Cellular mechanisms of osteoporosis: A comprehensive perspective on ferroptosis, cuproptosis and lipid metabolism abnormalities

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ABSTRACT

Osteoporosis is a prevalent skeletal disorder characterised by reduced bone mineral density and compromised bone microarchitecture, leading to increased bone fragility and increased risk of fracture. Recent studies have implicated ferroptosis, cuproptosis, and dysregulated lipid metabolism as pivotal factors in the pathogenesis of osteoporosis. Ferroptosis is an iron-dependent form of cell death that disrupts the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption by promoting lipid peroxidation and inducing cellular injury. Cuproptosis, associated with disruptions in copper homeostasis, influences bone cell integrity through oxidative stress and inflammatory responses, thereby impacting bone density. Aberrant lipid metabolism may exacerbate osteoporosis by disrupting bone-fat homeostasis, oxidative stress, and inflammatory responses. This review synthesizes the interplay between cuproptosis, ferroptosis, and lipid metabolism, elucidates the cellular mechanisms underlying osteoporosis, and accordingly provides novel therapeutic targets and intervention strategies, potentially enhancing osteoporosis prevention and treatment.

Keywords:
Cuproptosis; Ferroptosis; Lipid metabolism; Osteoporosis; Oxidative stress

1. Introduction

Osteoporosis is pathologically defined by diminished bone density and reduced bone mass, culminating in increased bone fragility and a heightened propensity for fractures.[1] According to a comprehensive global study, the prevalence of osteoporosis is estimated at 18.3%, with gender-specific rates of 23.1% in men and 11.7% in women.[2] Notably, substantial variations in prevalence are observed across different countries and regions.[3] Osteoporotic fractures not only pose a significant threat to public health, particularly among the elderly, but also incur substantial socioeconomic costs.[4] The aetiology of osteoporosis is intricately linked to the dysregulation of bone remodelling, a dynamic process involving the coupling of osteoclast-mediated bone resorption to osteoblast-mediated bone formation. Under homeostatic conditions, this balance is meticulously maintained; however, in the case of osteoporosis, this balance is perturbed, typically manifesting as elevated heightened osteoclast activity and/or attenuated osteoblast function.[5] Traditional research into osteoporosis pathogenesis has focused on hormonal imbalances, aberrant bone cell function, and inflammatory responses. Consequently, the pharmacotherapies currently used for osteoporosis, such as estrogen, bisphosphonates, denosumab, and calcitonin, are rooted in these research findings.[6,7] These medications, while effective in inhibiting osteoclast differentiation and activation, are not without adverse effects, including nausea, dizziness, limb pain, and rash (**Figure 1**).[4,8] Therefore, the exploration of novel osteoporosis mechanisms is of paramount importance for advancing clinical treatments and developing novel therapeutics.

Ferroptosis is an emerging form of regulated cell death that is contingent upon iron availability,[9] which has been implicated in a spectrum of diseases, including neurodegenerative disorders like Alzheimer's and Parkinson's diseases, cancer, cardiovascular diseases, and degenerative skeletal muscle diseases.[10,11] Cuproptosis, another

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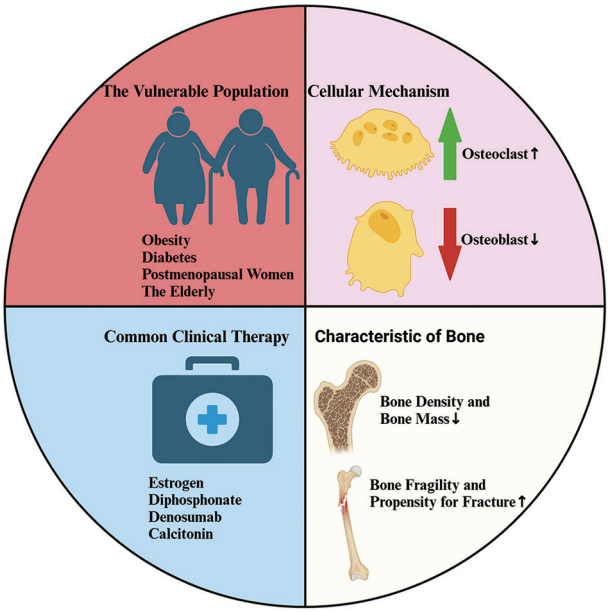

Figure 1. The introduction of osteoporosis

recently characterised cell death modality, is associated with various bone pathologies, such as rheumatoid arthritis, osteoporosis, and osteoarthritis.[12,13] The impact of these two novel cell death pathways on the aetiology of osteoporosis has garnered increasing research attention.

