Review article

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Advances in mechanism and management of bone homeostasis in osteonecrosis: a review article from basic to clinical applications

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Abstract

Osteonecrosis, characterized by bone cell death leading to impaired bone recovery, causes challenges in bone homeostasis maintenance. Bone homeostasis relies on the delicate balance between osteoclasts and osteoblasts, encompassing a series of complex and strictly regulated biological functions. Current treatments, including conservative therapies and surgeries, often fall short of expected outcomes, necessitating a reorientation towards more effective therapeutic strategies according to the pathogenesis. In this review, the authors hierarchically outlined risk factors, emerging mechanisms, and last-decade treatment approaches in osteonecrosis. By connecting mechanisms of bone homeostasis, the authors proposed future research directions should be focused on elucidating risk factors and key molecules, performing high-quality clinical trial, updating practice, and accelerating translational potential.

Keywords: bone homeostasis, osteonecrosis, pathogenesis, therapy

Introduction

Osteonecrosis, commonly referred to as avascular necrosis, atraumatic necrosis, aseptic necrosis, or ischemic necrosis, can result from trauma and has been regarded as a complication associated with autoimmune diseases[1]. The femoral head and jaw are the most affected parts during osteonecrosis, as a pathologic process of bone cell death partly due to an interruption of blood flow, limiting the delivery of oxygen and nutrients[2]. The mean age of presentation of osteonecrosis of the femoral head (ONFH) in the UK is 58.3 years, with a prevalence of 2 per 100 000 patients[3]. The incidence of osteonecrosis of the jaws ranges from 0.2 per 100 000[4] to 41.7%[5], depending on the received medication and primary diseases[6]. Some causative conditions have been reported, such as medication use, alcohol intake, hypercoagulation, bone marrow fat embolisms, high intraosseous pressure, and vascular endothelial dysfunction[7,8].

HIGHLIGHTS

- Osteonecrosis is related to the various regulatory mechanisms of bone homeostasis.
- Pregnancy, immune diseases (such as SLE, ALL, SCD), trauma, alcohol intake, glucocorticoid use, and bisphosphonates use are risks for osteonecrosis.
- Current pathways (such as PI3K/AKT, WNT/β-catenin, RANK-RANKL, IFN-β, JAK/STAT3, etc.) to the mechanisms and current treatments are logically connected and summarized hierarchically.
- Future research should be directed at identifying risk factors and key molecules, performing high-quality clinical trial, updating practice, and accelerating translational potential.

The most affected organ of this disease is bone, which ultimately results in structural changes, potential collapse, and destruction[9,10]. Bone undergoes a continuous cycle of formation by osteoblasts and resorption by osteoclasts, resulting in a dynamically changing tissue, even in the face of challenging conditions such as metabolic[11], immunological[12], or degenerative diseases[13]. Recent studies[14,15] have focused on the mechanisms that couple the relation between bone resorption and formation. Osteoblasts and osteoclasts, the primary cellular components of bone, delicately balance bone homeostasis. Additionally, osteocytes are ancient bone cells, and mechanosensing stellate cells that possess a remarkable ability to detect and respond to mechanical stimuli[16]. Osteocytes serve as crucial regulators of bone homeostasis by modulating osteoblast and osteoclast via the production of key signaling molecules in the WNT signaling and receptor activator of nuclear factor-κB ligand (RANKL) pathways[17]. These cells not only communicate among themselves[18], but also interact with other cells within the bone marrow, such as T and B cells, macrophages, adipocytes,

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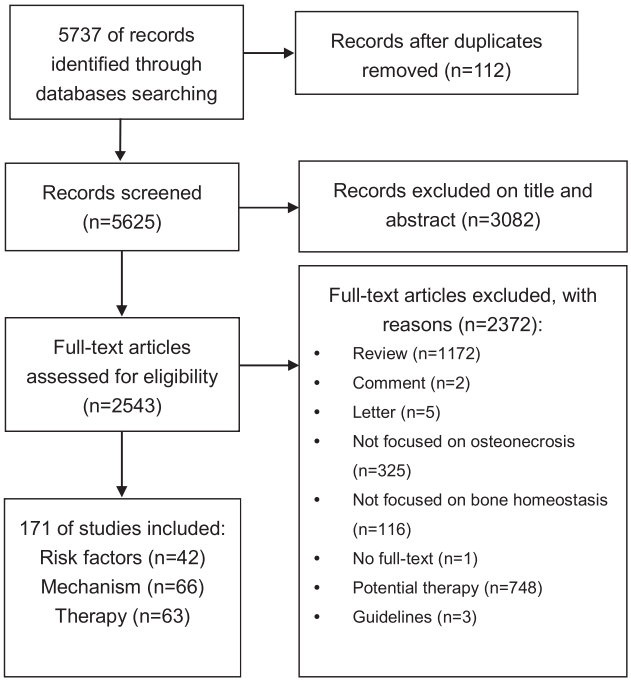

Figure 1. Study selection.

and hematopoietic pro-genitors[19,20]. Moreover, the processes of osteogenesis and angiogenesis are intricately connected, each relying on the other for proper function. Osteogenic cells secrete angiogenic factors to stimulate vessel growth and regulate functions, whereas endothelial cells secrete angiocrine signals that control bone remodeling[21].

Some guidelines and comments[22–24] about the prevention and treatment of ONFH and medication-related osteonecrosis of the jaw (MRONJ), especially by the Association Research Circulation Osseous (ARCO)[22], and the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO)[23] have published. The guidelines reported some strategies for therapy, and the clinical decision principally is made according to the disease stage and age. Among these, surgeries are important treatments for managing osteonecrosis, especially core decompression (CD). However, a meta-analysis study reported that the efficacy and effectiveness of CD alone for ONFH are no better than other joint-preserving strategies[25]. A clear summary with a classification of current therapies is necessary. Especially, with the development of regenerative medicine, surgeries with regenerative strategies should be comprehensively presented.

In general, the pathogenesis of osteonecrosis is complex and poorly understood. Moreover, the risk factors related to osteonecrosis should be presented to avoid. With the advancement of medical technology, more available therapies have emerged for use. Some novel technologies are still in the animal research stage, while others have already undergone clinical trials. In this review, we systematically searched and summarized recent evidence about the risk factors, pathogenesis of bone homeostasis, and treatment strategies in individuals with osteonecrosis. Moreover, we discussed the potential therapies that may be used for osteonecrosis in the future.

Methods

We searched Web of Science, PubMed, and Scopus Database from 2013 to December 2023, using the Mesh terms, keywords, and combinations, such as risk factor and (osteonecrosis or ONJ or ONFH), (pathology or molecular mechanism) and (osteonecrosis or ONJ or ONFH) and (bone homeostasis or osteoblast or osteoclast or MSC), (treatment or therapy or surgery or biomaterials) and (osteonecrosis or ONJ or ONFH) and clinical trials. The reference lists of the studies selected for full-text screening were manually searched to find potentially relevant articles. We included basic and experimental studies (*in vivo* or *in vitro*) that determined the molecular pathology. We also included the clinical studies that reported the risk factors of osteonecrosis and the current treatments for osteonecrosis. Comments, conference abstracts, reviews, guidelines, and letters to editors were not included in the review. Duplicate articles were eliminated, followed by a preliminary review based on titles and abstracts. Experimental studies about the management of osteonecrosis were excluded from the systematic review. The remaining relevant literature was incorporated based on the selection criteria outlined above after reviewing the full text.

Results

The flowchart demonstrates the study selection process in our study (Fig. 1). A total of 171 studies were included for describing the risk factors (42/171), basic studies that reported the potential bone homeostasis mechanisms of the disease (66/171), while others reflected the current therapy strategies for osteonecrosis (63/171).

Risk factors

Some diseases, such as immune-mediated diseases[26–37] and trauma[38–41] are known as usual risk factors. Moreover, the abusive consumption of alcohol[42–44] and prolonged use of steroids[45–50] have been recognized as promoting factors. Besides this, there are some conditions reported recently and the etiology of these risk factors and osteonecrosis need to be summarized. In this section, we focus on the relationships between the risk factors and osteonecrosis, and the risk factors and their associated incidence, prevalence, or relative risks are presented in Table 1.

Related primary diseases or history

The risk of osteonecrosis is highly associated with systemic lupus erythematosus (SLE), acute lymphoblastic leukemia (ALL)[26], sickle cell disease (SCD), and human immunodeficiency virus (HIV)[27,28], that requires dosage of steroids[29]. SLE is a chronic autoimmune systemic disease that requires high-dose initial corticosteroid treatment with a reported 26.9% of symptomatic osteonecrosis[30]. The incidence of osteonecrosis during antileukemic treatment has been investigated in many studies, but results range from 1.6 to 25%[31]. For ALL, hypertension is associated with an increased risk for symptomatic osteonecrosis[32]. Additionally, among children with ALL, increased risks were reported when receiving higher post-transplant steroid dosages and being older than ten years old at the time of transplantation[33–35]. SCD is one of the most common hereditary blood disorders and the prevalence of ONFH ranges from 3 to 50% among individuals with SCD, which is associated

Table 1

Summary table of risk factors and their associated epidemiology.

Classification	Risk factor	Epidemiology
Related primary diseases/history	SLE	Incidence: 26.9%[30]
	ALL	Incidence: 1.6–25%[31]
	SCD	Prevalence: 3–50%[36]
	HIV	Not specific
	Cancer (chemotherapy)	Incidence: 3.45% (HR for chemotherapy was 1.94)[51]
	Diabetes	1.16-fold increased risk vs. non-diabetes[52]
	Pregnancy	Prevalence: 0.375%[37]
Trauma/surgery	Fractures	Prevalence: 5%[39] (SIR 7.98/10 000 person-years[40])
	Tooth extraction	Incidence: 4.31%[53] (OR 7.6[54])
	Tooth extraction with periodontitis	HR 1.61[55]
Alcohol or medication use	Alcohol consumption	> 3-fold vs. non-drinkers[43,44]
	Bisphosphonates/denosumab	Varies with drug and duration. For bisphosphonates, HR was 2.62[56]. For denosumab, 1.95–3.49-fold increased risk vs. bisphosphonates[57]
	Glucocorticoids	Correlated with dose and duration

ALL, acute lymphoblastic leukemia; HR, hazard ratio; OR, odds ratio; SCD, sickle cell disease; SIR, standardized incidence ratios; SLE, systemic lupus erythematosus.

with the genotype and severity[36]. For the treatment of HIV, the mean daily oral dose of glucocorticoids (GCs) was 29 mg, and the average cumulative oral dose was 30 g over 5 years[27]. Moreover, women appear to have an increased relative risk of osteonecrosis during pregnancy[37]. Individuals receiving chemotherapy have a higher risk for MRONJ[51]. Additionally, patients with diabetes have an increased risk of developing osteonecrosis[58], which reported a 1.16-fold increased risk for ONFH[52].

