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Review Article

The role of bone marrow adiposity in rheumatoid arthritis pathogenesis

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ABSTRACT

Bone marrow adiposity (BMA) has historically been thought of as a passive energy reserve in the medullary cavity, new research indicates that it is actually a dynamic endocrine organ that affects immunological responses, bone remodeling, and hematopoiesis. Changes in BMA composition and behavior have been increasingly identified in rheumatoid arthritis (RA), an autoimmune disorder marked by joint damage and synovial inflammation. Immune dysregulation, decreased osteoblastogenesis, and osteoclast activation may be caused by dysregulated adipokine production, changed lipid metabolism, and compromised bone marrow microenvironment function. The physiological function of BMA, its changes in RA, and the mechanisms relating marrow fat to joint pathogenesis are all summarized in this paper. In addition, we go over cutting-edge imaging techniques for measuring BMA *in vivo*, provide an overview of clinical data regarding its involvement in the course of the disease, and investigate possible treatment approaches that target BMA modulation to enhance muscles and joints outcomes in RA. Gaining insight into this little-known facet of RA pathophysiology may pave the way for the development of biomarkers and focused therapeutic approaches.

Keywords: Bone marrow adiposity, Rheumatoid arthritis, Adipokines, Osteoclastogenesis, Bone remodeling, Inflammation

INTRODUCTION

Rheumatoid arthritis (RA), commonly known as "Gatiya" in India, is an inflammatory and autoimmune disease where the body's defenses attack healthy cells. Joint cartilage deterioration is the main effect of RA on joints throughout the human body, including the hands, fingers, legs, heels, and fingertips. Damage to tissues results in chronic discomfort. The pulmonary, cardiovascular, and ocular systems are among the many body cells and organs that RA may damage.[1] Deficits, dry mouth, burning eyes, appetite loss, mild fever, and itching were among the complications. Millions of people worldwide are affected by rheumatic diseases, which are considered serious public health issues that result in rising healthcare costs.[2] As an example, RA, just one type of rheumatic disease, received an aggregate of 128 billion US dollars in 2003. Roughly 14,000 US dollars were used to treat cardiovascular illnesses because RA is associated with a higher incidence of coronary artery disease, and 3.6 billion US dollars were used for pharmacological therapies.[2] According to US statistics, the number of new cases of RA increased roughly by one million each year from 2007 to 2009.[3] About 0.92% of India's elderly population suffers from RA. Serious disability may be avoided with early examination and aggressive treatment, although this is not necessarily feasible. Approximately 20 to 40 new cases per lac population are documented each year in India.[4] The two main causes thought to be responsible for the rise in RA patients are stress and environmental factors. According to research, using oral contraceptives, smoking, and drinking coffee may increase the risk of developing RA.[5] The only known approach to prevent the condition is to reduce risk factors. Maintaining muscle strength and function can be achieved by regular exercise.

Prolonged synovitis, increasing joint deterioration, and a variety of extra-articular symptoms are the hallmarks of

RA, a chronic systemic inflammatory disease.[6] Even with significant progress in our knowledge of immune-mediated bone degradation and synovial inflammation, little is known about how bone marrow contributes to the pathogenesis of RA. The most prevalent cell population among the various components of bone marrow, such as hematopoietic cells, endothelial cells, immunological cells, and stromal elements, are BMAs, which can make up to 70% of the adult marrow cavity.[7] Previously thought of being inactive "fillers" in the medullary space, BMAs have since been proven to be hormonally and metabolically active cells that have a major impact on immune modulation and bone homeostasis.[8]

According to new research, BMAs actively participate in the skeletal and immunological microenvironments rather than acting as passive observers. Like white adipose tissue, BMAs are endocrine organs that can release pro-inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) as well as adipokines like leptin and adiponectin.[9] By influencing immune system stimulation, osteoclast proliferation, and synovial fibroblast function, these bioactive chemicals establish a clear connection between BMA biology and the pathophysiology of RA. Additionally, there is geographical and functional heterogeneity in marrow adiposity: regulated BMAs (rBMAs) are scattered throughout hematopoietic tissue and continuously react to metabolic and inflammatory stimuli, whereas constitutive BMAs (cBMAs) are plentiful and stable at distal skeletal regions.[10] This flexibility implies that inflammation linked to RA may change the distribution and function of BMA, further influencing the course of the disease. Bone Marrow fat accumulation is associated with decreased osteoblastogenesis, increased osteoclast activity, and changed hematopoietic support, according to recent research on osteoporosis, metabolic bone disorder, and aging.[11] Similar mechanisms may be responsible for systemic osteoporosis, periarticular bone loss, and chronic immunological dysregulation in RA. Crucially, BMA volume and activity also seem to be altered by therapeutic interventions like glucocorticoids and biologic DMARDs, suggesting that BMAs may function as RA biomarkers and therapeutic targets.[12]

With an emphasis on their biological function, mechanistic connections to inflammatory processes and bone loss, developments in imaging for *in vivo* evaluation, and possible therapeutic implications, we provide an overview of the state of knowledge on BMAs' involvement in RA in this review. We want to offer a fresh viewpoint on the pathophysiology of the disease and potential future treatment approaches by drawing attention to this overlooked aspect of the RA microenvironment.

BMA IN HEALTH

Instead of being inert filler, BMA has since been shown to be an active and dynamic constituent of the microenvironment of the bone marrow. Mesenchymal stem cells (MSCs), who also produce osteoblasts, chondrocytes, and myocytes, are the source of BMAs.[13] Their common ancestry emphasizes how crucial a function they play in controlling the ratio of fat storage to bone formation in the bone cavity.

cBMAs and rBMAs are the two different forms of BMAs that have been identified. cBMAs emerge early in development, are mostly found in the distal skeleton, and are largely stable throughout life. On the other hand, controlled BMAs are found in proximal skeletal regions inside hematological marrow and exhibit significant plasticity, growing or contracting in response to indicators related to metabolism, hormones, and inflammation. They are distributed throughout hematological marrow in proximal skeletal areas. This variation implies that each population has distinct physiological roles.[14] BMAs are significant regional and systemic regulators under typical circumstances. They create cytokines that affect osteoblast and osteoclast activity, secrete adipokines like leptin and adiponectin, and store and release lipids to provide an energy reservoir. BMA supports hematopoietic stem cell function, skeletal balance, and systemic utilization of energy through these methods. Since excessive BMA expansion has been connected to compromised bone formation and altered hematological function, it is significant that the equilibrium between adipogenesis and osteoblastogenesis across the bone marrow is tightly regulated.[15]

As a result, BMA is a dynamic tissue that reacts to environmental stresses, hormone signaling, age, and nutritional condition. Conditions like dietary limitations, persistent infection, or systemic disease frequently cause the expansion of rBMAs, underscoring its function as a stress-resistant compartment. All of these observations show that BMA is a very active and multipurpose tissue that connects immune control, energy homeostasis, and skeletal biology.