Dysregulated lipid metabolism, characterised by aberrant lipid synthesis, degradation, digestion, absorption, and transport, results in ectopic lipid accumulation in various tissues, thereby impairing physiological functions. Such metabolic disorder has been shown to increase the risk of cardiovascular diseases, osteoarthritis, and osteoporosis.[14] Osteoporosis is more prevalent in postmenopausal women and patients with diabetes mellitus, with both populations frequently exhibiting dyslipidaemia.[15] Studies have indicated that over half of postmenopausal women suffer from metabolic syndrome, with nearly 60% presenting with dyslipidaemia.[16] Diabetic patients also exhibit dysregulated lipid metabolism, which is not only a significant risk factor for type 2 diabetes but also affects lipid synthesis and degradation through hyperinsulinemia.[17,18] Furthermore, aberrant lipid metabolism is intricately linked with ferroptosis and cuproptosis. This review will focus on the roles of cuproptosis, ferroptosis, and lipid metabolism in the pathogenesis of osteoporosis, providing a holistic perspective on the emerging aetiologies of osteoporosis in light of the latest research findings.

2. Ferroptosis and its effects on bone: Emerging mechanisms and therapeutic prospects

Osteotrophic balance and integrity are meticulously maintained through the balance between osteoclastic resorption and osteoblastic anabolism, which constitute a continuous cycle of bone tissue remodelling.[5] Osteoclasts are primarily responsible for the resorption phase, whereas osteoblasts are pivotal in bone remodelling, including the formation, mineralisation, and secretion activities of osteocytes. These cellular entities reciprocally restrict and modulate bone tissue metabolism.[19] A study has confirmed that iron metabolism disorders leading to iron overload can induce alterations in the activity of osteoblasts and osteoclasts, thereby precipitating osteoporosis.[20]

2.1. Potential mechanism of ferroptotic osteoblasts for promoting osteoporosis progression

Osteoblasts are essential for bone renewal and synthesis. Osteoporosis can be caused by diminished bone synthesis due to osteoblast injury, and ferroptosis is a contributing factor to such cellular injury (**Figure 2**).[21] It has been established that iron overload inhibits the osteogenic differentiation of bone marrow stromal cells. Tian *et al.*[22] demonstrated that downregulation of alpha-B crystallin (CRYAB) promotes the degradation of ferritin heavy chain 1 (FTH1), leading to elevated intracellular levels of iron and reactive oxygen species (ROS), ultimately promoting ferroptosis and impeding the osteogenic differentiation of bone marrow stromal cells. Lu *et al.*[23] identified that activating transcription factor 3 (ATF3) silencing can mitigate iron overload by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/hemo oxygenase 1 (HO-1) signalling pathway, thereby promoting the osteogenic differentiation of human periodontal ligament stem cells under lipopolysaccharide stimulation. Glucocorticoids, known to induce osteoporosis, have been shown to trigger ferroptosis in osteoblasts by downregulating glutathione peroxidase-4 (GPX4) (**Figure 3**).[24] Based on these findings, we propose that inhibition of ferroptosis may represent a novel therapeutic avenue for osteoporosis.

2.1.1. Iron overload and lipid peroxidation as emerging pathogens of osteoporosis

Iron overload is a prerequisite for ferroptosis, the core mechanism of which is lipid peroxidation.[11] Excessive accumulation of iron ions in osteoblasts catalyses lipid peroxidation, thereby compromising the functional integrity of osteoblasts, which is contingent upon the intactness of the lipid cell membrane. Additionally, by-products of lipid peroxidation, such as lipid peroxides, can further damage the membrane structure of osteoblasts, thereby disrupting their function and inhibiting their proliferation and differentiation.[25,26] Iron overload can also modulate mitochondrial function by mediating oxidative stress, leading to mitochondrial membrane destruction and energy metabolism disorders, and further impairing the function and survival of osteoblasts, ultimately leading to a decline in bone mass.[27] Besides, iron overload, acting as a potent oxidant, can also promote the generation of ROS.[28]

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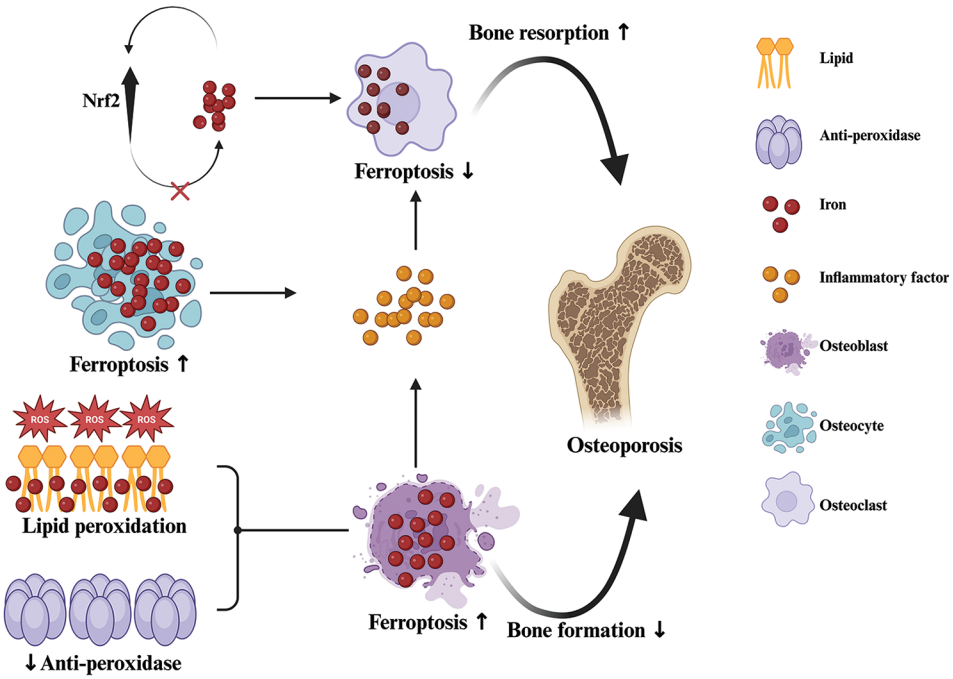