Trauma or surgery

Fractures of the proximal humerus, intertrochanteric fracture, and femoral neck fracture are common with a similar rate of 7% of fractures. Due to the specific vascular anatomy, these fractures predispose the humeral head to osteonecrosis after trauma[38]. Post-traumatic ONFH is a serious consequence of femoral neck fractures, which can lead to femoral head collapse and the development of osteoarthritis[39,40]. Spontaneous osteonecrosis of the knee referred a subchondral fracture in the medial condyle, resulting in the collapse and the formation of necrotic tissue[41]. Tooth extraction is an additional risk factor for individuals diagnosed as MRONJ[53–55]. Moreover, extracting a periodontally compromised tooth might increase the risk of osteonecrosis that may be associated with the previous inflammation[55,59,60]. Inflammatory response is also a key progress for diabetes associated MRONJ[61].

Alcohol or medication use

Alcohol intake also accounts for non-traumatic osteonecrosis[42] and clinical studies demonstrated that alcohol intake increased the incidence of ONFH to more than 3-fold than non-drinkers[43,44]. Nonetheless, this study also illustrated that the added effect of alcohol should not superpose the overwhelming effect of steroids[44].

MRONJ is a serious disease that occurs in the jawbones and is related to anti-bone resorption drugs and anti-angiogenesis drugs, such as bisphosphonates[62,63] and denosumab[56]. Bisphosphonates, including zoledronic acid or zoledronate, alendronate, and pamidronate, are important pharmacological agents against osteoclast-mediated bone loss associated with various conditions, like osteoporosis, osteogenesis imperfecta, Paget's disease, hypercalcemia, and metastatic bone malignancies[64]. These medications promote the apoptosis of osteoclasts and play an important role in maintaining osteocyte homeostasis, which is crucial for the degradation of minerals on the bone surface. However, long-term bisphosphonate treatment and old age are more likely to induce osteonecrosis of the maxillary and mandibular bones[65]. Receiving the treatment of denosumab might have a 1.95–3.49-fold increased risk than receiving bisphosphonates[66,67]. Worse dental health is regarded as a bad influence on MRONJ[57].

The use of GCs as an anti-inflammatory and immunomodulatory agent plays a critical role in treating various conditions, including metabolic issues like osteoporosis and obesity, but multiple side effects can produce significant morbidity, with osteonecrosis being the most common[45]. GCs contribute to the development of osteonecrosis by inhibiting osteogenesis and angiogenesis, inducing endothelial damage, and thereby reducing blood supply, which results in programmed cell death and collapse. Many clinical trials have indicated that the type of steroid used, initial steroid dosage, tapering speed, concurrent medications, cumulative dosage, and overall duration are significantly linked to the risk of osteonecrosis[46–50].

Mechanism of imbalanced bone homeostasis in osteonecrosis

Osteonecrosis is a multifactorial disease for which the pathogeny is still unknown. The main pathological feature is the progressive death of bone cells. Bone homeostasis is a dynamic and complicated physical process that involves many specific cells (Fig. 2). Cellularly, bone homeostasis is mainly maintained by osteoblasts and osteoclasts, but the dynamic balance is much more complex, and many gaps remain in our knowledge. Phenotypes and molecular mechanisms of bone homeostasis related to osteonecrosis are presented in Fig. 3.

Viability and death of bone cells

Osteoblasts programmed cell death: The proliferation of osteoblasts is inhibited, and apoptosis is induced by dexamethasone, a type of long-effect GCs. Dexamethasone potentially attenuated

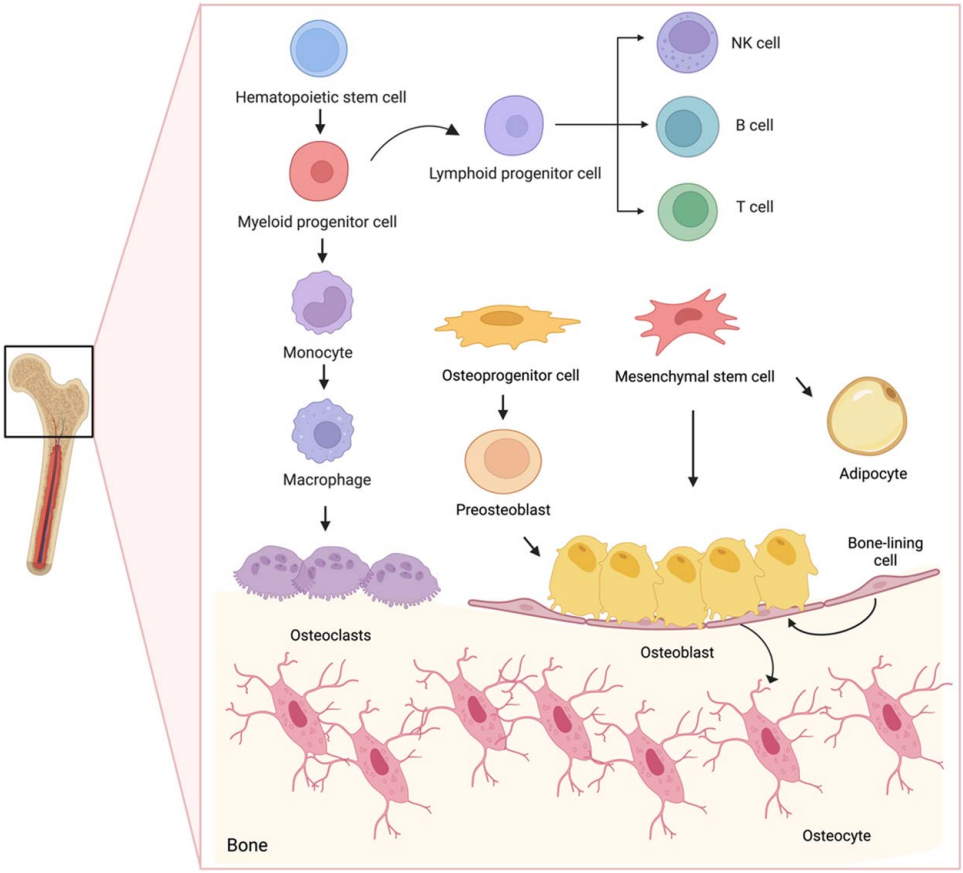

Figure 2. Overview of bone homeostasis and development of lineages. The delicate balance of bone homeostasis is accomplished by the actions of two types of cells: the osteoblast lineage and osteoclast lineage cells. Osteoblast lineage cells play a role in bone mineralization and the creation of osteocytes by excreting hydroxyapatite and calcium. In contrast, osteoclast lineage cells are involved in bone resorption.

osteoblast differentiation and increased intracellular reactive oxygen species (ROS) levels[68]. The activations of phosphatidylinositol 3-kinase (PI3K)/AKT pathway in osteoblasts were suppressed by down-regulating the expressions of p-PI3K and p-AKT, also the downstream (mTOR) was down-regulated[69]. Knockdown of glycogen synthase kinase 3β (GSK3β) alleviated dexamethasone-induced osteoblast apoptosis by decreasing the expressions of B-cell lymphoma-2 (BCL-2) Associated X Protein (BAX), cleaved-caspase-3, cleaved-caspase 9 and increased the expression of BCL-2[70,71]. Dexamethasone induction significantly reduced BCL-2 expression and increased the release of cytochrome c. Dexamethasone induced osteoblast apoptosis through the up-regulation of caspase-3 that mediated by signal transducer and activation of transcription (STAT) 1[72,73]. Yang *et al.*[74] found that the mediator of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family and apoptosis-related proteins, monoacylglycerol lipase (MAGL), was significantly upregulated during GCs treatment in osteoblasts. *Sirt6* is also affected in an osteonecrosis mouse model, and osteoblast/osteocyte-specific *Sirt6* knockout mice exhibited exacerbated bone loss and significant deformities[75]. Previous studies demonstrated that GCs upregulated antagonists for WNT/β-catenin signaling pathway, including Dickkopf1 (DKK-1) and secreted frizzled-related protein-1 (SFRP1) in osteoblasts[76]. As in mice, it displayed a three-fold rise in osteoblast apoptosis, and 28% of osteocyte apoptosis was detected in metaphyseal cortical bone[77]. Besides apoptosis, GCs induced ferroptosis of osteoblasts via P53/SLC7A11/GPX4 pathway[78].

Osteoclasts dysfunction: During homeostasis, osteoclasts meticulously resorb bone at specific locations, thereby ensuring the maintenance of a matrix with the appropriate levels of strength and resilience. A study indicated that the quantity, diameter, and nuclearity of osteoclasts were significantly elevated in specimens from individuals with MRONJ[79]. Furthermore, osteoclastic expression of nuclear factor of activated T cells-c1 (NFATc1), an essential regulator of osteoclastogenesis, was significantly increased[80,81] and the plasma levels of osteoprotegerin (OPG) and RANKL were notably higher in the individuals with ONFH than the health[82]. The RANK-RANKL axis was the most critical role in B-cell ALL-driven bone destruction[83]. NF-κB signaling also plays a critical role in the differentiation of osteoclasts. A study found that the level of IKKe was decreased in individuals with ONFH, and IKKe interacted with NF-κB-inducing kinase (NIK) to inhibit osteoclast activity by suppressing the transcription of *Nik*[84]. When the use of bisphosphonates combined with dexamethasone, the block of osteoclast differentiation was significant through the expression of IFN-β[85]. Furthermore, a study indicated that bromodomain-containing protein 9 (BRD9), a component of the non-canonical BAF chromatin remodeling complex, plays an important role in MRONJ. BRD9

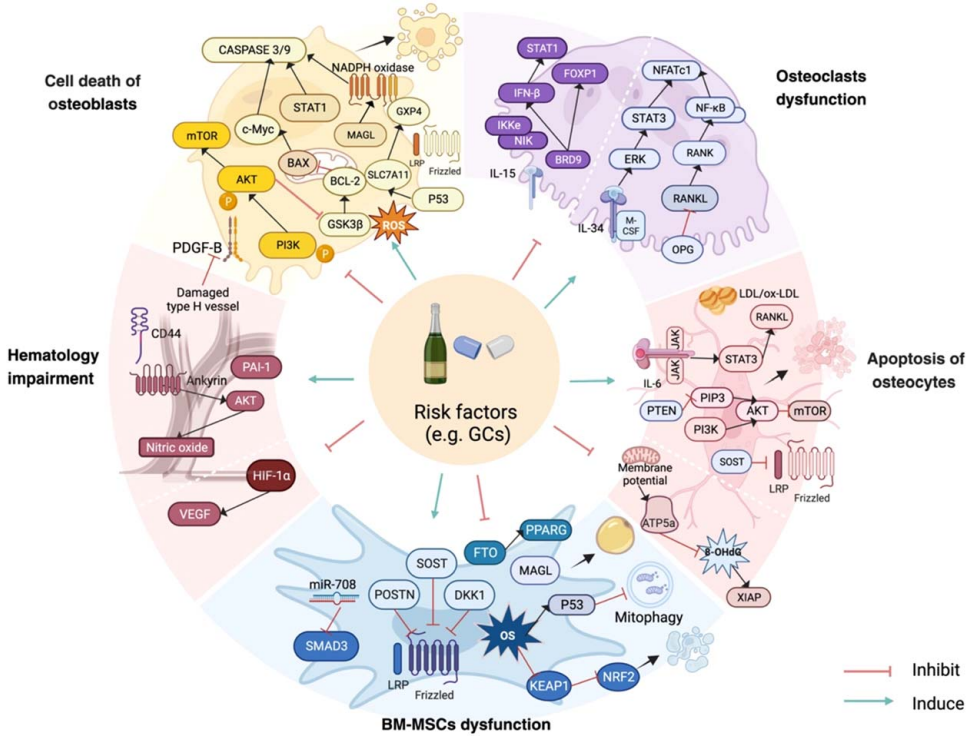

Figure 3. Phenotypes and molecular mechanisms of bone cells and vessels related to osteonecrosis. Osteonecrosis is a complex disease. Besides immune and inflammation factors, increased cell senescence, and fibrosis, it mainly involves the apoptosis of osteoblasts and osteocytes, adipogenic differentiation of BM-MSCs, and the dysfunction of osteoclasts and BM-MSCs with the existence of risk factors (e.g., the use of glucocorticoids). Moreover, hematology impairment also contributes to the progress and inhibits the AKT signaling pathway in osteoblasts. BM-MSC, bone marrow-derived-mesenchymal stromal cell; GC, glucocorticoids.

deficiency in the myeloid lineage promoted osteoclast differentiation and increased bone resorption by suppressing interferon-β signaling and interacting with the transcription factor FOXP1, which subsequently activated *Stat1* transcription[86].