CONSTITUTIVE VS. REGULATED BMAs IN HEALTH

Adipocytes from bone marrow are not a homogeneous population; instead, they vary in both function and location. Constitutive marrow adipocytes (cMAs) and regulated marrow adipocytes (rMAs) are the two main kinds that have been identified. The hands, feet, and long bone epiphyses are examples of the distal skeleton where cBMAs are primarily found. They are comparatively plentiful, show up early in development, and maintain a constant metabolism throughout life, even in the face of stress. On the other hand, hematopoietic-rich areas within the proximal skeleton, such as the vertebrae and pelvis, have controlled BMAs scattered throughout. Due to their high degree of plasticity, these adipocytes react quickly to stimuli related to metabolism, hormones, and inflammation.[16] For instance, rMAs may decrease under situations of elevated hematopoietic demand and may increase in response to dietary limitations, obesity, or

ongoing inflammatory conditions. This divergence highlights the dual function of marrow fat: rMAs function as responsive regulators of bone and immunological microenvironments, whilst cMAs offer a stable anatomical and physiological background.[13]

MECHANISTIC LINKS BETWEEN BMA AND RA

A key modulator of skeletal and immunological homeostasis, BMA having a significant impact on the pathophysiology of RA. In addition to being a store of energy, BMA is a functional endocrine organ that secretes cytokines and adipokines that regulate immune cell activation, inflammation, and bone remodeling (Figure 2).[17] A complicated interaction between immune activation, persistent synovial inflammation, and decreased bone density drives the pathophysiology of RA. By producing adipokines, cytokines and lipid mediators that affect osteoclast activity and immune cell function, BMA is actively involved in this process. These mediators link impaired marrow metabolism to the pathogenesis of RA by disrupting bone remodeling and exacerbating local inflammation as shown in Figure 1. In RA, dysregulated interactions among BMA, lymphocytes, and osteoclasts lead to joint degeneration, synovial inflammation, and changes in bone metabolism.

Adipokine–cytokine signaling from marrow fat

Adipokines (leptin, adiponectin, resistin, and visfatin) and inflammatory cytokines (e.g., IL-6, TNF-α) released by BMAs influence osseous and synovial immunology. Adipose tissue doesn't constitute the only source of adipokines in rheumatic disorders. These mediators are also produced by other cell types, such as synoviocytes and chondrocytes.[18] Adipokines play a significant role in the pathophysiology of musculoskeletal illnesses by targeting cells and tissues such bones, cartilage, and the synovial membrane through autocrine, paracrine, and endocrine pathways.[19] Research has shown that RA patients had higher amounts of adipokines in their serum and SF than healthy individuals.

Nevertheless, it was shown by Bilski et al that adipokine levels in the serum are not prognostic indicators of adipokine concentration in the SF.[20] Furthermore, their results show that adipokine levels in the synovial joint are controlled separately from serum.[21] Adipokines have drawn more attention in recent years as possible treatment targets and RA biomarkers.[20]

A multipurpose organ, adipose tissue is in charge of thermogenesis, lipid storage, the support and structural elements of numerous organs, including the skin, gastrointestinal tract, and joints, as well as what are now known as glandular and hormonal activities.[20]

Because it produces and secretes adipokines, which are crucial in the pathological processes of insulin resistance, inflammation, and atherogenesis, it is notable in this context for its function as an endocrine organ.[22]

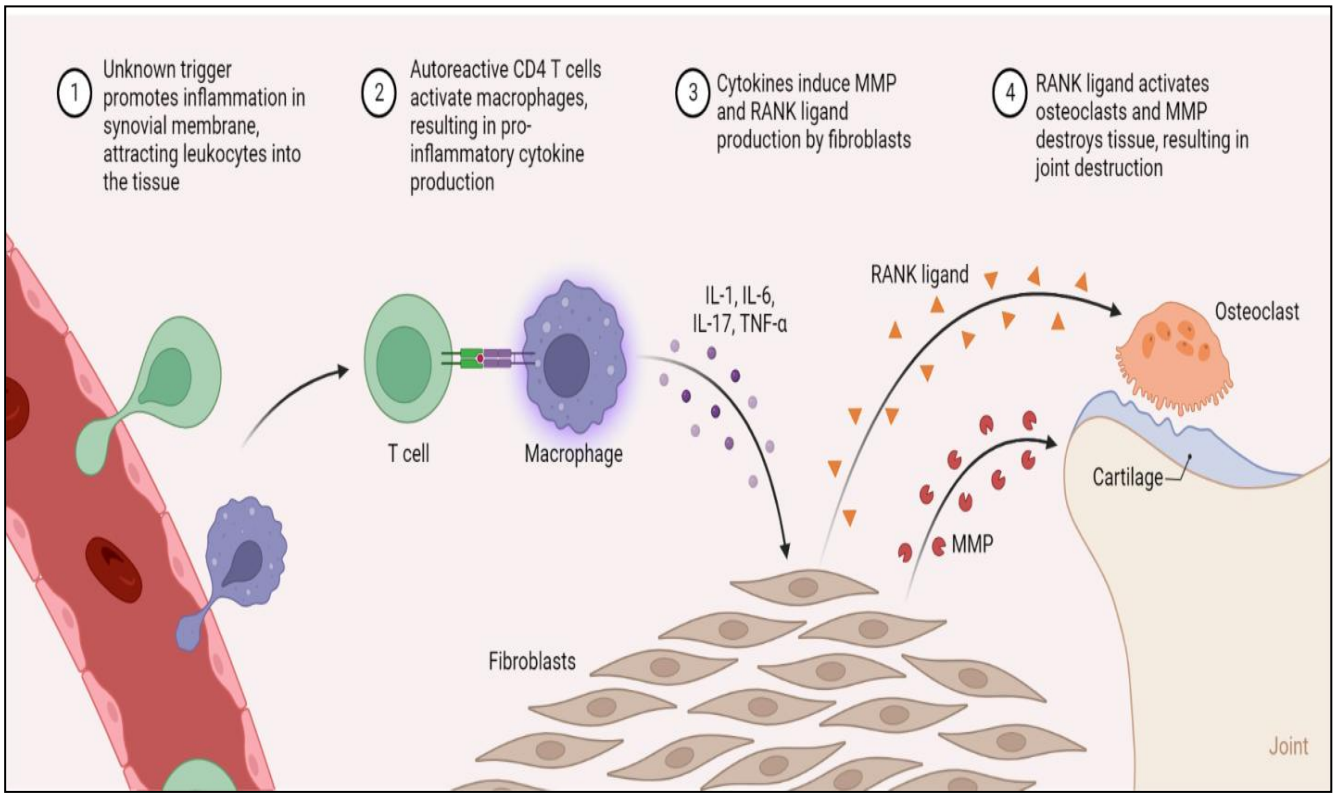

Figure 1: Pathogenesis of RA.[53]