Figure 2. The mechanism of osteoporosis induced by ferroptosis
Abbreviation: Nrf2: nuclear factor erythroid 2-related factor 2 .

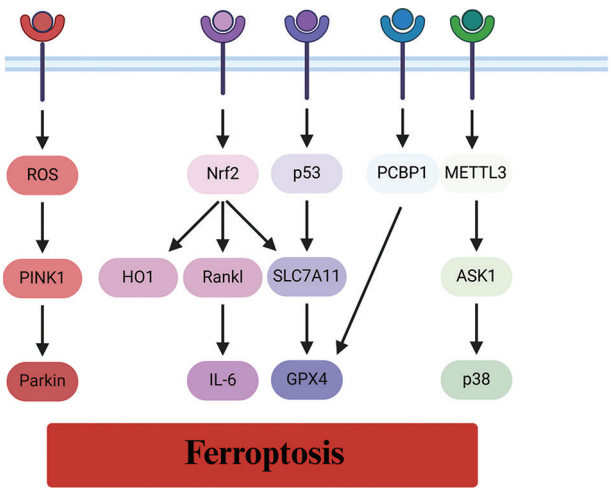

Figure 3. Signalling pathways involved in ferroptosis of osteoporosis. Abbreviations: ASK: Apoptosis signal-regulating kinase 1; GPX4: Glutathione peroxidase 4; HO1: Heme oxygenase 1; IL-6: Interleukin 6; METTL3: Methyltransferase like 3; Nrf2: Nuclear factor erythroid 2-related factor 2; p38: Mitogen-activated protein kinase 14; p53: Tumour protein p53; PCBP1: Poly(rC) binding protein 1; PINK1: PTEN induced putative kinase 1; Rankl: Receptor activator of nuclear factor kappa-B ligand; ROS: Reactive oxygen species; SLC7A11: Solute carrier family 7 member 11.

Diabetic osteoporosis has emerged as one of the severe complications associated with diabetes. A lot of research has demonstrated that hyperglycaemia plays a crucial role in the onset and progression of diabetic osteoporosis, as well as other complications. This is achieved by promoting alterations in upstream core regulatory substances, which in turn leads to iron overload and a decrease in antioxidant capacity.[29] Wang *et al.*[30] detected ferroptosis in the bone tissue of rats with type 2 diabetic osteoporosis and found that iron overload induced mitochondrial autophagy. Upon activation with carbonyl cyanide-m-chlorophenyl-hydrazine, a mitochondrial agonist, ferroptosis in osteoblasts was exacerbated. Concurrently, they observed that with the occurrence of ferroptosis, the levels of ROS and lipid peroxides increased in osteoblasts, whereas the expressions of osteocalcin, alkaline phosphatase, and osteopontin decreased, and mineralised nodules were reduced. The ferroptosis induced by carbonyl cyanide-m-chlorophenyl-hydrazine could be alleviated by the use of ferroptosis inhibitors. Ma *et al.*[31] found that high glucose induced ferroptosis in the bone tissue of rats with type 2 diabetic osteoporosis by increasing ROS/lipid peroxidation. Studies have also confirmed that diabetic patients are often complicated by abnormal iron metabolism, and that high glucose levels induce elevated ROS levels in MC3T3 cells, deeper mitochondrial and cell membrane staining, and significant damage to the intimal folds. Meanwhile, the ability of MC3T3 cells to differentiate into osteoblasts and form mineralised nodules is diminished in a high-glucose environment,[32] which has also been observed in studies related to mouse osteoblasts.[33] Furthermore, through the Fenton reaction, the overloaded iron produces a large number of hydroxyl radicals, which cause oxidative injury to osteoblasts.[34] In the past, the mechanism underlying diabetic osteoporosis was believed to be associated with the excretion of a large volume of glucosuria, which led to substantial losses of calcium and phosphorus in the urine. Additionally, insufficient insulin secretion, whether relative or absolute, affected the synthesis of collagen and osteocalcin by osteoblasts. As a result, bone resorption exceeded bone formation, ultimately leading to osteoporosis. Furthermore, diabetic vascular and neurological complications, as well as diabetic nephropathy, exacerbated bone mass loss and promoted the development of