Osteocytes apoptosis and differentiation: Osteonecrosis is characterized by excessive osteocyte death. For pathology, GCs induce osteocyte apoptosis, develop hyper-mineralization, and degeneration of the lacunocanalicular network rapidly, which resulting dysregulation of bone architecture and mineralization in human osteonecrosis[87]. Furthermore, there was a significant buildup of low-density lipoprotein (LDL)/oxidized LDL (ox-LDL) in the osteocytes (lacunae) of necrotic areas, in contrast to healthy regions. Cell studies demonstrated that ox-LDL reduced the viability of osteocytes and enhanced their apoptosis[88]. Both RANKL and sclerostin were markedly increased in bisphosphonates conditioned medium, moreover, Janus-activated kinase (JAK)/STAT3 pathway was subsequently activated with up-regulation of the RANKL[89]. Moreover, the phosphatase and tensin homolog (PTEN)-Protein kinase B (AKT) signaling[90,91] and PI3K/Akt/mTOR pathway[92] also participated in osteocyte apoptosis. Moreover, a study indicated that osteocytic cell death was linked to mitochondrial pathways. Exposure to either dexamethasone or hypoxia resulted in diminished mitochondrial membrane potential, reduced levels of ATP synthase (ATP5A), and increased expression of 8-OHdG, cleaved caspases, and the X-linked inhibitor of apoptosis protein (XIAP)[93]. Generally, the cross-talk between bone cells is complicated. A study showed that osteocytes in necrotic regions released damage-associated molecular patterns (DAMPs) which can be sensed by osteoclasts via macrophage-inducible C-type lectin (Mincle). Mincle activation triggered osteoclastogenesis via immunoreceptor tyrosine-based activation motif-based calcium signaling pathways, triggering bone loss[94].

BM-MSCs differentiation and apoptosis: An increase in bone marrow fat resulting from adipocyte accumulation is always regarded as a pathogenic process in osteonecrosis. Exposure to the saturated free fatty acids palmitate favored BM-MSCs (bone marrow-derived-mesenchymal stromal cells) differentiation through the adipogenic lineage at the expense of the osteoblastic phenotype. Additionally, BM-MSCs treated with steroids accumulated triglyceride, indicating that steroids increased the adipogenic differentiation of BM-MSCs[95]. Moreover, adipogenesis was intensified and the ability to differentiate into bone was deceased in BM-MSCs of osteonecrosis[96]. Fat mass and obesity (FTO), a key m^6A demethylase, was found to be significantly down-regulated in individuals with osteonecrosis by targeting PPARG and was markedly upregulated during the differentiation of human MSCs into osteoblasts[97]. One study indicated that the endogenous expression of periostin (POSTN) and SOST in BM-MSCs of ONFH was upregulated compared with developmental dysplasia of the hip group and partially inactivating the WNT/β-catenin signaling pathway[98]. The WNT pathway is a crucial signal transduction pathway. The extracellular protein DKK1 serves as. Corticosteroids upregulated DKK1 (a negative regulator in WNT signaling) expression in BM-MSCs, which led to the delay in bone phylogeny, regeneration, and remodeling[99,100].

The oxidative stress (OS) microenvironment of the necrotic regions leads to mitochondria damage ,stress-induced apoptosis, and senescence of BM-MSCs. The increased levels of protein 53 (P53) hindered the mitochondrial translocation of Parkin and activation of E3 ubiquitin ligase, leading to a reduction in mitophagy[101]. Moreover, the activation of SIRT3 is also related to OS[102]. A functional experiment demonstrated that inhibiting MAGL significantly decreased OS and partially protected BM-MSCs from apoptosis. Pathway analysis indicated that MAGL inhibition regulated oxidative stress in BM-MSCs through the Kelch-like ECH-associated protein 1 (KEAP1)/NRF2 pathway[74]. However, another study indicated BM-MSCs maintained mitochondrial function and exhibited reduced OS. Detailly, the mitochondrial membrane potentials remained stable[93].

Hematology impairment

Osteonecrosis involves the disruption of vascular supply to the bone and hypoxia microenvironment caused by impaired blood flow could be essential pathogenic factors. The increased levels of VEGF were reported to inhibit steroid-induced osteonecrosis in a rabbit model[46]. Additionally, VEGF, as a key mediator of angiogenesis, stimulated endothelial cell proliferation, differentiation, and survival that assessed by tube formation experiments and related to interferon-induced transmembrane protein 1[103]. It was challenging to detect HIF-1α and VEGF in the human femoral head at end-stage ONFH, which indicated that the impairment of vascular network formation and reduced osteogenic activity ultimately led to osteonecrosis[104]. Besides VEGF, ankyrin was a cytoskeletal protein that interacted with CD44 to promote endothelial nitric oxide synthase expression and tissue nitric oxide levels via the Akt signaling pathway[105]. Moreover, PTEN promoted endothelial progenitor cell apoptosis under GC condition[106]. Another reasonable mechanism was that increased PAI-1 reduced fibrinolytic function, and lastly accelerated the process of ONFH by reducing the femoral head blood flow[67]. In juvenile mice induced by GCs, it was reported that bone angiogenesis and type H vessel (in the primary spongiosa, where trabecular bone formation begins) were disrupted, which was linked to reduced PDGF-B expression in preosteoclasts[107].

Immune and inflammation factors

The immune and skeletal system have been revealed that crossly interacted by cytokines, chemokines, receptors, signaling molecules, and transcription factors. Previous studies have suggested that activated T/Th1 cells and B cells stimulated the high expressions of RANKL and OPG in individuals with ONFH. In detail, $CD4^{+}$Th17 cells raised the levels of RANKL and cytokines (such as TNF-α, IL-23, IL-17[83], and IL-15[108]). IL-34 alone or works in coordination with macrophage-colony-stimulating factor (M-CSF) to promote osteoclastogenesis and activate extracellular regulated protein kinases (ERK), STAT3, and non-canonical NF-κB pathways, which may contribute to ONFH[109]. Moreover, immunohistochemistry results indicated that the M1/M2 polarization ratio increased from 3 to 10 as the condition progressed from the progressive to the end stage[110]. As for MRONJ a significant increase in M1 polarization also contributed to the progress[111]. Moreover, the establishment of unique bacterial communities, along with a weakened innate immune response, could be likely to influence disease progression[112]. Bisphosphonates treatment of dendritic cells caused an impairment in immune functions including differentiation, maturation, migration, antigen presentation, and T-cell activation *in vitro*[113]. After injecting mice with bisphosphonates and tooth extraction, immune cells from bone marrow and spleen, and purified natural killer cells from the spleen showed high induction of IFN-γ and natural killer cell-mediated cytotoxicity except for gingiva in which immune cells were in contrast[114,115]. Moreover, exposure to bisphosphonates resulted to impaired neutrophil chemotaxis, decreased neutrophil NADPH oxidase activity, and a lower number of circulating neutrophils[116].

The production of inflammatory cytokines plays an important role in the pathogenesis. Nod-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome, caspase-1, and IL-1β in macrophages contributed to the persistent inflammation[61,117]. There was a debate about the existence of TNF-α. Zheng and their colleague figured that TNF-α induces the apoptosis of osteoblasts with a high expression in necrotic regions[118], while Fang *et al.*[119] demonstrated that the content of TNF-α in necrotic tissue is much lower than that of normal tissue. TNF-α is also related to autophagy, which is beneficial for interrupting the process of osteonecrosis, therefore TNF-α might should not be considered as a therapeutic target. IL-9 was also highly expressed in osteonecrosis, leading to an elevated level of inflammation-related cytokines and cartilage matrix-degrading enzymes, alongside heightened activation of JAK-STAT signaling[120].

Fibrosis and other novel findings

A recent study figured that the extension of fibrosis on specimens from biopsies in ONFH is a predictor of the outcome of the core decompression[121]. In Legg-Calvé-Perthes disease (LCPD), an increased fibrous tissue and adipose tissue was detected in the bone marrow space and a decreased osteogenesis was reported in a piglet model[122]. However, the mechanisms of fibrosis are merely explored.

Chen *et al.* found that hsa-miR-200b-3p and hsa-miR-206 in urinary exosomes might serve as non-invasive biomarkers for GCs-induced ONFH and the Hippo, PI3K-AKT, TGF-β and Wnt signaling were enriched in bioinformation analysis[123]. Shen and their colleague indicated that zoledronic acid activated the NF-κB signaling pathway and macrophages derived miR-149-5p regulate biological functions of endothelial cells via the Rap1a/Rap1b/VEGFR2 pathway[124]. MiR-708 was also found to be upregulated in individuals with ONFH and in cell experiments. It targeted SMAD3 and inhibited osteogenic differentiation and adipogenesis of MSCs[125]. An increase in miR-141[126] and reductions in miR-17-5p[127], miR-21-5p[128], miR-4523[129], miR-122-5p[130], and miR-26a[131] are potential mechanisms for ONFH. Furthermore, Fang *et al.*[132] found that tsRNA-10277 was significantly down-regulated in plasma exosomes of individuals with GCs-induce ONFH compared to that in healthy individuals and tsRNA-10277 showed positive effects on osteogenic differentiation ability of BM-MSCs *in vitro*.

Advancements in decade for prevention and treatment of osteonecrosis

The studies published in the past decade related to clinical use and effectiveness included in this review are summarized in Table 2. A

Table 2

Characteristics of included studies about clinical use and effectiveness.