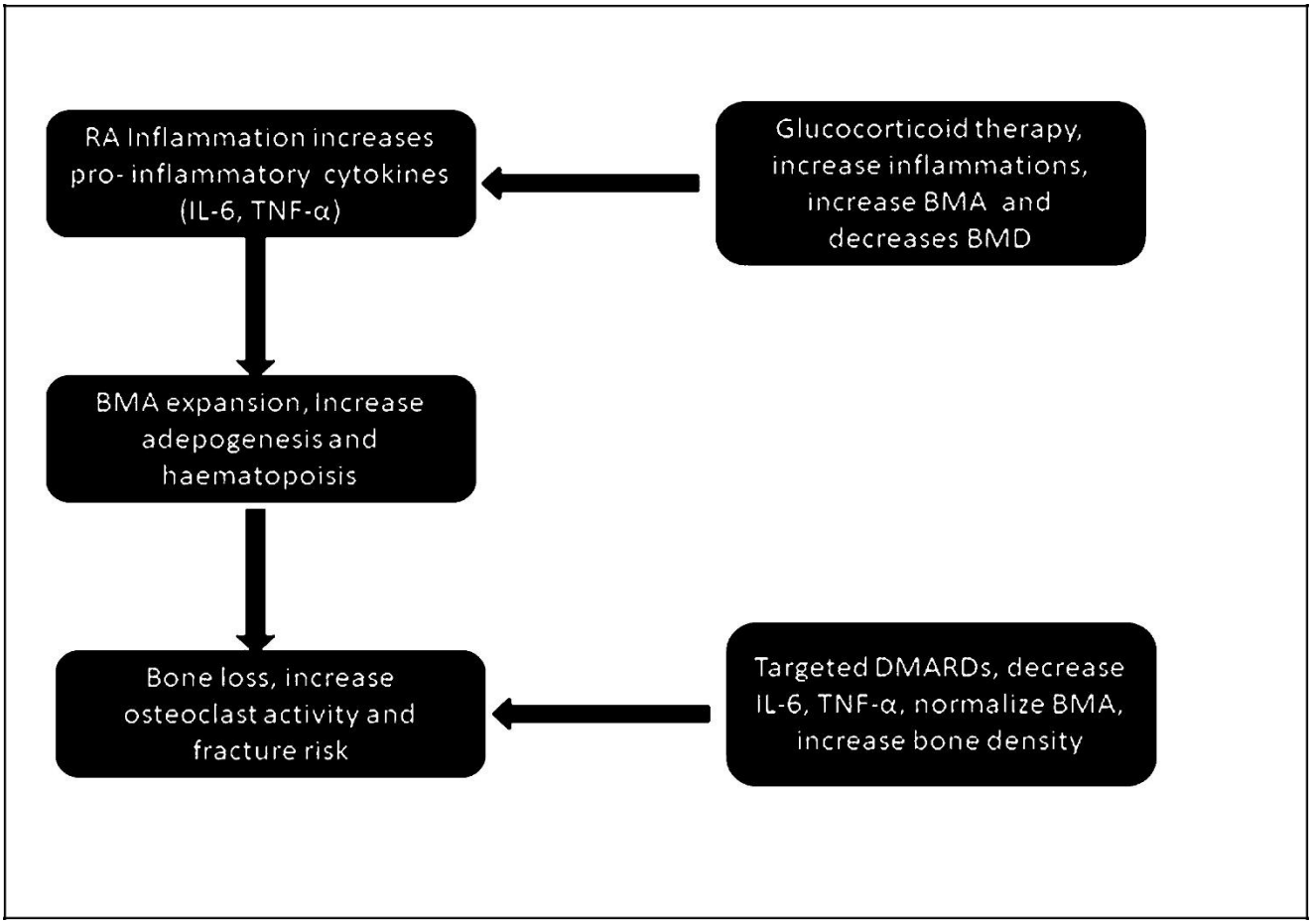

Figure 2: Mechanistic links between RA, bone marrow adiposity, and therapeutic interventions.

A common response to a number of clinical conditions and medications, including diabetes, obesity, anorexia, senescence, and glucocorticoid therapy, is a rise in BMAT. According to the function of BMAs, influencing the differentiation fate of BMSCs is a practical approach to treating bone marrow-related disorders, and regulating bone marrow adipogenesis is a viable strategy. The differentiation of BMSCs involves a number of regulators.), PPARγ, C/EBPα, platelet-derived growth factor receptor β, and zinc finger proteins 423, 467, and 521 are well-known elements necessary for adipogenesis; more regulators are being studied. Forkhead box P1 (FOXP1) can control BMSC destiny switches by interacting with RBPjκ and the CEBPβ/δ complex. Thy-1 (CD90), a glycosylphosphatidyl-anchored protein belonging to the immunoglobulin family, is expressed on BMSCs.[20] Thy-1 deficiency causes a decrease in Wnt ligand along with an overexpression of the Wnt inhibitors dickkopt-1 and sclerostin, which impede osteogenesis. Additionally, Thy-1-deficient mice exhibit enhanced adipogenesis. Through controlling the mRNA degradation of target mRNA, microRNAs (miRs) contribute to cell metabolism. MiR-188 antagonism can influence BMSC differentiation outcomes and encourage bone development. Histone demethylases KDM4B and KDM6B prevent adipogenic development of BMSCs by removing $H_3K_9me_3$ and $H_3K_{27}me_3$, demonstrating that BMSC maturation is also epigenetically controlled.[19]

Information that controls BMSC lineage commitment is also provided by the bone marrow niche. By suppressing sympathetic nerve activity, sensory nerves can cause BMSCs to undergo osteogenic differentiation. According to Hu et al localized increases in prostaglandin E2 decrease adipogenesis via activating EP4 receptors in sensory neurons.[23] Mechanical stresses prevent the synthesis of BMA and promote the osteogenic development of BMSCs. Actin modulation controls the ERK and AKT pathways during mechanical loading, which results in the differentiation of BMSCs. Additionally; strain-induced cytoskeletal rearrangement is influenced by mTORC2. In BMSCs, mTORC2 deletion promotes adipogenic differentiation while eliminating osteogenic differentiation. BMSC differentiation is also influenced by endocrine chemicals. It has been demonstrated that estrogen inhibits adipogenesis by acting on the estrogen receptor-α. Follicle-stimulating hormone (FSH) receptors are expressed by both BMSCs and BMAs, and adipogenesis is inhibited when their interaction with FSH is inhibited. Parathyroid hormone (PTH) controls bone metabolism and prevents BMSCs from differentiating into BMAs. Adipogenic lipolysis can be induced by PTH, which further reduces adipogenesis in the bone marrow

niche.[24] Additionally, BMAs express PTH1R. Additionally, leptin controls bone metabolism; leptin administered hypothalamically or subcutaneously has been demonstrated to reduce marrow adiposity brought on by obesity. Overall, a number of factors influence the differentiation fate of BMSCs, and more research is required to find new regulators.

Osteoclastogenesis driven by BMA lineage cells

It is now known that BMA-lineage cells are direct producers of RANKL, which is necessary for the production of trabecular osteoclasts, in addition to paracrine effects. *In vivo*, conditional RANKL knockdown in adipose-lineage hematopoietic cells decreases osteoclasts and preserves cancellous bone. BMA is positioned as an active driver of bone resorption important to RA bone loss, especially when combined with evidence suggesting that adipogenic precursors provide osteoclast-supporting cues (e. g., CSF1). The production of osteoclasts and bone remodeling depend on a receptor activator for NF-κB ligand (RANKL). However, the exact cellular origin of RANKL for osteoclastogenesis remains unknown. Bone marrow (BM) adipose lineage cells are derived from bone marrow mesenchymal stem cells (BMSCs), which is distinct from peripheral adipose tissue. Here, we show that bone marrow adipose lineage cells can be targeted by adiponectin promoter-driven Cre expression ($Adipoq^{Cre}$).[25] To conditionally remove RANKL from BM adipose lineage cells, we cross $Adipoq^{Cre}$ mice with $rankl^{fl/fl}$ mice. By decreasing trabecular osteoclast development and preventing bone resorption, conditional deletion of RANKL enhances the annular bone mass of long bones in mice. However, this has no effect on cortical bone thickness or calcified cartilage resorption. $Adipoq^{Cre}$; $rankl^{fl/fl}$ mice demonstrate bone loss brought on by unloading but are resistant to trabecular bone loss caused by rosiglitazone (ROS) and estrogen deprivation. Therefore, BM adipose lineage cells are a crucial source of RANKL for the development of trabecula osteoclasts and cancellous bone resorption during remodeling in both healthy and diseased situations.[23] Avoiding pathological bone loss may be possible by addressing bone marrow obesity.