osteoporosis.[35] These mechanisms were previously considered to be confined to the level of organ function. Ferroptosis, as a novel mode of cell death, can provide us with a better understanding of the pathogenesis of diabetic osteoporosis. In the aforementioned study, high glucose was found to promote ferroptosis by regulating upstream core substances, thereby directly reducing the osteogenic capacity of cells. Other studies have also demonstrated that high glucose can induce ferroptosis in various other cell types, such as nerve cells and renal tubular epithelial cells. These cells are involved in complications like diabetic nephropathy and neuropathy, and their ferroptosis indirectly contributes to the development of osteoporosis.[36] Iron overload can generate a plethora of ROS and hydroxyl radicals by catalysing lipid peroxidation and inducing oxidative stress, causing mitochondrial and cell membrane damage, and thus leading to the occurrence and progression of osteoporosis.

Therefore, while employing hypoglycaemic agents such as insulin, gliclazide, and metformin, the regulation of iron levels in the body and the intervention of lipid peroxidation may represent an effective strategy for the prevention and treatment of diabetic osteoporosis.

2.1.2. Contribution of ferroptosis to impaired antioxidant oxidase function and reduced bone mass

Cells contain numerous antioxidant enzymes, such as GPX, superoxide dismutase (SOD), and thioredoxin, which play a crucial role in protecting cells from oxidative stress and free radical damage.[37,38] These enzymes maintain cellular redox balance by neutralising ROS and lipid peroxides.[39] GPX4 is a pivotal antioxidant enzyme that mitigates the accumulation of lipid peroxides, maintains cellular stability, and modulates the progression of ferroptosis.[40] Xu *et al.*[41] demonstrated that vitamin D receptor activation can reduce ferroptosis and senescence of osteoblasts in age-related osteoporosis by stimulating the Nrf2/GPX4 pathway. Deng *et al.*[42] found that mangiferin can inhibit ferroptosis in osteoblasts through the kelch-like ECH-associated protein 1 (Keap1)/Nrf2/solute carrier family 7-member 11 (SLC7A11)/GPX4 pathway, thereby alleviating osteoporosis. Thus, GPX4 is an essential factor in inhibiting cellular ferroptosis and mitigating osteoporosis. However, in the case of nutrient metabolism disorders, inflammatory responses, or alterations in the cellular microenvironment, GPX4 dysfunction in osteoblasts can lead to insufficient cellular antioxidant defences and promote ferroptosis, which in turn trigger osteoblast apoptosis or dysfunction, directly affecting bone matrix synthesis and mineralisation, and reducing bone formation.[43] Moreover, high-fat diet has been shown to induce the downregulation of the expression of ferroptosis suppressor proteins SLC7A11 and GPX4 in the bone tissue of obese rats.[44] Chen *et al.*[45] discovered that tumour necrosis factor alpha (TNF-α) can cause ROS accumulation in human osteoblast-like MG63 cells and human umbilical vein endothelial cells by impairing GPX4 function and promoting ferroptosis in these cells, thus resulting in decreased osteogenesis and angiogenesis. SOD is a crucial intracellular antioxidant enzyme that catalyses the conversion of highly reactive superoxide radicals into the less harmful hydrogen peroxide.[46] It also plays a significant role in preventing ferroptosis during the progression of osteoporosis. Several studies have demonstrated that when osteoblasts are subjected to ferroptosis, there is often a downregulation of SOD expression or a reduction in its activity, accompanied by an accumulation of ROS, which frequently impedes osteogenesis.[47,48] Jiang *et al.*[47] investigated the effects of treating osteoblasts, which had been subjected to iron overload, with ferroptosis inhibitors such as desferrioxamine and ferrostatin-1. These treatments were found to enhance SOD and glutathione levels, thereby protecting osteoblasts from oxidative damage induced by iron overload. SOD is a crucial intracellular antioxidant enzyme that catalyses the conversion of highly reactive superoxide radicals into the less harmful hydrogen peroxide.[46] It also plays a significant role in preventing ferroptosis during the progression of osteoporosis. Several studies have demonstrated that when osteoblasts are subjected to ferroptosis, there is often a downregulation of SOD expression or a reduction in its activity, accompanied by an accumulation of ROS, which frequently impedes osteogenesis.[47-49] Jiang *et al.*[47] investigated the effects of treating osteoblasts, which had been subjected to iron overload, with ferroptosis inhibitors such as desferrioxamine and ferrostatin-1. These treatments were found to enhance SOD and glutathione levels, thereby protecting osteoblasts from oxidative damage induced by iron overload.

Therefore, ferroptosis in osteoblasts induced by antioxidant enzyme dysfunction can also lead to reduced bone matrix production, blocked bone mineralisation processes, and ultimately reduced bone mass. Strengthening the antioxidant defence system may be a key strategy for the prevention and treatment of osteoporosis.