Author, year	Study design	Disease type	Sample size (*M*)	Dosage	Intervention	Comparison	Outcomes	Finding	Ref.
Hernigou *et al.* 2018	Case series	ONFH after pregnancy	145	150 ml of marrow	MSCs	NA	HHS, VAS, MRI, and conversion rate to THA	Patients with ONFH following pregnancy had a low conversion rate to THA when treated early with cell therapy.	[37]
Hernigou *et al.* 2021	Case-control study	Osteonecrosis of the humeral head	64	20 ml, average 8500 MSCs/ml (range 3430–17 540)	CD+BM-MSCs	CD	Rate of collapses and humeral head survival rate	BM-MSCs therapy reduced the rate of collapses and shoulder arthroplasty.	[38]
Hernigou *et al.* 2021	Case-control study	ONFH	46	20 ml, 9300 MSCs/ml (range 3930–19 800)	BM-MSCs	THA	VAS, HHS, and radiographs	For BM-MSCs therapy, better survival time before revision were obtained for treatment at early stages before collapse.	[39]
Vezzani *et al.* 2017	Case series	ONFH	23	100% oxygen at 2.4 ATA in a multi-place pressure chamber for 90 min using an over- board demand regulator while breathing through an oral-nasal mask for 5 days/week, 6 weeks	Hyperbaric oxygen therapy	NA	VAS, MRI, and serum OPG	HBOT significantly reduced pain and lesion size, and increased serum OPG levels.	[133]
Wang *et al.* 2016	RCT	ONFH	33	2000/4000/6000 impulses of ESWT at 24 Kv	ESWT	Differed impulses	VAS, HHS, MRI, plasma volume, and blood tests	Significant differences of pain and HHS were noticed, and high dosage ESWT is more effective in early-stage ONFH.	[134]
An *et al.* 2022	Non-RCT	ONFH	71	O_2–O_3 mixture was 30 ml at a concentration of 30 μg/ml	Ozone therapy	Protected weight bearing	VAS, HHS, bone marrow edema examination, and conversion to THA	Ozone therapy effectively improves pain function, bone marrow edema of the femoral head, and delay the need for THA.	[135]
Marcheggiani Muccioli *et al.* 2013	Case series	Osteonecrosis of the knee	28	6 h daily for 90 days, 1.5 mT, 75 Hz and a duty-cycle of 10%	PEMFs	NA	MRI, VAS, KSS, EQ-5D scales, and failures	PEMFs significantly reduced knee pain and necrosis area, preserving 86% of knees from prosthetic surgery at 24-month follow-up.	[136]
Atoun *et al.* 2016	Case series	SONK	17	10 min/day during the first week, while performing daily routine (accumulating 5 min of walk), then gradually increased walking time reaching 60 min/day (accumulating 30 min of walk)	Biomechanical device consisted of two convex-shaped biomechanical elements	NA	Spatiotemporal gait assessment, WOMAC, SF-36	A significant reduction in pain and improvement in function was seen after 3 months of therapy with additional improvement after 6 months of therapy.	[137]
Hernigou *et al.* 2021	RCT	Ankle osteonecrosis	51	5 or 10 ml (<11 or >10 years old), 1021 MSCs/ml (range 314–3015)	BM-MSCs ± CD	Without treatment	Pain, foot and ankle deformity according to the Mazur score, and MRI	Autologous BM-MSCs can improve the quality of life of leukemia survivors with ankle osteonecrosis.	[138]
de Rojas *et al.* 2018	Case study	MRONJ	2	50×10^6 BM-MSCs	BM-MSCs	NA	HHS, VAS, Gait analysis, consecutive radiographs, and MRI	Autologous MSCs can relief pain and improve function for children and young adults after overcoming ALL without positive outcomes in radiographs.	[139]
Hernigou *et al.* 2018	RCT	Osteonecrosis of the knee	30	6500 MSCs/ml	Subchondral stem cell therapy	Contralateral TKA	Subsequent re-operations, KSS, radiographs, MRI, and safety	Improvements on KSS and radiographs were similar and a higher number of thrombophlebitis was observed on the side with TKA (15%).	[140]
Pan *et al.* 2020	Cohort study	ONFH	35	GCSF (5 μg/kg/day, 5 days), $(5–8)\times 10^8$ cells/kg	Autologous PBSCs	NT	Hip-preservation failure, BMI, HHS, and necrotic volume	Intra-arterial infusion of autologous PBSCs prolonged femoral head survival. Age, BMI, HHS, and necrotic volume can influence the efficacy.	[141]
Chen *et al.*	Case series	ONFH	9	MSCs (10 ml) with a cell density of	Transplant of hUC-	NA	Oxygen delivery index, MRI, and	Intra-arterially infused hUC-MSCs migrate into	[142]

Table 2

(*Continued*)

Author, year	Study design	Disease type	Sample size (*M*)	Dosage	Intervention	Comparison	Outcomes	Finding	Ref.
2016	study			$5–10\times10^6$/ml	MSCs		adverse events	the necrotic field of femoral heads and differentiate into osteoblasts, thus improving the necrosis of femoral heads.	
Mao *et al.* 2013	Case series	ONFH	62	BM-MNCs (30–60 ml) were gained from autologous bone marrow (100–200 ml)	BM-MNCs	NA	Ficat stage, HHS, and rate of THA	BM-MNCs relieved symptoms, improved hip function and delayed the progression of ONFH.	[143]
Meier *et al.* 2014	RCT	Osteonecrosis of knee	30	Cumulative dose, 13.5 mg, 12 weeks	Diclofenac (70 mg) +calcium carbonate (500 mg)+vitamin D (400 IU) +ibandronate	Diclofenac (70 mg) +calcium carbonate (500 mg) +vitamin D (400 IU)	VAS, WOMAC, IKDC, and MRI	Bisphosphonate treatment has no beneficial effect over and above anti-inflammatory medication for spontaneous osteonecrosis of the knee	[144]
Pichardo *et al.* 2018	Case study	MRONJ	15	NT	Surgery+soft diet +antimicrobials	Surgery	Panoramic radiographs	Surgical and/or antimicrobial approach, combined with intermaxillary fixation on occasion can lead to consolidation.	[145]
Sim *et al.* 2020	RCT	MRONJ	34	20 μg/day, 8 weeks	Calcium and vitamin D supplementation +teriparatide	Calcium and vitamin D supplementation	Radiographs, osteoblastic responses, and changes in quality of life	Teriparatide was associated with a greater rate of resolution of MRONJ lesions and reduced bony defects.	[146]
Jung *et al.* 2017	Case-control study	MRONJ	17	Absorbable collagen plugs soaked by rhBMP-2 for 20 min, a daily subcutaneous injection of 20 μg teriparatide for 1–4 months	rhBMP-2 ± teriparatide	Seques rectomy	CT, serum osteocalcin, and serum C-terminal telopeptide cross-link of type I collagen	Significantly greater amount of bone formation was observed in the group teriparatide+BMP than in the BMP and sequestrectomy groups.	[147]
Laimer *et al.* 2017	Case study	MRONJ	3	ActiV.A.C. therapy unit (V.A.C. Therapy, KCl USA, Inc., San Antonio, TX)	VAC	NA	VAS and descriptive analysis of sites	Intraoral VAC therapy promoted formation of new granulation tissue, cessation of pain and pus suppuration without significant side effects.	[148]
Yue *et al.* 2020	Case study	ONFH	53	NA	Double-channel CD +bone grafting	NA	Need for arthroplasty, HHS and CT	This way was effective, and 4 hips were found to require arthroplasty.	[149]
Wang *et al.* 2020	Cohort study	ONFH	125	NT	Light bulb procedure through the direct anterior approach	CD	Length of surgery, intraoperative blood loss, VAS and range of hip motion	There was no significant difference in quality of functional recovery and clinical outcomes within 1 year after surgery between the 2 groups.	[150]
Civinini *et al.* 2017	Self-controlled study	ONFH	12	$CaSO_4$:$CaPO_4$ = 3:1	CD+$CaSO_4$/$CaPO_4$ composite	NA	CT	The mean Hounsfield units in the immediate postoperative period was 1445, and CaSO4-CaPO4 ceramic composite provided an ideal environment for the direct new bone growth.	[151]
Landgraeber *et al.* 2017	Case series study	ONFH	25	A cylinder with a length of about 3.5–4 cm	CD+autologous bone impaction	NA	The survival rate of the femoral head, HHS, VAS, MRIs, and X-rays	This surgery reduced pain and increased function in all participants with a hip survival rate of 75.9%.	[152]
Fontecha *et al.* 2016	Case series study	ONFH	9	The fibular grafts were divided into three regions: greater trochanter, femoral neck, and femoral head	Bone grafting	NA	HHS, graft failure, and SPECT/CT	HHS increased and SPECT/CT findings revealed a progressive increase of femoral head uptake, suggesting subchondral graft bone viability. No progressive deformation was evidenced in radiographic evaluation.	[153]
Cao *et al.* 2017	RCT	ONFH	33	NT	Vascularized fibular grafting	CD	SPECT/CT, MRI, ARCO staging, and HHS	A vascularized fibular grafting was better than CD as measured by improved vascularity and less progression and better function.	[154]

Chen *et al.* 2019	RCT	ONFH	66	Metal trabecular bone with bone dust or free fibula bone (6–8 cm)	Metal trabecular bone reconstruction system	Free vascularized fibular graft	Stress concentration, stress peak value, HHS, VAS, and SF-36	Metal trabecular bone reconstruction system provided less operation time, blood loss, and the total length of postoperative hospital stay and promoted bone reconstruction, increased bone mineral density and HHS.	[155]
Sun *et al.* 2023	RCT	ONFH	37	3×3×1 cm	Biodegradable magnesium screw in pedicled vascularized iliac bone graft transfer	Titanium screw and direct embedding fixation	HHS, MRI, and serum magnesium	Pedicled vascularized iliac bone graft transfer improved HHS, and biodegradable magnesium screws was better for angiogenesis.	[156]
Zhang *et al.* 2022	Case study	ONFH	1	(4–5) cm×(1.5–2) cm×(1.5–2) cm	Vascularized bone grafting	NA	HHS, CT, and mechanical analysis	One year after operation, HHS was improved to 81 points, and no local collapse or micro-fracture occurred.	[157]
Aoyama *et al.* 2014	Case series	ONFH	10	Aspirated bone marrow (25 ml)	BMSCs+bone grafts	NA	X-ray, CT, hip score defined by the JOA, and adverse event	Progression of the radiological stage and changes in bone volume at the femoral head, and clinical score.	[158]
Zhao *et al.* 2016	Self-control study	ONFH	48	Elastic modulus of pure Mg ranged from 38–45 GPa	Vascularized bone grafting fixed+Mg screws	Vascularized bone grafting fixed	HHS, X-ray, and postoperative serum levels of Ca, Mg, and P	The use of biodegradable Mg screws improved HHS and may provide a promising bone graft–screw fixation route in treating ONFH.	[159]
Kang *et al.* 2013	Self-control study	ONFH	52	2.7×10^7 BMSCs	BMSCs+bone grafts	NA	X-ray and MRI	For medium-sized lesions, this procedure generated clinical results comparable to those of other head preserving procedures.	[160]
Windisch *et al.* 2014	RCT	ONFH	35	20 Hz, 5 mT	Bone grafting +electromagnetic field	Bone grafting	VAS, HHS, and MRI	Electromagnetic field treatment as an adjunct to curettage and autologous bone grafting to treat ONFH did not produce better clinical results	[161]
Morita *et al.* 2017	Case study	ONFH	90	NA	Transtrochanteric rotational osteotomy	NA	Conversion to THA and radiological failure	Survival rates at 15 years with conversion to THA and radiological failure as the endpoint were 59% and 30%, respectively.	[162]
Utsunomiya *et al.* 2017	Case study	ONFH	20	NA	Transtrochanteric rotational osteotomy +THA	THA	HHS, ROM, operation time and greater intraoperative blood	THA after osteotomy were comparable with those of THA without any antecedent surgery for ONFH.	[163]
Osawa *et al.* 2020	Case study	ONFH	105	NA	Curved Intertrochanteric Varus Osteotomy	THA	HHS, SF-36, JHEQ, UCLA, OHS, complication and survival rates	Functional outcomes, survival rate, and sporting activities for patients <50 years old were comparable after a 10 years follow-up.	[164]
Osawa *et al.* 2021	Cohort study	ONFH	81	NT	Osteotomy+bone grafting	Osteotomy	ROM, HHS, OHS, and JHEQ	No improvements in treatment results with the concomitant use of bone grafting.	[165]
Miladi *et al.* 2018	Comparative Study	ONFH	16	RHINO (ATF, Marignier, France) vs. Osteal (CERAVER, Roissyen-France, France)	Uncemented short arthroplasty	cemented conventional arthroplasty	VAS, PMA, HHS, and radiography	Uncemented short stems total hip arthroplasties gained similar results for pain and function, but less stress shielding and a bone stock economy.	[166]
Kim *et al.* 2021	Cohort Study	ONFH	150	A cementless THA was performed using hemispheric porous-coated acetabular components	Allogeneic bone marrow transplantation+THA	THA	HHS, rates of reoperation, a 90-day readmission, and mortality	Contemporary cementless THA in young hematological disease patients after allogeneic bone marrow transplantation was not associated with a higher risk.	[167]
Voss *et al.* 2017	Case study	MRONJ	6	60 ml of bone marrow cells	Surgical resection of necrotic bone followed by MSCs grafting	NA	X-ray, CT, and description about wound closure	Surgical management in combination with MSCs trans- plantation showed satisfactory healing with no signs of wound infection.	[168]
Calvani *et al.* 2018	Case-control	MRONJ	26	15% bovine lactoferrin	Antibiotic therapy +surgery+bovine lactoferrin	Antibiotic therapy +surgery	Healing of wounds	Bovine lactoferrin leaded a significant shorter time of wound closure.	[169]