Receptor activator of NF-κB (RANK) and its ligand RANKL are essential for osteoclastogenesis.[23] Osteocytes, hypertrophic chondrocytes, and osteoblasts are the main sources of RANKL, which binds to the RANK of osteoclast progenitors to trigger osteoclastogenesis. Interestingly, RANKL is also expressed by BMAs. In order to specifically knock out Rankl in adipogenic lineage cells ($Adipoq^{cre}$; $Rankl^{fl/fl}$) crossed Rankl-floxed mice with the Adipoq-Cre line. These animals displayed compromised osteoclastogenesis and bone resorption in physiological settings. Following Rankl deletion in adipose cells, we observed no reduction in cancellous bone density or cortical bone thickness in ovariectomy-induced osteoporosis. $Adipoq^{cre}$; $Rankl^{fl/fl}$ mice were given the PPARγ activator rosiglitazone to enhance bone marrow adipogenesis and the risk of fracture in order to investigate the role of RANKL in pathological BMA expansion. In comparison to control $Rankl^{fl/fl}$ mice, Adipoqcre; Ranklfl/fl animals displayed comparable BMA growth but fewer osteoclasts. These results imply that enhanced osteoclastogenesis and bone resorption depend on expanded BMA as a source of RANKL. Overall, these two separate investigations demonstrated that BMAs regulate osteoclastogenesis in both healthy and pathological conditions through RANK/RANKL-dependent mechanisms, hence mediating bone remodeling.[25] In order to cure osteoporosis, it may be helpful to target bone marrow adipogenesis and RANKL signaling in BMAs.

Hematopoietic niche modulation

Because rBMAs live in highly cellular, perivascular niches and affect hematopoiesis through growth factors and chemokines, changes in BMA composition can alter myeloid production, antigen presentation, and macrophage/T-cell migration in the marrow next to inflamed joints, which feed back into synovitis. MAds have a crucial role in the hematopoietic microenvironment. The way they were able to exert a variety of regulatory functions is directed by their heterogeneity and is contingent upon their biological, geographical, and hierarchical context.[52] When analyzing effects in hematopoiesis, it is crucial to develop experimental techniques and nomenclature that address phase-specificity and heterogeneity throughout the BMSC-BMAd differentiation axis, interpret gene reporter investigations within this framework and quantify alterations in all three components (hematopoiesis, adiposity, and bone) when dealing with interdependency. This complexity is highlighted by this complexity.[26]

Hematopoiesis is negatively regulated by BMAs, according to evidence. Compared to adipocyte-free thoracic vertebrae, adipocyte-rich caudal vertebrae retain fewer hematopoietic stem cells (HSCs) and short-term progenitors pharmaceutical additionally, it speeds up hematopoietic recovery following radiation therapy and bone marrow transplantation and inhibits genetic adipogenesis. It is yet unknown, nevertheless, if this is due to a secondary effect on the marrow environment or the influence of BMAs on HSCs. According to current research, adipocytes in long bones aid in hematological recovery after radiation therapy by supplying stem cell factor (SCF), which is essential for HSC survival. In contrast, adipocytes in tail vertebrae impede hematopoiesis. Following irradiation, fatless A-ZIP/F1 mice show a greater number of HSCs and marrow cells in the caudal vertebrae but less overall in the long bones. This discrepancy was ascribed to the significant quantity of blood arteries in the A-ZIP/F1 mice's tail vertebrae, a feature not observed in the femurs. Hematopoietic regeneration and HSC frequency are hampered by suppression of marrow vascularization. BMAs produce leptin and adiponectin in addition to SCF, which encourages HSC proliferation. These observations

indicate that adipogenesis is an emergency response that creates HSC niche factors and stimulates hematopoiesis in the majority of bones, despite the fact that the finding that BMA growth is associated with decreased hematopoiesis has traditionally been interpreted as reflecting the inhibitory impact of BMA on hematopoiesis.

Adipogenesis, which entails promoting bone vascularization, is a quicker method of producing HSC niche factors than creating new perivascular niches. The rhesus macaque model has been utilized to demonstrate how hematopoietic stem and progenitor cells (HSPCs) lie ahead of BMAs, further confirming the links between BMAs and hematopoiesis in primates. Additionally, BMAT-conditioned media encourages HSPCs to proliferate and differentiate *in vivo.*[13] A quantitative proteomic analysis of the BMAT-conditioned media was carried out in order to investigate the underlying mechanism. 994 proteins, including TGFB1, FBLN1, IGFBP2, LGALS1, TIMP1, and C3, were shown to be released from BMAT. These proteins have been revealed to be positive regulators of HSPC adhesion, motility, and differentiation. Of these, 430 proteins have microvesicular or exosomal origins, suggesting paracrine function and complex composition.

Notably, BMAT includes a variety of cell types besides BMAs, such as monocytes/macrophages and granulocytes. These cellular communities of BMAs are the source of several proteins found in BMAT. Thus, through these immune cells, BMAs may also control the activity of HSPCs. BMAs' role in leukemia is controversial and varies with lineage. According to in vitro and *in vivo* research, BMAs prevent T-ALL proliferation in acute lymphoblastic leukemia (ALL). According to Shafat et al AML blasts cocultured with BMA exhibit increased proliferation and decreased apoptosis in AML. The fatty acids produced by BMA lipolysis are transferred from BMAs to AML cells for β-oxidation by AML blasts.[26]

But according to a new study, AML reduced the number of adipocytes in human bone marrow and AML xenografts. This suggests that AML primarily affects the adipocyte population in addition to encouraging the lipolysis of preexisting adipocytes. Additionally, adipogenic differentiation is hampered by AML, according to global transcriptome study of BMSCs either AML patients or healthy bone marrow donors. The researchers used Transwell assays to further investigate the connection between BMA decline and impaired myelo erythropoiesis in AML. The results demonstrated that BMAs stimulate the maturation of myeloid and erythroid lineages. When used to promote adipogenesis, the PPARγ agonist GW1929 was found to reduce leukemic development and rescue hematopoietic maturation. In general, BMAs support healthy myeloerythroid maturation and could be a helpful therapeutic target to treat AML's bone marrow failure. Further research is required to completely understand the role of BMA in physiology and various pathological diseases, since its great sensitivity to changes in metabolic status makes it difficult to define its function in specific clinical scenarios.