2.2. Potential mechanism of ferroptosis for enhancing osteoclast activity

Enhanced osteoclast activity leads to greater bone resorption than bone formation, resulting in decreased bone mass and degradated bone microstructure.[50] Cellular ferroptosis is one of the leading causes of the increased osteoclast activity.[51] Jiang *et al.*[52] found that in ovariectomised mice with an osteoblast/osteoclast co-culture system and GPX4 gene knockout, ferroptosis in osteocytes contributed to the occurrence and development of postmenopausal osteoporosis, which was related to the over-activation of osteoclasts. Ferroptosis in osteocytes interferes with the expression of receptor activator of nuclear factor kappa B (NF-κB) ligand (RANKL) through Nrf2-mediated regulation of DNA methylation level of RANKL, thereby affecting osteoclast formation. Zhang *et al.*[53] showed that in animals without iron overload, *Nrf2* knockdown can induce oxidative stress and promote osteoclast differentiation, while having the opposite effect in animals with iron overload. Therefore, when iron overload occurs, *Nrf2* knockdown can induce oxidative stress and promote osteoclast differentiation. Nrf2 activation plays a role in osteoclast differentiation by enhancing the antioxidant capacity of histocytes and reducing intracellular iron content. The aforementioned studies confirm that Nrf2 is an important factor affecting osteoclast differentiation in the process of ferroptosis in osteocytes or osteoclasts. In addition, ferroptosis also triggers intracellular

inflammatory responses and increases the release of pro-inflammatory factors (such as interleukin 6 (IL-6) and TNF-α),[54] which further stimulate osteoclast generation and affect their activity to promote bone resorption.[55] Tang *et al.*[56] identified siderophilic osteocytes and osteoblasts in inflammatory alveolar bone. When ferroptosis is activated in the cells, severe bone resorption and inflammation occur in the alveolar bone, accompanied by impaired osteoclast formation and osteogenic potential, and ferroptosis can enhance the expression of RANKL and IL-6 in osteocytes. Jiang *et al.*[52] reported elevated iron concentrations in the bone tissue of mice within an osteoporosis model established through ovariectomy. Their study also identified that ferroptotic osteocytes secrete various proinflammatory factors involved in osteoclastogenesis, including IL-1β, IL-6, and TNF-α. Numerous experiments have demonstrated that IL-1, IL-6, and TNF-α facilitate osteoclast formation, thereby contributing to osteoporosis progression.[57-59] Furthermore, TNF-α has been confirmed to enhance osteoclast differentiation via RANKL expression in osteoblasts.[60,61] Conversely, IL-6 has been observed to exert an inhibitory effect on osteoclast proliferation, potentially due to its capacity to interfere with RANKL-mediated osteoclast differentiation.[62,63] Thus, ferroptosis in osteocytes may stimulate osteoclast formation by secreting inflammatory cytokines and inhibiting osteoblast function. Ferroptosis in osteocytes can cause inflammatory changes in the osteoclast microenvironment, which indirectly affects the formation and activity of osteoclasts. Based on the aforementioned studies, it is suggested that ferroptosis may affect osteoclast function by promoting inflammation and regulating the Nrf2 pathway.

In summary, ferroptosis can influence bone through a variety of mechanisms, including reduced bone formation due to osteoblast injury and increased bone resorption due to enhanced osteoclast activity, both of which compromise the quality of the bone matrix. Ferroptosis-induced osteoblast injury directly affects bone formation, leading to decreased production of bone matrix proteins, blocked mineral deposition processes, and reduced bone density and strength. Enhanced osteoclast activity induced by ferroptosis increases the absorption of bone matrix proteins and reduces mineral deposition, leading to excessive degradation of the bone matrix and further reducing bone density and strength (**Table 1**). However, the reduction in bone density and strength directly increases the risk of fractures, thereby diminishing the bone's capacity to withstand external forces and predisposing it to fractures. Ferroptosis-induced lipid peroxidation, depletion of the antioxidant

Table 1. Relationship between ferroptosis and osteoporosis

Cell/model	Intervention	Mechanism	Effect	References
BMSCs	Crystallin alpha B	1. Bound to FTH1 2. Stabilised FTH1 protein	1. Increased cellular Fe and ROS levels; 2. Improved the ferroptosis and reduced the osteogenic differentiation	22
MC3T3-E1 cells	Dexamethasone	p53/SLC7A11/GPX4 pathway	Induced ferroptosis in MC3T3-E1 cells	24
MC3T3-E1 cells, rats	High glucose and fat	METTL3/ASK1-p38 pathway	Increased ferroptosis in osteoblasts	44
hFOB1.19 cells	CCCP	ROS/PINK1/Parkin pathway	Increased ferroptosis in osteoblasts after activating mitophagy	30
hFOB1.19 cells	High glucose	PCBP1-GPX4 pathway	1. Decreased the viability of osteoblasts; 2. Increased the number of atrophic mitochondria	31
MG63 cells, HUVECs, rats	High fat	TNF-α	Induced osteogenic and angiogenic dysfunction based on its regulatory role of ferroptosis	45
Osteocyte/osteoclast co-culture system, *GPX4* knockout ovariectomised mice	Etrogen	Nrf2-Rankl pathway	1. Induced iron accumulation in the skeleton and the ferroptosis of osteocytes; 2. Resulted in reduced bone mineral density	32
BMSCs, type 2 diabetic mice	Vitamin K2	AMPK/SIRT1 pathway	Inhibited HG-mediated bone loss and ferroptosis	33
hFOB1.19 cells	Mitochondrial ferritin	ROS/PINK1/Parkin pathway	Inhibited the occurrence of ferroptosis in osteoblasts by reducing oxidative stress caused by excess ions	30
Murine periodontitis model	Erastin	Rankl and IL-6	1. Severe bone resorption and inflammation; 2. Increased osteoclast formation and impaired osteogenic potential	56
hPDLSCs	ATF3	Nrf2/HO-1 pathway	1. ATF3 silencing promoted hPDLSC mineralisation and cell differentiation; 2. Increased the levels of OCN2, RUNX2 and BMP2	23
Ovariectomised mice, iron-overloaded mice, Nrf2 knockout mice	Mangiferin	Nrf2/SLC7A11/GPX4 pathway	Promoted bone formation and alleviated osteoporosis	42

