfering with the JNK/STAT3 signaling pathway, Exp. Ther. Med. 17 (5) (2019), https://doi.org/10.3892/ETM.2019.7347.

[124] T.D. Challa, N. Beaton, M. Arnold, G. Rudofsky, W. Langhans, C. Wolfrum, Regulation of adipocyte formation by GLP-1/GLP-1R signaling, J. Biol. Chem. 287 (9) (2012) 6421–6430, https://doi.org/10.1074/jbc.M111.310342.

[125] C. Sanz, P. Vázquez, C. Blázquez, P.A. Barrio, M.D.M. Alvarez, E. Blázquez, Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow, Am. J. Physiol. Endocrinol. Metab. 298 (3) (2010) 634–643, https://doi.org/10.1152/AJPENDO.00460.2009/SUPPL_FILE/TABLES1.PDF.

[126] H. Bliddal, H. Bays, S. Czernichow, J.U. Hemmingsson, J. Hjelmesæth, T.H. Morville, et al., Semaglutide 2.4 mg efficacy and safety in people with obesity and knee osteoarthritis: results: from the STEP 9 randomised clinical trial, Osteoarthritis Cartilage 32 (6) (2024) 745–746, https://doi.org/10.1016/j.joca.2024.03.003.

[127] Novo dordisk. Company announcement. https://ml-eu.globenewswire.com/Resource/Download/b4ae7c0b-df06-49cd-a1b9-50d5d566e6bc, 2024. (Accessed 5 February 2024).

[128] H. Zhu, L. Zhou, Q. Wang, Q. Cai, F. Yang, H. Jin, et al., Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort, Ann. Rheum. Dis. 82 (9) (2023) 1218–1226, https://doi.org/10.1136/ARD-2023-223845.