Immunometabolic support of inflammation

Complex immune systems processes that start prior to clinical symptoms appear are the driving force behind RA. Environmental influences and epigenetic changes cause after-translational citrullination of proteins including collagen and vimentin during pre-RA phase, producing neoantigens that help genetically predisposed people avoid immunological tolerance (HLA-DR1, HLA-DR4).[27] Production of pathogenic autoantibodies, particularly rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), is triggered by CD4 T cells, which are activated by antigen-presenting cells. In the synovial fluid, these autoantibodies create immunological complexes that sustain complement activation and joint inflammation.[28] This inflammatory cycle is substantially maintained by immunometabolic inputs. Reactive oxygen species (ROS) and air pollution stimulate the release of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6), improve citrullination, and activate NF-κB signaling.[29] Immune modulation is further compromised by vitamin D insufficiency through compromised VDR signaling. By changing intestinal permeability, triggering APCs via TLRs/NLRs and encouraging Th17 differentiation all of which are associated with increased autoimmunity gut dysbiosis also plays a role.[30]

In the joint, fibroblast-like synoviocytes (FLS), infiltrating neutrophils, and synovial macrophages produce cytokines, proteases, and ROS that promote osteoclastogenesis, pannus growth, and cartilage degradation. VEGF and other proangiogenic mediators promote vascular invasion, which makes it possible to recruit more immune cells. All immunological and metabolic factors work together to support systemic immune activation, tissue damage, and chronic inflammation in RA (Figure 3).[31]

BMAs play a role in bone marrow inflammatory processes and plasma cell dysfunction. To offer defense against recurring infections, memory T cells along with long-lasting plasma cells mostly settle in the bone marrow. Global gene expression analysis was used to evaluate the mRNA gene expression in adipocytes between adult BMAs and white adipose tissue (WAT) in order to examine the role of BMAs in immunological modulation.[28] BMAs had higher levels of several cytokines, such as CCL2, CCL5, IL6, IL8, IL10, IL15, CCR7, CCRL2, and CXCL1, suggesting that the bone marrow has an immune-regulating role. Additionally, BMAs have higher levels of reactive oxygen species (ROS) generation. IgG-producing plasma cells are inhibited due to ROS release. When under dietary restriction (DR), BMAs encourage the bone marrow to produce more memory T cells. After calorie restriction, WAT falls, but BMAs paradoxically rise, albeit it's unclear why. According to recent research, memory T cells respond to the dietary stress by moving from the outermost

layer within the bone marrow. The Adipoq-CreERT2×Rosa26 DTA mice were created to eliminate BMAs in order to ascertain if BMA expansion has a role in memory T cell survival and aggregation. A loxP-tagged stop cassette connected to the active portion of diphtheria toxin is present in Rosa26-DTA mice. Adipocytes are specifically ablated whenever crossed with Adipoq-Cre animals. Memory T cells are not maintained in the marrow following DR in mice with decreased BMAs, suggesting that BMAs are crucial for memory T cells to homing to the bone marrow.[29] Additionally, these T cells exhibit enhanced defense against infections and subsequent malignancies. Long-chain fatty acids have been shown to be essential for T cell survival in earlier research, but it is yet unknown how BMAs affect memory T cell homing and maintenance. BMAs work together to optimize and sustain immune retention following DR through an unknown method.

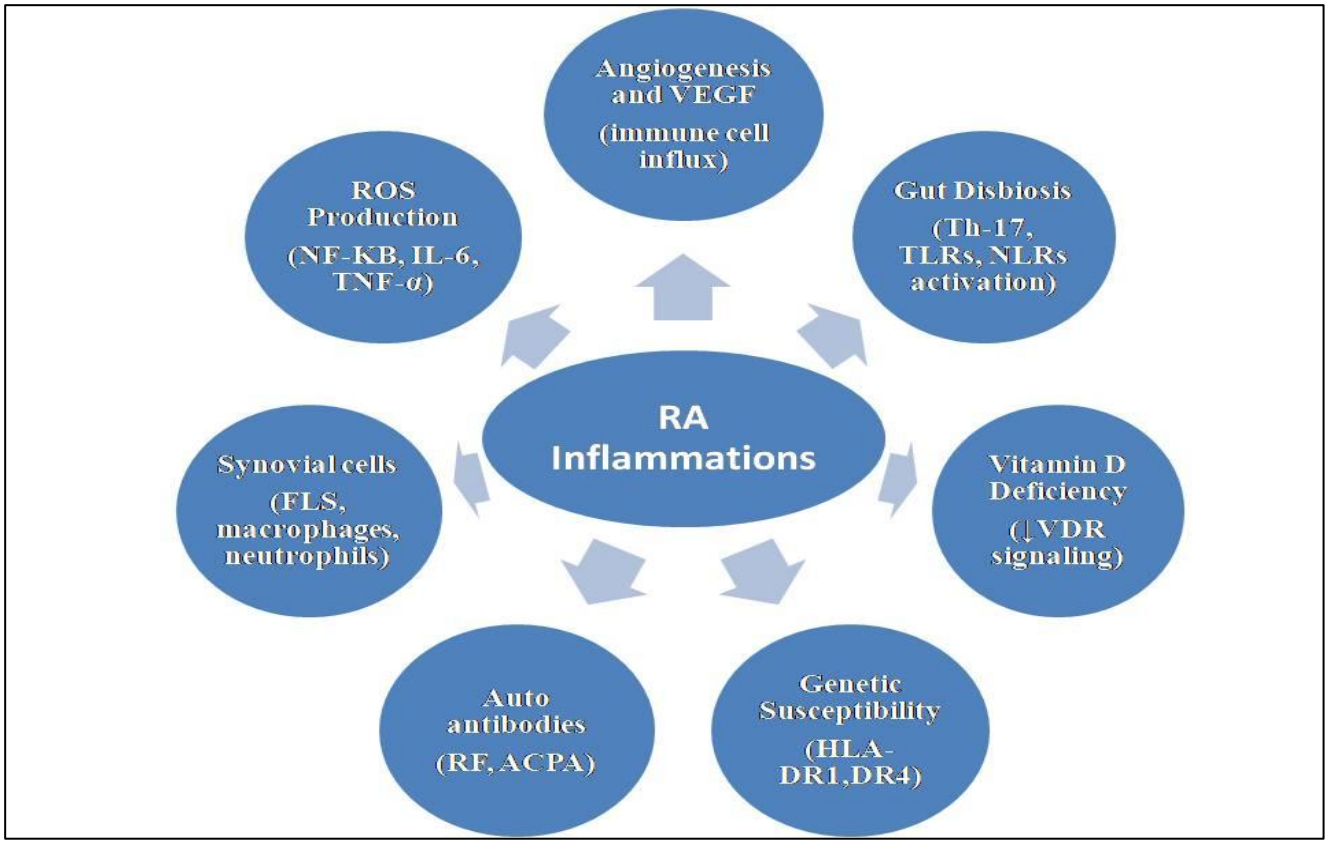

Figure 3: Different immunometabolic and environmental factors contribute to RA inflammation.

CLINICAL EVIDENCE

The importance of BMA in RA is being shown by a growing body of clinical and imaging research. BMA changes are correlated both bone quality and morphological outcomes, manifest early in the course of the disease, and are impacted by treatment measures. Comprehending these clinical trends reveals important information on the role that bone marrow fat plays in joint damage, as well as possible biomarkers for therapy monitoring and prognosis.

BMA alterations in early RA

The marrow fat component in periarticular bone compartments is larger in individuals with early RA, according to imaging studies, especially water-fat MRI and magnetic resonance spectroscopy (MRS). This occurrence suggests that marrow fat alterations are an early marker of RA pathogenesis, as it manifests even before overt erosions are detectable on conventional radiographs.[25] Crucially, regions that have elevated marrow adiposity frequently combine with bone marrow edema (BME), a powerful predictor of later joint erosions. According to Fan et al this coexistence suggests that a shift from hematological to adipose-rich marrow niches may result in a milieu that is more susceptible to trabecular disintegration and osteoclastic activation.[24] Its potential as a predictive biomarker is further supported by early longitudinal data showing that elevated periarticular BMA in early RA is linked to greater quantities of systemic inflammation (CRP, IL-6) and a higher chance of structural progression over the next 12 to 24 months.[7]

BMA changes under glucocorticoid therapy

Because of their strong anti-inflammatory properties and quick symptom relief, glucocorticoids continue to be a mainstay of RA treatment. However, more people are becoming aware of their skeletal adverse effects.