Abbreviations: AMPK: AMP-activated protein kinase; ASK1: Apoptosis signal-regulating kinase 1; ATF3: Activating transcription factor 3; BMP2: Bone morphogenetic protein 2; BMSC: Bone marrow stromal cell; CCCP: Carbonyl cyanide m-chlorophenyl hydrazone; Fe: Ferric ion (iron); FTH1: Ferritin heavy chain 1; GPX4: Glutathione peroxidase 4; HG: High glucose; HO-1: Heme oxygenase 1; hPDLSC: Human periodontal ligament stem cell; HUVEC: Human umbilical vein endothelial cell; IL-6: Interleukin 6; METTL3: Methyltransferas like 3; Nrf2: Nuclear factor erythroid 2-related factor 2; OCN2: Osteocalcin 2; p38: Mitogen-activated protein kinase 14; p53: Tumour protein p53; PINK1: PTEN induced putative kinase 1; Rankl: Receptor activator of nuclear factor kappa-B ligand; ROS: Reactive oxygen species; RUNX2: Runt-related transcription factor 2; SIRT1: Sirtuin 1; SLC7A11: Solute carrier family 7 member 11; TNF-α: Tumour necrosis factor alpha.

defence system, and the impact of inflammation on bone are the focal points of further research and exploration in this field. Understanding the mechanisms of these processes will aid in the development of new treatment options to mitigate the adverse effects of ferroptosis on osteoporosis and enhance the efficacy of osteoporosis treatment.

3. Cuproptosis and its effects on bone: Emerging mechanisms and therapeutic potential

Copper, an essential trace element for bone formation, is implicated in the synthesis and mineralisation of bone matrix. Perturbations in copper homeostasis can lead to apoptosis or necrosis of osteocytes, thereby compromising bone health and structural integrity. Consequently, investigating cuproptosis is instrumental in elucidating the mechanisms underlying bone remodelling imbalance in osteoporosis. In this section, we will discuss the mechanisms by which cuproptosis affects the pathogenesis of osteoporosis, focusing on osteoblast function, osteoclast function, inflammatory responses, and bone mineralisation (**Figure 4**).

3.1. Potential mechanism of cuproptosis in osteoblasts for promoting osteoporosis progression

Menkes disease is a disorder of copper metabolism arising from ATPase copper transporting alpha (ATP7A) copper transporter dysfunction, the typical clinical manifestation of which is osteoporosis.[64] Kim *et al.*[65] observed that cellular copper utilisation dysfunction in patients with Menkes disease results in decreased alkaline phosphatase activity and calcium mineralisation in mesenchymal stem cells, and concurrently downregulates the expression of osteogenic marker genes, thus affecting osteogenic differentiation and development. Hepatolenticular degeneration (Wilson's disease) is an autosomal recessive genetic disorder that usually manifests as bone mass loss or osteoporosis linked to *ATP7B* gene mutations, which lead to excessive copper deposition in osteoblasts.[66] Such deposition downregulates osteoblast gene expression and mineralisation levels, reducing osteoblast activity.[67,68] Excessive accumulation of copper ions can interfere with cellular physiological functions, affect bone matrix formation, and compromise the overall structure of bone tissue, leading to reduced bone formation. Excess copper ions can also impair the function of osteoblasts by promoting ROS production and inhibiting the activity of antioxidant enzymes such as SOD and GPX.[69,70] Qi *et al.*[71] demonstrated that copper chloride can enhance ROS production in osteoblasts while suppressing the activity of SOD and glutathione peroxidase, further inducing osteoblast injury. Therefore, excessive accumulation of copper ions may impair osteoblast function by promoting ROS production and inhibiting the activity of SOD and GPX (**Figure 5**).