Table 2

(*Continued*)

Author, year	Study design	Disease type	Sample size (*M*)	Dosage	Intervention	Comparison	Outcomes	Finding	Ref.
Mao *et al.* 2015	RCT	ONFH	55	COBE spectra apheresis system	Porous tantalum rod implantation +PBSCs	Porous tantalum rod implantation	HHS, X-ray, and rate of THA	PBSCs showed a significant difference in the survival time to THA and improvement in HHS.	[170]
Hauzeur *et al.* 2018	RCT	ONFH	19	400 ml of bone marrow	CD+BMAC	CD	VAS, WOMAC, MRI, decision to THR, and safety	No differences were found between the groups for THR requirements, clinical tests, and radiological evolution.	[171]
Boontanapibul *et al.* 2021	Retrospective study	ONFH	66	5 ml	CD+BMAC	CD	Rates of femoral head collapse, conversion THA, and survival rates	BMAC had more reliable outcomes than isolated core decompression for pre-collapse ONFH	[172]
Hernigou *et al.* 2021	RCT	Shoulder osteonecrosis	50	20 ml	CD+BM-MSCs	CD	VAS, Constant score, number of collapse, and survival rates for further shoulder arthroplasty	CD with cell therapy was a safe and effective procedure for relief pain and improving function, which reduced the rate of collapses and the need of shoulder arthroplasty.	[173]
Daltro *et al.* 2015	Non controlled study	ONFH	89	30 ml of stem cells	CD+BM-MSCs	CD	VAS, HHS, radiography, and specific biomolecular characteristics	The autologous BM-MSC implantation with a minimally invasive technique resulted in significant pain relief and halted the progression of early stages of ONFH in SCD patients.	[174]
Lim *et al.* 2013	Case-control	ONFH	128	30 ml of stem cells injected ($CD34^+$ cells were 1.69×10^7 cells	Multiple drilling and stem cell implantation	CD and bone graft	HHS, X-ray, and rate of success (HHS > 75 and no need for surgery)	There were no statistically significant differences between the groups in terms of success rate or in the clinical and radiographic results of the two methods.	[175]
Blanco *et al.* 2023	Case series	ONFH	8	5 ml with 20×10^6 cells/ml	MSCs after surgery	NA	VAS, HHS, SF-36, and CT	Use of autologous MSCs for patients with ONFH improved pain and radiology.	[176]
Mardones *et al.* 2019	Case series	ONFH	5	40×10^6 ex vivo-expanded BM-MSCs	CD+Ex vivo-expanded BM-MSCs	NA	HHS, VAS, X-ray, and MRI	Ex vivo-expanded BM-MSCs combined with CD improved the symptoms and radiography.	[177]
Hernigou *et al.* 2018	Case-control study	ONFH	125	152 ± 16 ml of marrow	CD+percutaneous BM-MSCs injection	CD	Rate of collapse, need for THA, MRI	CD with bone marrow injection improved the prevalence of collapse, need for THA, and percentage of the necrosis volume of the femoral head as compared with CD alone in the same individual.	[178]
Hernigou *et al.* 2018	Cohort study	Talus osteonecrosis	45	124×10^3 cells	CD+BM-MSCs	CD	Clinical, radiographic evolution, and colony forming unit	Collapse frequency was lower, and follow-up showed longer duration of survival before collapse for concentrate bone marrow grafting.	[179]
Wu *et al.* 2020	Case series	ONFH	30	Patients received recombinant GCSF (30IU IM qd×5 days), 100 ml of bone marrow and 100 ml of peripheral blood	CD+BM-MSCs	NA	HHS, MRI, and osteogenic and chondrogenic differentiation of BM-MSCs	Higher osteogenic and chondrogenic differentiation ability leaded to better repair in the necrotic area and clinical outcomes.	[180]
Emadedin *et al.* 2019	Case series	ONFH	9	Isolated $CD133^+$ cells (from 100–150 ml of heparinized bone marrow) in 30 ml normal saline that contained 2% autologous serum	CD+Autologous bone marrow-derived $CD133^+$ cells	NA	MRI, VAS, HHS, WOMAC and walking distance	A single bone marrow-derived $CD133^+$ cell injection during CD was effective in providing significant, clinically relevant pain relief and function.	[181]
Aoyama *et al.* 2015	Case series	ONFH	10	ROM, progressive muscle-strengthening and aerobic exercises with target heart	Exercise after MSC transplantation	NA	ROM, muscle strength, Timed Up and Go test, and SF-36	External rotation ROM as well as extensor and abductor muscle strength significantly	[182]

				rate of 220×(age×0.6)	augmented by vascularized bone grafting			improved, improvements were also seen in physical function, role physical, and bodily pain subgroup scores of the SF-36.	
Jayankura *et al.* 2023	RCT	ONFH	49	(0.5–1)×10^6 cells/kg	CD+autologous osteoblastic cell transplantation	CD	WOMAC pain subscale, radiologic response, adverse events, and serious adverse events	No advantage of autologous osteoblastic cells to improve the results of core decompression in early-stage (pre-collapse) ONFH.	[183]
Hauzeur *et al.* 2020	RCT	ONFH	56	400 ± 85 ml of autologous bone marrow	CD+osteoblastic cell therapy	CD+BMAC	VAS, WOMAC, and the Lequesne indexes	For pain relief and function, no benefit to osteoblastic cells over BMAC in patients with pre-collapse ONFH.	[184]
Hernandez *et al.* 2020	Self-controlled study	ONFH	13	60 ml of bone marrow (10 ml of progenitor stem cells)	CD+autologous BMAC+tricalcium phosphate	NA	HHS, radiological data, time of femoral head collapse and need for THA	HHS was improved, but no improvement in preventing progression to collapse. Overall median survival with the THA was 23 months.	[185]
Kuroda *et al.* 2016	Case study	ONFH	10	800 μg	Gelatin hydrogel impregnated with rhFGF-2	NA	VAS, UCLA activity score, HHS, and CT	Clinical application of rhFGF-2-impregnated gelatin hydrogel for patients with pre-collapse ONFH reduced pain and improved function.	[186]
Kuroda *et al.* 2021	Self-controlled study	ONFH	64	800 μg	Recombinant human FGF-2	NA	Collapse rate, assessment of imaging for bone regeneration, HHS, UCLA activity rating scale, and adverse events	Recombinant human FGF-2 safely increased the joint preservation time with activity improvement and radiological bone regeneration.	[187]
Gao *et al.* 2016	Case series study	ONFH	51	100–180 ml of bone marrow blood, 4 mg rhBMP-2 injected into the femoral head	CD+BMSCs +rhBMP-2	NA	VAS, HHS, and X-ray	86.3% patients had improved clinical outcome, and 17.6% of the hips exhibited collapse onset or progression radiologically.	[188]
Ragazzo *et al.* 2022	RCT	MRONJ	27	3×3 cm patches and cryopreserved	Surgery+HAM	Surgery	VAS and orthopantomography	HAM reduced the pain and did not lead to relapse.	[189]
Odet *et al.* 2022	Case series	MRONJ	8	4.7 cm in diameter or 3×3 cm patches and cryopreserved	HAM+Surgery	HAM	Bone re-exposure, VAS, positron-emission tomography, and adverse events	HAM showed immediate significant pain relief with no infections.	[190]
Bouland *et al.* 2021	Case report	MRONJ	2	30 mL of AT, and 48.1×10^6 viable cells in the L-PRF	Surgery+SVF+MSC +EPC+L-PRF	NA	Orthopantomogram and CT-scan	The buccal mucosa was closed within a month. No recurrence was observed.	[191]
Park *et al.* 2017	Case-control study	MRONJ	55	20 ml of blood was collected without anticoagulant and centrifuged at 3000 rpm for 10 min, 0.5 ml rhBMP-2 solution and hydroxyapatite	Surgery+L-PRF +rhBMP-2	Surgery+L-PRF	Presence of exposed bone, mucosal swelling and erythema, purulent drainage, intraoral or extraoral fistula, and discomfort associated with the surgical site	rhBMP-2 significantly promoted complete resolution of the lesions and MRONJ healing.	[192]
Yüce *et al.* 2021	RCT	MRONJ	28	Venous blood samples (4×9 cc) immediately centrifuged	Surgery+CGF	Surgery	Number of healings and number of infections	No significant difference in healing data but the rate of recurrent infection was lower.	[193]

ARCO, Association Research Circulation Osseous; ATA, atmospheres absolute; BMAC, bone marrow aspirate concentrates; BM-MNCs, bone marrow-derived mononuclear cells; BM-MSCs, bone marrow-derived MSCs; CD, core decompression; CGF, concentrated growth factor; CT, computed tomography; EPC, endothelial progenitor cells; EQ-5D, EuroQol-5 Dimension; ESWT, extracorporeal shock wave therapy; GCSF, granulocyte colony-stimulating factor; HAM, human amniotic membrane; HBOT, Hyperbaric oxygen therapy; HEQ, Japanese Orthopaedic Association Hip-Disease Evaluation Questionnaire; HHS, Harris Hip Score; hUC-MSCs, human umbilical cord-derived MSCs; IKDC, Knee Documentation Committee subjective knee form; JHEQ, Japanese Orthopaedic Association Hip-Disease Evaluation Questionnaire; JOA, Japanese Orthopaedic Association; KSS, knee society score; L-PRF, L-Platelet-Rich Fibrin; MRONJ, medication-related osteonecrosis of the jaw; MSCs, mesenchymal stromal cells; NA, not applied; NT, not mentioned; OHS, Oxford Hip Score; ONFH, osteonecrosis of the femoral head; OPG, osteoprotegerin; PBSCs, peripheral blood stem cells; PEMFs, pulsed electromagnetic fields therapy; PMA, Postel and Merle d'Aubigné score; RCT, randomized controlled trial; rhBMP-2, recombinant human bone morphogenetic protein-2; rhFGF, recombinant human fibroblast growth factor; ROM, range-of-motion; SCD, sickle cell disease; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SONK, spontaneous osteonecrosis of the knee; SPECT, single photon emission computed tomography; SVF, Adipose-Tissue Stromal Vascular Fraction; THA, total hip arthroplasty; TKA, total knee arthroplasty; VAC, vacuum-assisted closure; VAS, Visual Analog Scale; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis.