Mesenchymal stromal cell (MSC) lineage commitment is changed by prolonged glucocorticoid exposure, which inhibits osteoblast differentiation and increases adipogenesis.[32] Clinically, this shows up as increased risk for fractures, particularly in vertebral sites, decreased bone mineral density (BMD), and an increase in marrow fat.[33,34] Long-term corticosteroid users had greater marrow fat depots, which correlate with decreased arterial thickness and increased porosity, according to advanced MRI studies. In RA patients receiving glucocorticoid therapy, this paradox effective inflammatory control but harmful bone remodeling-highlights the necessity of concurrent bone-protective measures (e.g., bisphosphonates, vitamin D, exercise).

Impact of biologic and targeted therapies

Recent data indicates that specific synthetic DMARDs (tsDMARDs) and biologic DMARDs (bDMARDs) alter bone marrow obesity in addition to suppressing inflammation. Adipose distribution inside bone marrow niches appears to return to normal when systemic inflammatory cytokines are reduced by TNF-α antagonists, IL-6 receptor blockers, and JAK inhibitors.[35] According to small-scale MRI investigations, after TNF suppression, periarticular BMA expansion decreases, trabecular bone density increases, and erosion progression slows.[36,37] Early biologic therapy initiation may even completely prevent abnormal marrow fat buildup, according to certain data.

This suggests that, in addition to traditional disease activity measurements (DAS28, CRP), BMA decrease may act as a surrogate imaging biomarker for therapy success. These preliminary results imply that effective inflammation suppression indirectly modifies the marrow microenvironment, supporting bone health, although larger longterm investigations are required.

Translational significance

When considered collectively, clinical data indicates that BMA is a changing and susceptible to treatment compartment in RA rather than a passive bystander. In early RA, elevated marrow adiposity may serve as a possible target for treatment as well as a biomarker of the disease's progression.[38]

On the other hand, microstructural repair and decreased erosion risk may be reflected in the stabilization of marrow fat components with successful therapy.

In terms of translation, this creates three opportunities:

BMA as a diagnosing marker

Imaging-based measurement of bone marrow fat may enable early identification of RA, particularly in seronegative individuals with mild synovial alterations.[39]

BMA as a prognostic biomarker

Decisions on the strength of treatment may be guided by higher baseline BMA fractions, which may indicate more aggressive disease trajectories.[40]

BMA as a target for therapy

Rebalancing marrow microenvironments by the integration of pharmacological (DMARDs, metabolic modulators) and alternatives to drugs (exercise, nutrition) treatments may improve clinical outcomes and bone preservation.[41]

In order to determine causal links between BMA modulation and skeletal outcomes, future clinical research should combine quantitative imaging (MRI, MRS), serum adipokine profiling (leptin, adiponectin, resistin), and, if feasible, histological validation.

THERAPEUTIC IMPLICATIONS

Therapeutic approaches must go beyond merely controlling inflammation in light of the growing role that BMA plays in the etiology and development of RA.[42] Directly addressing BMA or indirectly through dietary, lifestyle, and metabolic changes provide a new complement to disease-modifying treatments.

These integrative methods may enhance long-term patient outcomes in addition to maintaining skeletal integrity (Table 1).

Lifestyle interventions

The compartment of BMA is dynamic and reacts to external biomechanical stimuli. In addition to inhibiting marrow adipogenesis, mechanical loading from weightlifting, resistance training, and organized physical activity promotes the osteogenic transformation of MSCs. In mice, treadmill running dramatically decreased BMA while increasing trabecular bone growth.[43] Exercise also causes the bone marrow microenvironment to change in favor of an osteogenic phenotype.[44]

Exercise therapies have been demonstrated in clinical settings to reduce functional impairment, maintain muscle mass, and increase BMD in RA patients without worsening inflammation.

Resistance training increases skeletal loading and osteogenesis, while low-impact aerobic exercises (such as walking, cycling, and swimming) improve systemic metabolism. Significantly, exercise lowers systemic inflammatory markers (TNF-α, IL-6, and CRP), which are strongly linked to the growth of marrow adipocytes.[45]

Lifestyle therapies therefore offer two advantages: (i) they prevent bone fragility and sarcopenia in RA, and (ii) they reduce the inflammatory contribution of marrow obesity to

the course of the disease. Personalized fitness programs could be a cheap and useful supplement to medication for the treatment of RA.

Metabolic modulators

A possible translational strategy is to pharmacologically target marrow adipogenesis. MSC differentiation is redirected toward osteoblasts and away from adipocytes by PPARγ antagonists like GW9662.[46] Such manipulation decreased marrow fat content and enhanced trabecular bone morphology in experimental models.

By decreasing bone marrow fat and promoting osteoblast development through AMPK activation, the popular antidiabetic medication metformin has demonstrated bone-protective properties.[47] It's possible repurposing in RA may assist the skeleton as well as the metabolism, particularly considering the high incidence of metabolic disorders in RA patients.

Because of their pleiotropic actions, statins increase osteoblast activity, decrease adipogenesis, and improve vascularization in bone marrow niches.[48] Additionally, they might reduce inflammatory signals, which would further connect immunoregulation and metabolic modification in RA. GLP-1 agonists, sclerostin inhibitors, and adipokine-targeted treatments (such as resistin or leptin modulators) are other possible metabolic regulators being studied. The impact they have on bone-fat crosstalk imply therapeutic efficacy, even though they haven't been studied in RA-specific cohorts yet.

Nutritional strategies

A convenient way to control BMA and systemic inflammation is by nutritional treatments. Omega-3 polyunsaturated fatty acids (PUFAs; EPA, DHA) decrease osteoclastogenesis, downregulate NF-κB signaling, and limit the release of pro-inflammatory adipokines.[49]

By reducing inflammation scores (DAS28) and NSAID needs, omega-3 supplementation has already demonstrated therapeutic benefits in RA, indicating an indirect function in BMA modulation.

Table 1: Therapeutic strategies targeting BMA in RA.

Interventions	Mode of action	Expected outcomes
Lifestyle interventions[44,49]	Reduce fat accumulation, increase osteoblast differentiation, reduce inflammation (CRP, IL-6, TNF-α)	Reduced BMA, increase trabecular bone density, improved physical function
Metabolic modulators[45,46]	Redirect MSCs from adipogenesis to osteogenesis; AMPK activation; reduce inflammatory signaling	Suppress adiopgenesis, increase osteogenesis, improved metabolic functions
Nutritional strategies[49,50]	No Pro-inflammatory adipokines, Activate Wnt/β-catenin signaling, reduce oxidative stress	Attenuation of marrow inflammation, improved BMD, reduced RA activity
Integration with DMARD therapy[10,51]	Reduce Inflammation driven BMA expansion, synergistic effects when combined with lifestyle/metabolic/ nutritional approaches	Superior structural preservation, reduced erosive damage, enhanced response rates

In RA, vitamin D insufficiency is common and is linked to increased bone fragility and BMA. According to Xu et al vitamin D increases osteoblastogenesis through Wnt/β-catenin signaling while suppressing adipogenesis.[50] In addition to increasing bone density and calcium balance, supplements help lessen the buildup of marrow fat. Marrow microenvironments may also be favorably impacted by other dietary elements such high-protein diets and polyphenols (curcumin, resveratrol). While a sufficient protein intake is necessary to maintain muscle mass, which implicitly guards versus marrow adiposity by enhancing biomechanical loading, polyphenols lower inflammation and oxidative stress. When combined, dietary modification targets both skeletal integrity and systemic inflammation, providing a preventive and supplemental approach to conventional RA treatment.