3.2. Potential mechanism of cuproptosis for altering osteoclast activity

Copper ions play a crucial role in maintaining bone homeostasis, and copper-containing biomaterial models are frequently employed to investigate the role of copper in this process. For instance, copper-modified cobalt-chromium particles have been found to reduce inflammation and osteoclast formation induced by wear particles. Additionally, magnesium oxide nanoparticles loaded with copper ions exhibit a dose-dependent inhibitory effect on osteoclast formation.[72,73] Therefore, copper ions are likely to exert their primary effects on osteoclasts, which in turn can influence bone metabolism. This suggests that copper ions may play a pivotal role in modulating bone resorption processes, thereby impacting overall bone health. Bernhardt *et al.*[74] discovered that osteoclast differentiation in the presence of copper ions inhibits extracellular bone matrix absorption. Notably, copper's impact on osteoclasts is primarily manifested during their formation stage, with minimal effects on the function of mature osteoclasts. These findings suggest that copper may modulate bone resorption by altering osteoclast differentiation.

It has also been shown that the activity of tartrate-resistant acid phosphatase in osteoclasts is significantly increased at high concentrations of copper ions, without a corresponding up-regulation of gene expression, possibly due to the copper-induced elevation of ROS levels, leading to enhanced detection of tartrate-resistant acid phosphatase activity.[75] SOD can catalyse the disproportionation of superoxide to generate molecular

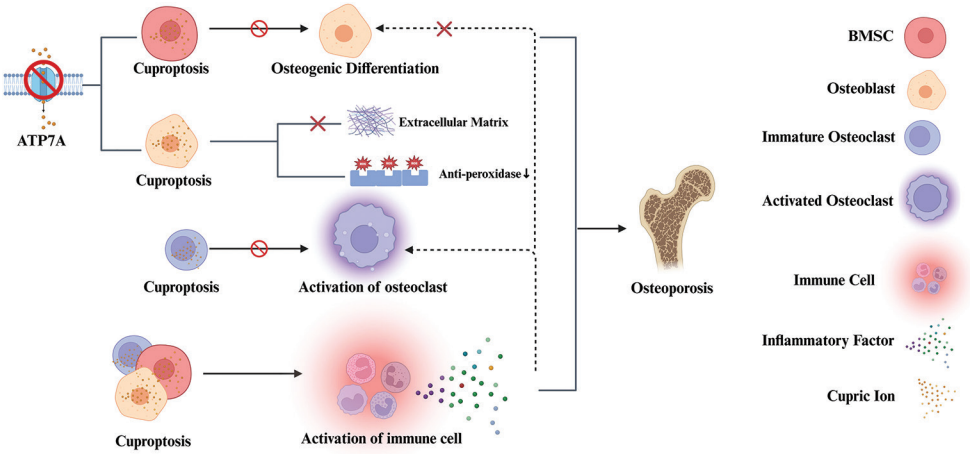

Figure 4. Mechanism of osteoporosis induced by cuproptosis
Abbreviations: ATP7A: ATPase copper transporting alpha; BMSC: Bone marrow mesenchymal stem cell.

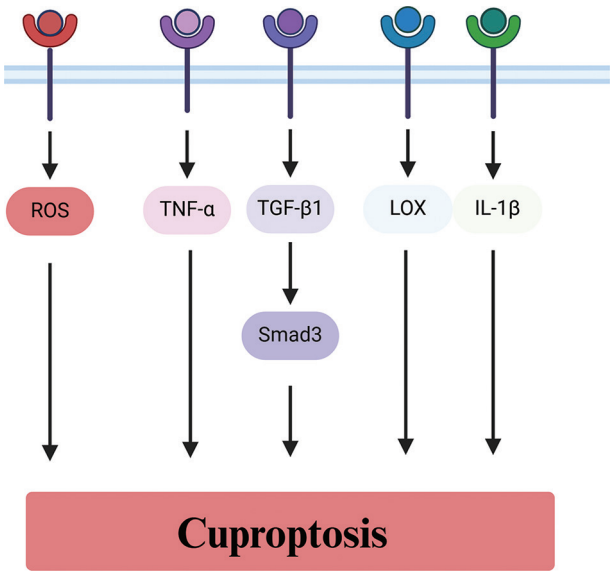

Figure 5. The signalling pathways involved in cuproptosis of osteoporosis
Abbreviations: IL-1β: Interleukin 1 beta; LOX: Lipoxygenase; ROS: Reactive oxygen species; TGF-β1: Transforming growth factor beta 1; TNF-α: Tumour necrosis factor alpha.

oxygen and hydrogen peroxide. When copper is deficient, the expression of copper-zinc SOD, which is encoded by the SOD1 gene, is decreased. Nojiri *et al.*[76] discovered that the numbers of osteoblasts and osteoclasts in the bones of SOD1-deficient mice were reduced. Moreover, the deficiency of SOD1 impairs the activity and function of osteoblasts through redox imbalance. However, it does not directly damage the function and viability of mature osteoclasts.[76,77] We propose that copper deficiency or excessive copper deposition in immature osteoclasts may inhibit their differentiation by suppressing peroxidase levels, but its function remains unchanged in mature osteoclasts. This dual mechanism offers a novel perspective on the role of copper in bone metabolism.