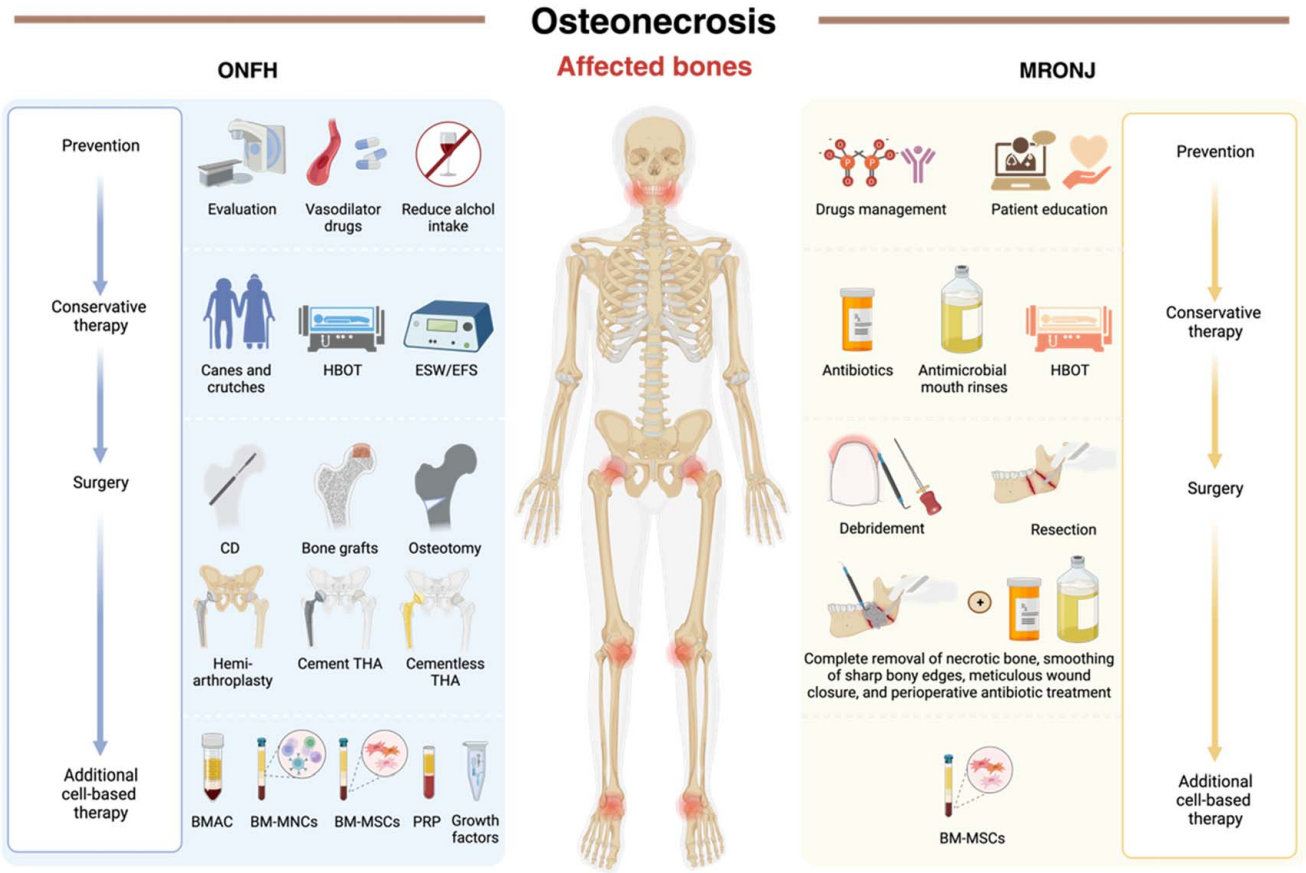

Figure 4. Current prevention and treatment of osteonecrosis. BMAC, bone marrow aspirate concentrates; BM-MNCs, bone marrow-derived mononuclear cells; CD, core decompression; HBOT, hyperbaric oxygen therapy; PRP, platelet-rich plasma; THA, total hip arthroplasty.

well-established staging system should be used, in general, these treatments can be divided into prevention, conservative therapies, surgeries, and surgeries with additional therapies (Fig. 4). The advantages and disadvantages of various treatments are listed in Table 3.

Prevention of osteonecrosis

For osteonecrosis, early diagnosis, coordination of care, and regular visits play important roles in the management. For traumatic ONFH, the blood supply for the femoral head should be evaluated regularly and should be protected during internal fixation[194]. For the long-term use of steroids, vasodilator drugs may be considered. In general, individuals with risks of osteonecrosis should be aware of these risk factors during patient education and try to avoid the mentioned risks.

Conservative therapy

For ONFH, the consensus has reported that orthotics (canes and crutches) could promote pain relief and walking ability by reducing weight-bearing loading. Hyperbaric oxygen therapy (HBOT) has beneficial effects, and its mechanism might include upregulating serum OPG and/or inhibiting osteoclast activation. HBOT significantly reduced lesion size in early-stage patients[133]. Significant changes in serum biomarkers for angiogenesis, osteogenesis, anti-inflammation, pain threshold, and tissue regeneration were also reported after extracorporeal shock waves[134]. Ozone therapy also has the potential to improve symptoms and delay the need for total hip arthroplasty (THA)[135]. Pulsed electromagnetic fields therapy with a dosage of 6 h daily for 90 days reduced knee pain and necrosis area of knee[136]. For spontaneous osteonecrosis of the knee, Atoun and colleagues reported that a biomechanical therapy (an orthosis for the foot) could reduce pain and increase activity[137]. For MSCs, BM-MSCs alone improved the quality of life of leukemia survivors with ankle osteonecrosis[138], and ONFH in females after pregnancy[37]. Hernigou *et al.*[39] reported that BM-MSCs obtained better survival time before revision compared to THA. De Rojas *et al.*[139] reported that BM-MSCs therapy was a novel treatment for children and young adults with ONFH after overcoming ALL, although the X-ray and MRI imaging of the femoral head deteriorated. Hernigou *et al.*[140] also indicated that BM-MSCs gained similar improvement with a lower rate of complications compared with total knee arthroplasty. Autologous peripheral blood stem cells[141] and umbilical cord-derived MSCs[142] were proven to be another origin of MSCs. Besides MSCs, bone marrow-derived mononuclear cells (BM-MNCs) also showed similar effects[143]. Moreover, bisphosphonate treatment should not be considered as a potential therapy for preventing osteonecrosis[144].

For MRONJ, conservative measures may include the use of antimicrobial mouth rinses and antibiotics[145], effective oral

Table 3

Summary of the advantages and disadvantages of different treatments.

Strategy	Disease stage	Related mechanisms	Advantages	Disadvantages	Ref.
Vasodilator drugs	Early	Angiogenesis	Retardant progress of disease, and non-invasive treatment	Limited effects	[194]
Orthosis	Early	NT	Pain relief, increase in activity, and non-invasive treatment	Limited effects	[137]
HBOT	Early	Reduce osteoclasts dysfunction	Lesion size reduction and non-invasive treatment	Limited effects	[133]
ESWT	Early	Angiogenesis, osteogenesis, anti-inflammation	Pain relief, lesion size reduction, and non-invasive treatment	Limited effects	[134]
Ozone therapy	Early	Angiogenesis	Pain relief, bone marrow edema reduction, and non-invasive treatment	Limited effects	[135]
PEMFs	Early	NT	Pain relief, lesion size reduction, and non-invasive treatment	Limited effects	[136]
Antimicrobial mouth rinses and antibiotics	Early	Anti-immune and inflammation factors	Convenient and non-invasive treatment	Limited effects	[145]
Teriparatide	Early	Osteogenesis	Lesion size reduction and non-invasive treatment	Limited effects	[146,147]
Intraoral vacuum-assisted closure therapy	Early	Anti-inflammation	Pain relief, the degree of cleanliness increase, and non-invasive treatment	Limited effects	[148]
Cell therapy (MSCs and MNCs)	Early (stage I or II)	Osteogenesis	Improvement in quality of life, better survival time and lower rate of complications compared to arthroplasty, and minimal invasive treatment	X-ray and MRI imaging of the femoral head still deteriorated	[37,39,138–140,143]
CD	Early to middle	Reduce bone marrow pressure	Basic and classical surgery, and symptom relief	Limited effects without other strategies, and invasive treatment	[149–152]
Non-vascularized bone grafting	Middle to later	Anti-inflammation and osteogenesis	Basic and classical surgery, and similar effects with CD	Limited effects, invasive treatment, other bones need to be cut, and effects might be insufficient than vascularized bone grafting	[150,153]
Vascularized bone grafting	Middle to later	Anti-inflammation, angiogenesis and osteogenesis	More beneficial for large joints, and long-term (1 year) function improvement	Invasive treatment, cell therapy may be needed for medium-sized lesions, effect might be insufficient than metal trabecular bone with bone dust	[154–157]
Femoral transtrochanteric rotational osteotomy	Middle to later	Angiogenesis and osteogenesis	Symptoms relief and progression prevention, similar effects with THA	Require for sufficient intact area at the lateral femoral head, and invasive treatment	[162,163]
Curved varus osteotomy	Middle to later	Angiogenesis and osteogenesis	Similar effects with THA in individuals < 50 years old, and effects may be better with bone impaction grafting	Require for $> 1/3$ coverage of the weight-bearing region with an intact articular surface, and invasive treatment	[164,165]
Hemiarthroplasty	Early to later	Mechanical support	Mid-to-long-term results in the early stage might be generally good	Postoperative buttock and groin pain and migration of the outer head may occur, and invasive treatment	[166]
THA	Later	Mechanical support	A generally good and useful treatment for symptoms relief	Cemented THA might undergo a hip revision, cementless THA might increase the risk of stress shielding and thigh pain, and invasive treatment	[166,167]
Debridement to relieve soft-tissue irritation	Middle	Anti-immune and inflammation factors	Symptoms relief, and suitable for soft-tissue inflammatory swelling or infection	Invasive treatment	[168]
Debridement with resection	Later	Anti-immune and inflammation factors	Accompanied by perioperative antibiotic treatment generally considered to be the most suitable approach	Invasive treatment	[168]
Surgery with cell-based therapy	Early to later	Cell proliferation, angiogenesis and osteogenesis	Bone regeneration in the early stages, pain relief and function improvement. BM-MSCs, BM-MNCs, PBSCs, amniotic membrane, L-PRF, and PRP might proper regenerative strategies. Rehabilitation may enlarge the effects.	CD with cell therapy showed no improvement at the later stage, osteoblastic cells were useless, the differentiation ability of MSCs affected the outcomes and invasive treatment	[38,168,170–173, 179,181,189,190, 195]
Surgery with medication	Early to later	Osteogenesis, and cell proliferation	Activity and joint preservation time improvement. rhFGF-2 and BMP-2 might proper medication	Require for bone grafting and might be beneficial for young individuals	[186–188,192]