Integration with DMARD therapy

Because inflammation and BMA interact, treatment approaches shouldn't be divided into categories that are only immunosuppressive or skeletal-targeted. Although marrow fat distribution is normalized and systemic inflammation is decreased by biologic and targeted synthetic DMARDs (e.g., TNF-α inhibitors, IL-6 receptor blockers, and JAK inhibitors), their effects on BMA are indirect.[52] Through distinct but complementary processes, supplementary strategies exercise, metabolism modulators, and nutrition directly change the biology of BMAs and improve osteogenic pathways. Combining these strategies could have a synergistic impact that lowers local bone fragility and systemic inflammation.

In order to track changes in BMA in addition to more conventional outcomes (BMD, erosion scores), future clinical trials should: Include cutting-edge techniques for imaging (water-fat MRI, MR spectroscopy). To determine additive advantages, consider combinatorial approaches such as JAK inhibition with metformin or TNF-α blocker plus exercise. Examine biomarker-guided therapies, such as those that use circulating adipokines (leptin, adiponectin) as markers of therapeutic response.[51]

CONCLUSION

Once thought to be passive filler, BMA is now a very dynamic neuroendocrine and immunometabolic regulator that has a major impact on the pathophysiology of RA. According to clinical and experimental data, changed marrow fat dynamics happen early in the illness, frequently corresponding with BME and acting as an indicator of joint erosions. Beyond its link to skeletal fragility, BMA plays a key role in RA at the nexus of inflammatory and structural damage by actively influencing immune response, mesenchymal mesenchymal cell fate, and bone remodeling. The clinical significance of BMA is further demonstrated by therapeutic therapies. Biologics and specific synthetic DMARDs seem to be able to partially normalize myeloid fat distribution and restore bone microarchitecture, whereas glucocorticoids encourage marrow adipogenesis at the price of bone development. These findings demonstrate BMA's dual function as a possible biomarker of treatment response and a molecular cause of pathogenesis.

In order to establish BMA as a trustworthy clinical biomarker, it will be essential to combine serum adipokine profiling, histological investigations, and sophisticated imaging modalities as water-fat MRI and MR spectroscopy. Additionally, studies on lifestyle-based tactics, nutritional interventions, and metabolic modulators present intriguing chances to support immunosuppressive treatments in the treatment of RA. Future longitudinal research should concentrate on distinguishing between the adaptive and causative functions of BMA in order to ascertain whether modifying it directly results in better skeletal and functioning results. In conclusion, BMA is a translationally significant biomarker in RA as well as a unique pathogenic target. In addition to improving rapid detection and disease monitoring, a better knowledge of its biology may pave the way for integrative therapy methods that aim to reduce inflammation while maintaining skeletal integrity.

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REFERENCES

1. Raluchukwu EOO, Onubuogu AC, Ugochi CMJ, Tobechukwu OL. Status of erythrocyte sedimentation rate, platelet counts and serum phosphate in patients with rheumatoid arthritis in Owerri. Global Health Dynamics. 2025;1(1):14-9.
2. Chen Y, Deng B, Nie Y. Global burden and trend of rheumatic heart disease among women of childbearing age, 1990-2021, with projection to 2040. BMC Cardiovascular Disorders. 2025;25(1):580.
3. Finckh A, Gilbert B, Hodkinson, B. Global epidemiology of rheumatoid arthritis. Nature Rev Rheumatol. 2022;18(10):591-602.
4. Chopra A. Disease burden of rheumatic diseases in India: COPCORD perspective. Indian J Rheumatol. 2015;10(2):70-7.
5. Zúñiga A, Álvarez ALL, Carbal-Reyes L, Daniel R, Juan-Camilo D, Gloria V, et al. Survey to evaluate exposure to environmental factors in patients with rheumatoid arthritis. Reumatol Clín. 2025;21(6):501916.
6. Kumari M, Sadhu P, Shah N, Talele C, Gohil D. Comprehensive review of rheumatoid arthritis: insights, challenges, and prospects. J Adv Zool. 2024;45(1):567-75.
7. Moscatelli F, Monda A, Messina G, Elisabetta P, Marcellino M, Marilena DP, et al. Exploring the interplay between bone marrow stem cells and obesity. Int J Molecular Sci. 2024;25(5):2715.
8. Gao C. Preclinical assessment of novel strategies to enhance bone regeneration. Montreal, QC: McGill University. 2014.
9. Shin E, Koo JS. The role of adipokines and bone marrow adipocytes in breast cancer bone metastasis. Int J Molecular Sci. 2020;21(14):4967.
10. Li Y, Cao S, Gaculenko A, Yifan Z, Aline B, Xiaoxiang C. Distinct metabolism of bone marrow adipocytes and their role in bone metastasis. Front Endocrinol. 2022;13:902033.
11. Hawkes CP, Mostoufi-Moab S. Fat-bone interaction within the bone marrow milieu: impact on hematopoiesis and systemic energy metabolism. Bone. 2019;119:57-64.
12. Riaz M, Rasool G, Yousaf R, Hina F, Naveed M, Hasan E. Anti-rheumatic potential of biological DMARDs and protagonistic role of biomarkers in early detection and management of rheumatoid arthritis. Innate Immunity. 2025;31:17534259251324820.
13. Wang L, Zhang H, Wang S, Chen X, Su J. Bone marrow adipocytes: a critical player in the bone marrow microenvironment. Front Cell Developmental Biol. 2021;9:770705.
14. Mercier FE, Ragu C, Scadden DT. The bone marrow at the crossroads of blood and immunity. Nature Rev Immunol. 2012;12(1):49-60.
15. Pierce JL, Begun DL, Westendorf JJ, McGee-Lawrence ME. Defining osteoblast and adipocyte lineages in the bone marrow. Bone. 2019;118:2-7.
16. Zhang X, Tian L, Majumdar A, Scheller EL. Function and regulation of bone marrow adipose tissue in health and disease: state of the field and clinical

considerations. Comprehensive Physiol. 2024;14(3):5521-79.
17. Tencerova M, Ferencakova M, Kassem M. Bone marrow adipose tissue: role in bone remodeling and energy metabolism. Best Pract Res Clin Endocrinol Metabol. 2021;35(4):101545.
18. Nisar A, Jagtap S, Vyavahare S, Manasi D, Abhay H, Prabhakar R, et al. Phytochemicals in the treatment of inflammation-associated diseases: the journey from preclinical trials to clinical practice. Front Pharmacol. 2023;14:1177050.
19. Toussirot E. The contribution of adipokines to joint inflammation in inflammatory rheumatic diseases. Front Endocrinol. 2020;11:606560.
20. Bilski J, Schramm-Łuc A, Szczepanik M, Agnieszka Irena MB, Joanna B, Kevin L, et al. Adipokines in rheumatoid arthritis: emerging biomarkers and therapeutic targets. Biomedicines. 2023;11(11):2998.
21. Zhu J, Ruan G, Cen H, Tao M, Shuang Z, Yuanyuan W, et al. Association of serum levels of inflammatory markers and adipokines with joint symptoms and structures in participants with knee osteoarthritis. Rheumatology (Oxford). 2022;61(3):1044-52.
22. Roy PK, Islam J, Lalhlenmawia H. Prospects of potential adipokines as therapeutic agents in obesity-linked atherogenic dyslipidemia and insulin resistance. Egyptian Heart J. 2023;75(1):24.
23. Hu Y, Li X, Zhi X, Wei C, Biaotong H, Huiwen C, et al. RANKL from bone marrow adipose lineage cells promotes osteoclast formation and bone loss. EMBO Rep. 2021;22(7):e52481.
24. Fan Y, Elkhalek M, Zhang Y, Lu L, Qi T, Nareekarn C, et al. Bone marrow adipocytes: key players in vascular niches, aging, and disease. Front Cell Developmental Biol. 2025;13:1633801.
25. Mukohira H, Hara T, Abe S, Tani-Ichi S, Sehara-Fujisawa A, Nagasawa T, et al. Mesenchymal stromal cells in bone marrow express adiponectin and are efficiently targeted by an adiponectin promoter-driven Cre transgene. Int Immunol. 2019;31(11):729-42.
26. Comazzetto S, Shen B, Morrison SJ. Niches that regulate stem cells and hematopoiesis in adult bone marrow. Developmental Cell. 2021;56(13):1848-60.
27. Lundgren H, Martinsson K, Cederbrant K, Johan J, Daniel M, Madeyski-Bengtson K, et al. HLA-DR7 and HLA-DQ2: transgenic mouse strains tested as a model system for ximelagatran hepatotoxicity. PLoS ONE. 2019;12(9):e0184744.
28. Catrina A, Krishnamurthy A, Rethi B. Current view on the pathogenic role of anti-citrullinated protein antibodies in rheumatoid arthritis. RMD Open. 2021;7(1):e001228.
29. Ranneh Y, Ali F, Akim AM. Crosstalk between reactive oxygen species and pro-inflammatory markers in developing various chronic diseases: a review. Applied Biolog Chem. 2017;60(3):327-38.
30. Zhang S, Paul S, Kundu P. NF-κB regulation by gut microbiota decides homeostasis or disease outcome during ageing. Front Cell Developmental Biol. 2022;10:874940.
31. Melincovici CS, Boşca AB, Şuşman S, Mariana M, Carina M, Mihnea I, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Roma J Morphol Embryol. 2018;59(2):455-67.
32. Han L, Wang B, Wang R, Song G, Guo C, Weihua X, et al. The shift in the balance between osteoblastogenesis and adipogenesis of mesenchymal stem cells mediated by glucocorticoid receptor. Stem Cell Res Therapy. 2019;10(1):377.
33. Sheu Y, Amati F, Schwartz AV, Michelle ED, Xiaojuan L, Robert B, et al. Vertebral bone marrow fat, bone mineral density and diabetes: the Osteoporotic Fractures in Men (MrOS) study. Bone. 2017;97:299-305.
34. Kadri A, Binkley N, Daffner SD, Anderson PA. Clinical risk factor status in patients with vertebral fracture but normal bone mineral density. Spine J. 2022;22(10):1634-41.
35. Labella R, Vujačić M, Trivanović D. Bone marrow adipose tissue: regulation of osteoblastic niche, hematopoiesis and hematological malignancies. Stem Cell Rev Rep. 2023;19(5):1135-51.
36. Zerbini CAF, Clark P, Mendez-Sanchez L, Pereira RMR, Messina OD, Uña CR, et al. Biologic therapies and bone loss in rheumatoid arthritis. Osteoporosis Int. 2017;28(2):429-46.
37. Seo SS, Lee IS, Lee GH. Intra-articular injection therapy and biologic treatment. In A Strategic Approach to Knee Arthritis Treatment: From Non-Pharmacologic Management to Surgery. Singapore: Springer Singapore. 2021;171-212.
38. Veldhuis-Vlug AG, Rosen CJ. Clinical implications of bone marrow adiposity. J Internal Med. 2018;283(2):121-39.
39. de Sousa RN, Tascilar K, Corte G, Armin A, Ioanna M, Sarah O, et al. Metabolic and molecular imaging in inflammatory arthritis. RMD Open. 2024;10(1):e003880.
40. Chakraborty R, Majhail NS. Treatment and disease-related complications in multiple myeloma: implications for survivorship. Am J Hematol. 2020;95(6):672-90.
41. Lana JF, Purita J, Jeyaraman M, de Souza BF, Rodrigues BL, Huber SC, et al. Innovative approaches in knee osteoarthritis treatment: a comprehensive review of bone marrow-derived products. Biomedicines. 2024;12(12):2812.
42. Marinelli Busilacchi E, Morsia E, Poloni A. Bone marrow adipose tissue. Cells. 2024;13(9):724.
43. Gardinier JD, Rostami N, Juliano L, Zhang C. Bone adaptation in response to treadmill exercise in young and adult mice. Bone Rep. 2018;8:29-37.
44. Shi Z, Wang L, Luan J, Liqin Y, Xiaohui J, Wenqian Z, et al. Exercise promotes bone marrow microenvironment by inhibiting adipsin in diet-induced male obese mice. Nutrients. 2022;15(1):19.
45. Li Y, Jin D, Xie W, Longfei W, Weijian C, Jixi X, et al. PPAR-γ and Wnt regulate the differentiation of

MSCs into adipocytes and osteoblasts respectively. Current Stem Cell Res Therapy. 2018;13(3):185-92.
46. Mu W, Liang G, Feng Y, Jiang Y, Qu F. The potential therapeutic role of metformin in diabetic and non-diabetic bone impairment. Pharmaceuticals (Basel). 2022;15(10):1274.
47. Chamani S, Liberale L, Mobasheri L, Fabrizio M, Al-Rasadi K, Jamialahmadi T, et al. The role of statins in the differentiation and function of bone cells. Europ J Clin Investigat. 2021;51(7):e13534.
48. Abshirini M, Ilesanmi-Oyelere BL, Kruger MC. Potential modulatory mechanisms of action by long-chain polyunsaturated fatty acids on bone cell and chondrocyte metabolism. Progress Lipid Res. 2021;83:101113.
49. Sirico F, Bianco A, D'Alicandro G, Clotilde C, Stefania M, Rocco S, et al. Effects of physical exercise on adiponectin, leptin, and inflammatory markers in childhood obesity: systematic review and meta-analysis. Childhood Obesity. 2018;14(4):207-17.
50. Xu D, Gao HJ, Lu CY, Tian HM, Yu XJ. Vitamin D inhibits bone loss in mice with thyrotoxicosis by activating the OPG/RANKL and Wnt/β-catenin signaling pathways. Front Endocrinol. 2022;13:1066089.
51. Blaess J, Walther J, Petitdemange A, Jacques-Eric G, Jean S, Laurent A, et al. Immunosuppressive agents for rheumatoid arthritis: a systematic review of clinical trials and their current development stage. Therapeutic Adv Musculoskeletal Dis. 2020;12:1759720X20959971.
52. Li J, Wu J, Xie Y, Yu X. Bone marrow adipocytes and lung cancer bone metastasis: unraveling the role of adipokines in the tumor microenvironment. Front Oncol. 2024;14:1360471.
53. Howlader MSL, Das H. Multifaceted Role of Osteoclast in Bone Regeneratiom. In: Das, H. (eds) Tissue Repair and Regeneration. Springer, Cham. 2025.

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