BM-MSCs, bone marrow-derived MSCs; CD, core decompression; ESWT, extracorporeal shock wave therapy; HBOT, hyperbaric oxygen therapy; L-PRF, L-platelet-rich fibrin; MNC, mononuclear cells; MSCs, mesenchymal stromal cells; NT, not mentioned; PBSCs, peripheral blood stem cells; PEMFs, pulsed electromagnetic fields therapy; PRP, platelet-rich plasma; rhBMP-2, recombinant human bone morphogenetic protein-2; rhFGF, recombinant human fibroblast growth factor; THA, total hip arthroplasty.

hygiene, and conservative surgical interventions. Moreover, Sim *et al.*[146] reported that teriparatide (an osteoanabolic medication) provided another choice for treating lesions in MRONJ, which is consistent with the study of Jung and colleagues[147]. Laimer *et al.*[148] reported that intraoral vacuum-assisted closure therapy can reduce pain and increase the degree of cleanliness that provides a good condition for healing the closure.

Invasive operation

Surgery: The intramedullary pressure has been reported to be elevated in individuals with ONFH, and the high bone marrow pressure was regarded as one of the most common reasons for the development of ONFH. Regarding this, CD was considered as a useful technique for intramedullary decompression of the osteonecrosis regions. In general, Kirschner wire was placed to locate the necrotic area and direction of the wire, then a suitable support rod was inserted toward the anterolateral necrotic area of the femoral head until it was safe beneath the subchondral bone. Moreover, Yue *et al.*[149] designed a novel method, called a single approach to double-channel CD and bone grafting with structural bone support. After CD, one of the two channels (top one) was filled with a support rod and grafting bone, while the bottle one only filled with bone matrix. Researchers often designed the CD as an intervention in a control group according to the publishments in the last 10 years. Wang and colleagues reported that the light bulb technique (one of the non-vascularized bone grafting techniques) had similar outcomes to CD[150]. Civinini and colleagues reported that CD with a calcium sulfate/calcium phosphate bioceramic could make progress in a quantitative computed tomography analysis[151]. Another study combined autologous bone and CD, which was also reported positively[152].

Bone grafting transfer is a common surgical strategy for ONFH[153]. Wang *et al.*[150] reported the light bulb technique through a direct anterior approach, which allowed the removal of more necrotic bone by making a round bone window 1.0 cm in diameter using osteotomes and then a high-speed drill and a curette. Compared to non-vascularized bone grafting, vascularized bone grafting seems to be more beneficial for large joints, such as the hip. In general, a bone (usually fibula) was cut, a bone groove was made as before, the distal end of the fibula was grafted, and then the free peroneal vessels and the lateral femoral circumflex artery and vein were sutured[154,155]. Cao and their colleague performed a study to compare the effect of vascularized fibular grafting and CD, and the results supported the application of free vascularized fibular grafting[154]. Sun *et al.*[156] reported pedicled vascularized iliac bone grafting transfer improved function 6 months after surgery and Zhang *et al.*[157] reported similar outcomes one year after the operation. Bone grafts combined with BMSCs[158] and biomaterial bone grafts seem to be effective treatment methods[159]. Kang and the colleague figured that bone grafts combined with BMSCs might be more effective for individuals with medium-sized lesions[160]. Nevertheless, Chen and the colleague reported that the metal trabecular bone with bone dust of the femoral trochanteric region and femur neck was superior to free vascularized fibular graft[155]. Electromagnetic field stimulation as an additional treatment to autologous bone grafting might not have some extra beneficial effects[161].

Femoral transtrochanteric rotational osteotomy, a wildly known technique to alleviate symptoms and prevent the deterioration of ONFH, required sufficient intact area at the lateral femoral head. The bone cut was through the trochanter, and the femoral head was anterior or posterior rotated properly to improve its position within the hip socket[162]. Utsunomiya and their colleagues reviewed previous patients who underwent THA after Sugioka transtrochanteric anterior rotational osteotomy, and considered the effects to be comparable to those of THA[163]. Curved varus osteotomy was conducted on patients who exhibited more than one-third coverage of the weight-bearing region with an intact articular surface. A curved osteotomy and a varus position were needed for performing this surgery. For patients younger than 50 years, curved varus osteotomy was comparable with THA for functional outcomes, survival rate, and sporting activities after a mean follow-up period of 10 years[164]. Curved intertrochanteric varus osteotomy combined with bone impaction grafting yielded more positive outcomes when participants were carefully selected, and the procedure was executed accurately[165].

The last two choices of surgery are hemiarthroplasty and THA. A recent decade of studies merely reported the outcomes of bipolar hemiarthroplasty for ONFH. The reason might be the mid-to-long-term results in the early stage might be generally good, nonetheless, individuals may experience postoperative pain in the buttocks and groin, along with the potential migration of the outer head. The long-term results indicated that cemented THA using modern cementing techniques might be an effective and beneficial treatment option. However, using a cemented conventional stem as the femoral component may lead to a subset of requires for hip revision[166]. Hence, cementless THA was considered, although the risk of stress shielding along with some thigh pain increased. The long-term results from a large cohort multicenter survey indicated that contemporary cementless THA in young individuals with hematological disease following bone marrow transplantation did not increase the surgical complications, revision, reoperation, readmission, or mortality[167].

For MRONJ, recent American Association of Oral and Maxillofacial Surgeons guidance recommended debridement to relieve soft-tissue irritation and infection control at stage 2 (soft-tissue inflammatory swelling or infection), with resection considered at stage 3 (radiographic evidence of osteolysis extending to the inferior border of mandible). Voss *et al.*[168] figured that surgical management with MSCs further promoted the healing of MRONJ. A comprehensive strategy for achieving healing in MRONJ may involve thoroughly removing necrotic bone, smoothing sharp bony edges, and carefully closing the wound, all supported by perioperative antibiotic treatment. Calvani *et al.*[169] reported bovine lactoferrin could promote wound repair in individuals with suffering from MRONJ with the progressive destruction of bone.

Additional therapy: Last decade, cell-based therapy was rapidly developed and usually combined with orthopedic surgery. However, the necessity for the application of cell therapy is still controversial[24]. Among the substantial regenerative options of cell-based therapy, bone marrow aspirate concentrates (BMAC) was frequently used mainly in Europe and the United States, while BM-MNCs, BM-MSCs, PBSCs[170], and platelet-rich plasma (PRP)[195] were also applied. Many clinical studies[171,172] have investigated the effect of BMAC combined with CD, which indicated the elimination of cell proliferation but did not produce any improvement at the later stage. Moreover, BM-MSCs therapy with CD improved the outcome of the

humeral head osteonecrosis[38,173] and ONFH and bone regeneration in the early stages of ONFH[174–178]. For talus osteonecrosis, Hernigou *et al.* found similar results[179]. Wu *et al.*[180] indicated that the clinical effect was related to the quality of BM-MSCs, in detail, the repair of the necrosis area was a positive correlation to the osteogenic and chondrogenic differentiation ability. Emadedin *et al.*[181] injected bone marrow-derived $CD133^+$ cells (an early hematopoietic stem cell marker) during CD, which significantly and clinically improved pain relief and function. The rehabilitation program after BM-MNCs injection significantly improved the external rotation range of motion and strength of extensor and abductor muscle compared with that before treatment[182]. Nonetheless, Jayankura and colleagues[183] indicated that autologous osteoblastic cells addicted to CD did not take extra benefits in early-stage ONFH patients. Moreover, Hauzeur reported that osteoblast therapy obtained similar effects with BMAC[184]. Hernandez *et al.*[185] also reported that CD combined autologous BMAC and tricalcium phosphate therapy show no improvement in preventing progression to collapse.

Growth factors have been suggested, but their efficacy remained uncertain. Regarding growth factors, recombinant human BMP-2 and BMP-7 were combined with bone grafting. Additionally, clinical trials using gelatin hydrogel impregnated with recombinant human fibroblast growth factor (rhFGF)-2 were performed for individuals with pre-collapse ONFH[186]. Kuroda and colleague[187] also figured that rhFGF-2 treatment alone also had positive effects on activity and joint preservation time improvement. Gao and colleagues combined BMP-2 and bone marrow-derived cells during CD, which also prevented the progression of osteonecrosis in young individuals[188].

For MRONJ, the human amniotic membrane is used as a low immunogenicity regenerative strategy and is reported to help reduce pain[189] and promote wound healing[190]. Bouland and their colleagues[191] designed a leukocyte-rich platelet-rich fibrin seeded with stromal vascular fraction, which was available and promoted the healing of buccal mucosa. Besides this, Park *et al.*[192] combined leukocyte-rich platelet-rich fibrin with rhBMP-2, which also promoted MRONJ healing. Concentrated growth factor may provide limited advantages in promoting the healing of surgical sites[193].

Discussion

Scope

This review aims to comprehensively sum up the risk factors for osteonecrosis. For individuals with high-risk primary diseases, they should monitor the susceptible structure of osteonecrosis, and prevent the development of disease. For traumatic damaged vessels, surgeons should repair the vessels as soon as they can and monitor the blood supply on time. For the overused steroids, proper prescription and prevention treatment can be used. Secondly, this review aims to outline various mechanisms of osteonecrosis, especially for ONFH and MRONJ. Besides a deeper understanding of the disease, comprehensively demonstrating the mechanisms could promote the development and application of potential biotherapies. Lastly, we aim to classify the current therapeutic strategies for osteonecrosis, and hope could help make the standard process. Some of the treatment strategies focused on the prevention of disease progression, recovery of blood supply, and the surrounding environment. Others reported the application of different surgeries. It is worth noticing that additional cell-based injections or implants with orthopedic surgery, such as CD have been applied more and more in clinics[196]. The effectiveness of additional cell-based therapy requires more high-quality clinical trials with consistent cell preparation and intervention methods.

Limitations of osteonecrosis research

Although there already exist many therapeutic strategies for osteonecrosis, efficacy and effectiveness are still controversial for medical decisions. Revision surgery may be required and symptoms (such as pain) remain[167]. Developing novel, valuable, and highly efficient treatments is still an urgent problem and a big challenge. We figured out the current limitations of studies of osteonecrosis and tried to identify future solution ideas as below and presented in Fig. 5.

Undetermined risk factors and complex mechanisms with primary diseases

With the development of epidemiology, the risk factors of osteonecrosis have gradually become clear. However, the results were various among different areas and populations. Additionally, although we summarized several mechanisms about the imbalanced bone hemostasis during osteonecrosis, merely basic studies focused on the primary diseases that might increase the occurrence of osteonecrosis. Moreover, current research often reported the phenotypes, rather than molecular mechanisms.

Vacant position for superior treatment and insufficient evidence for regenerative medicine

Despite we classified the current therapeutic strategies for osteonecrosis, there are still limitations in choosing the most effective treatment. Although the study of Hernigou and colleague reported that MSCs transplantation was better than arthroplasty[140], the conclusion may be various among other locations of osteonecrosis. According to the publishments in decade, the combination of regenerative medicine and surgeries gained more focus. Nonetheless, the study design of these studies mostly was case series, and lack of comparisons and results of long-term follow-up. The low-grade evidence for additional cell-based therapy might limit the applications.

Roadblocks in translational medicine

Although studies over the last decades have provided much progression, the integration of these findings into a reproducible treatment strategy applicable to the entire spectrum of osteonecrosis remains a challenge. Additionally, we still need to consider the common gaps for translational medicine, such as resolution of drugs, immune aggravation, low proportion of cells surviving after transplant, inflammation, fibrosis, and how to control the "growth-stop signals" and modulation of various signaling pathways[197].

Future directions of osteonecrosis research

Identify risk factors and key molecules

A long follow-up and worldwide cohort study may be urgent and necessary for identifying more risk factors. Avoid the risk factors

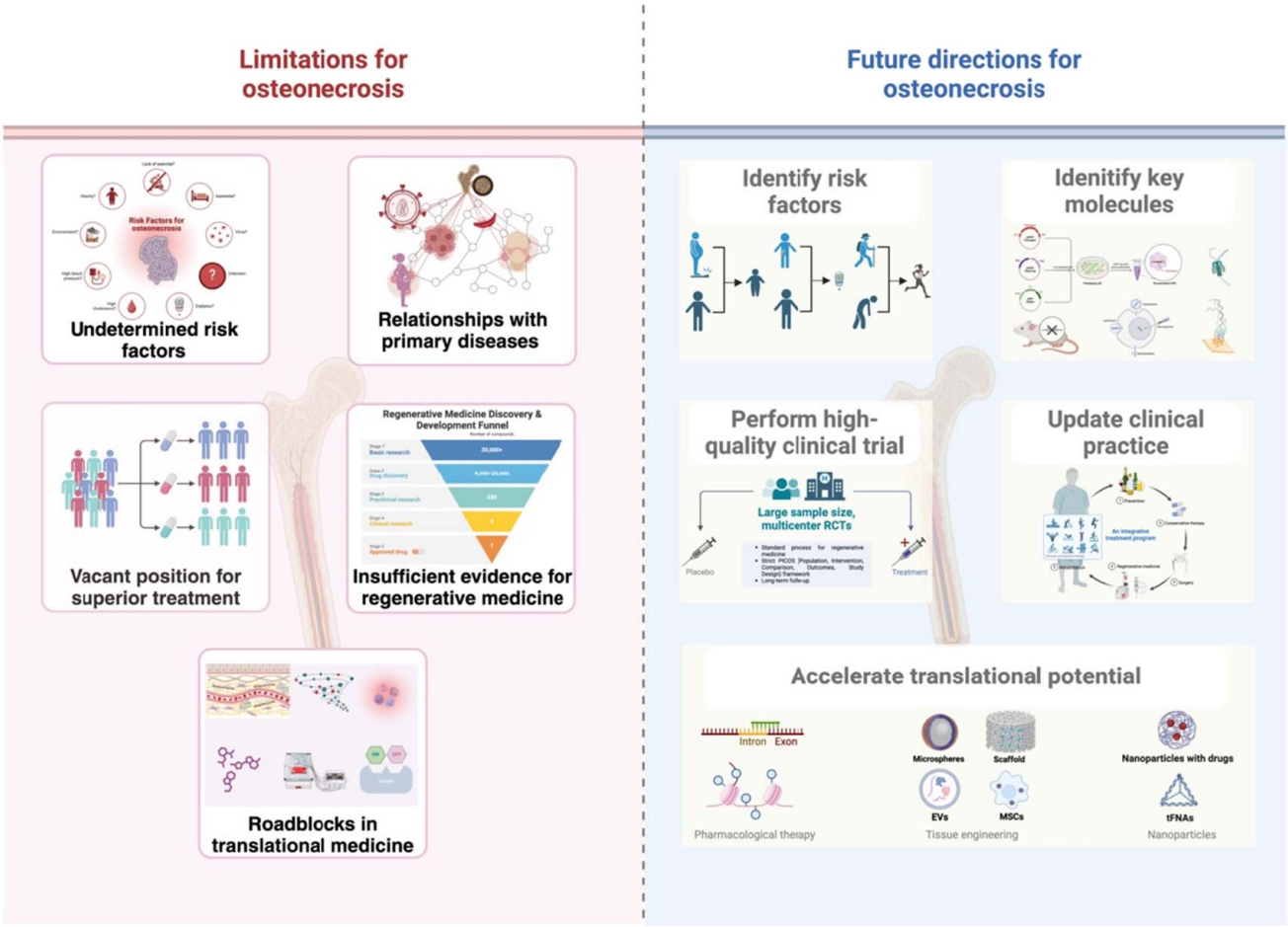

Figure 5. Limitations and future directions of osteonecrosis. EVs, extracellular vehicles; MSCs, mesenchymal stromal cells; RCT, randomized controlled trials; tFNAs, tetrahedral framework nucleic acids.

and get prevention as soon as possible could slow the process of disease. For basic study, gene knockout or gene targeting techniques may result in a deeper understanding of the pathology of osteonecrosis. Additionally, upcoming research could aim to clarify the molecular mechanisms that contribute to the protective effects of gene therapy, such as PGK1. Functional studies *in vitro* demonstrated that phosphoglycerate kinase 1 (PGK1) shRNA largely attenuated dexamethasone-induced ROS following the death of osteoblasts[198]. Investigating the regulation of these key targets with signaling pathways involved in bone homeostasis could provide valuable insights for novel therapies.

Perform high-quality clinical trial and update practice

Owing to the study design and different sites of osteonecrosis, popularize of findings from clinical studies is challenging. Well-designed multicenter RCTs could solve the clinical and methodological heterogeneity, which are essential for the current treatments, especially for conservative treatments and additional therapies with CD or bone grafting. Moreover, a long-term follow-up (such as 3–10 years) should be designed for clinical studies involving MSCs. Moreover, consistent cell preparation (such as cell origin, cell viability, and differentiation potency) and intervention methods (volume and the same combinational strategy) should be considered since the report of Wu *et al.*[180] indicated that the quality of BM-MSCs affected the clinical effectiveness.

For clinical practice, cell-based therapies or drugs with surgeries has becoming a trend. Besides current additional therapies, exercise and physical therapies before and after operation may also help return to life[182]. An integrative treatment that contains conservative treatment, surgery, regenerative medicine should be performed in future research. Additionally, translational medicine implements with CD, which as the most classical technique should be considered by investigators moving forwards.

Accelerate translational potential

An ideal pharmacological therapy for osteonecrosis should help reduce the inflammatory and promote bone repair by stimulating blood supply aiming at inducing progenitor growth and improving the microenvironment. Epigenetic modification (such as miR-214[199] and miR-26a[131]) and modulation of various signaling pathways (such as a local delivery system with pharmacological mediator of BRD9 and flexible injectable silk fibroin hydrogel[86], BMP-2[188], and FGF-2[186,187]) are potential therapeutic avenues and proved in pre-clinical trials.

For tissue engineering, scaffolds can serve as mechanical support or carriers. Researchers aim to develop innovative

biomaterial strategies that enhance bone regeneration and provide low-grade evidence (animal and cell experiments), such as poly (lactic-co-glycolic acid)/β-calcium phosphate/icariin (PLGA/TCP[200–203]), synthetic calcium phosphate ceramics[204], injectable hydrogel with microsphere bone cement[205], magnesium-based layered double hydroxide nanosheets[206], strontium-doped calcium polyphosphate (SCPP)[207], and biodegradable poly (ethylene glycol) maleate citrate (PEGMC). MSCs, extracellular vehicles (EVs), miRNAs (such as MiR@TDNs/Li-hep-gel[100], which upregulated the Wnt signaling pathway), and proteins (such as VEGF-loaded gelatin microspheres[208] and BMP-VEGF-PLGA-calcium polyphosphate composite[209]) are also used and could as common seeds combined with scaffolds.

Lastly, the current study emphasized that nanoparticles may serve as potential carriers for gene therapy and drug delivery. Nano-hydroxyapatite-copper-lithium (Cu-Li-nHA) composite[104] and tetrahedral framework nucleic acids (tFNAs) were innovative nanomaterials showing potential for drug delivery, and recent studies indicated that tFNAs restored osteogenesis dysfunction and attenuated BM-MSCs apoptosis in treating ONFH[210], and promoted angiogenesis in treating MRONJ[211].

Conclusion

Osteonecrosis is a refractory disease marked by the death of bone cells, and maintaining bone homeostasis is a challenge for this disease. In this review, we have discussed the roles of osteoblasts, osteoclasts, osteocytes, BM-MSCs, and bone marrow niche and angiogenesis. Pregnancy, diseases (such as SLE, ALL, SCD, HIV), trauma, alcohol intake, GCs use, and bisphosphonates use are risks for osteonecrosis. There are several proven mechanisms of impairment in bone homeostasis for osteonecrosis, including apoptosis of osteoblasts, osteocytes and BM-MSCs, dysfunction of osteoclasts, immune and inflammation, adipogenic differentiation, cell senescence, hematology impairment, and fibrosis. We have attempted to logically connect current pathways to these mechanisms and summarize the current treatments hierarchically. However, some limitations still exist, including undetermined risk factors, complex mechanisms with primary diseases, vacant positions for superior treatment, insufficient evidence for regenerative medicine, and roadblocks in translational medicine. Ongoing and future research should be directed at elucidating risk factors and identifying new targets, performing high-quality clinical trial, clarifying the standard quality of cell therapies, updating clinical practice (combination of conservative treatments, surgeries and regenerative medicine), accelerating translational medicine by developing pharmacological therapies, tissue engineering, and nanotechnology.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author contribution

X.N.X.: conceptualization, investigation, visualization, writing—original draft. H.C.H.: writing—review and editing, supervision. C.Q.H.: conceptualization, writing—review, supervision, funding acquisition. All the authors approve and agree with the content of the review.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

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Guarantor

Cheng-Qi He.

Data availability statement

This manuscript is a review and makes use of publicly available data from published studies, therefore, no original data are available for sharing.

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