3.3. Exacerbation of bone loss by cuproptosis-induced immune disorders

Immune disorder is considered to be one of the pathogeneses of osteoporosis, and the imbalance of immune microenvironments caused by cuproptosis has been confirmed in various diseases.[78,79] Zhang *et al.*[80] found that the cuproptosis pattern of cells in ankylosing spondylitis is closely related to activated immune cells such as B cells, CD4+ T cells, and hypertrophic cells. Additionally, bioinformatic analysis of cuproptosis-related genes revealed a high correlation between the cuproptosis-induced immune infiltration and the prognosis of osteoporosis.[81,82] It is believed that cuproptosis is one of the factors causing immune microenvironment disorders in osteoporosis. Cuproptosis may promote the release of inflammatory factors (such as IL-1β, IL-6, and TNF-α) through the activation of various immune cells, thereby stimulating osteoclast generation and activity and reducing the osteogenic capacity of osteoblasts.[83,84] Such change in the immune microenvironment not only exacerbates bone loss but may also increase the risk of fractures, which underscores the potential value of regulating cuproptosis in the prevention and treatment of osteoporosis.

3.4. High copper levels causing bone mineralisation disorders

Copper is an essential trace element in the process of bone mineralisation, which is involved in the synthesis of bone matrix and the function of various mineralising enzymes. Studies have found that although moderate amounts of copper added to bioactive materials can promote bone regeneration, high serum copper levels are significantly associated with fracture incidence.[85,86] It is thought that excessive accumulation of copper ions may lead to insufficient bone matrix synthesis and mineralisation, thereby increasing the risk of fractures. Moreover, disturbances in copper homeostasis are closely related to rheumatoid arthritis-associated osteoporosis.[87,88] Excessive amounts of copper ions may affect the composition and mechanical properties of the extracellular matrix by altering the ratio of collagen to non-collagen proteins and promote the progression of osteoporosis.[76,89] Excessive accumulation of copper ions can also affect the expression of regulatory factors such as osteocalcin and osteopontin during mineralisation, resulting in abnormal bone mineralisation.[71,90] Therefore, maintaining appropriate copper levels is not only essential for bone mineralisation, but also provides new insights into the prevention of osteoporosis.

In conclusion, excessive copper deposition primarily leads to the impaired formation and function of osteoblasts, which in turn causes cuproptosis of osteoblasts and reduces bone formation. At the same time, excessive accumulation of copper also impedes bone mineralisation by affecting the proportion of bone matrix components and regulatory factors in the mineralisation process. In contrast, mature osteoclasts appear not to be directly affected by excessive copper accumulation and can still maintain their bone resorption function (**Table 2**). However, the immune response triggered by osteoblast cuproptosis increases pro-inflammatory factors in the microenvironment, which may indirectly promote bone resorption. Therefore, it is believed that excessive copper deposition can lead to bone formation and bone mineralisation disorders as well as enhanced bone resorption, thereby triggering osteoporosis. Understanding the specific mechanism of cuproptosis on bone is of great significance for developing therapeutic strategies for cuproptosis and alleviating osteoporosis symptoms.

4. Lipid metabolism and osteoporosis: Interrelated mechanisms and therapeutic potential

Lipid metabolism influences bone health through a multitude of biological pathways. An abundance of studies has demonstrated a strong correlation between conditions related to dysregulated lipid metabolism, such as obesity and metabolic syndrome, and osteoporosis (**Figure 6**). In this section, we will dissect the mechanisms by which lipid metabolism intersects with osteoporosis, focusing on lipid peroxidation, secreted factors from adipose tissue, and the complexities of obesity.

Table 2. Relationship between cuproptosis and osteoporosis

Cell/ model	Intervention	Mechanism	Effect	References
iPSCs	ATP7A	LOX	Impaired osteogenesis in MD by decreasing ALP activity and mineralisation	65
Osteoblasts	$CuCl_2$	TGF-β1/Smad3 pathway	Induced oxidative stress, osteoblast mineralisation, and inflammation cytokine	71
PBMCs, osteoclasts	Cu^{2+} doping of brushite cements	TNF-α and IL-1β	Cause cytotoxic reactions against osteoclasts and osteoclast precursors during initial burst release of Cu^{2+}	74
	Cu^{2+}	ROS, TRAP	1. Decreased resorptive activity of osteoclasts in vitro; 2. Differentiated osteoclasts did not decrease neither osteoclast number or resorptive activity	75

Abbreviations: ALP: Alkaline phosphatase; ATP7A: ATPase copper transporting alpha; Cu^{2+}: Copper ion (copper(II) ion); $CuCl_2$: Copper(II)chloride; IL-1β: Interleukin 1 beta; iPSC: Induced pluripotent stem cell; LOX: Lipoxygenase; MD: Menkes disease; PBMC: Peripheral blood mononuclear cell; ROS: Reactive oxygen species; TGF-β1: Transforming growth factor beta 1; TNF-α: Tumour necrosis factor alpha; TRAP: Tartrate-resistant acid phosphatase.

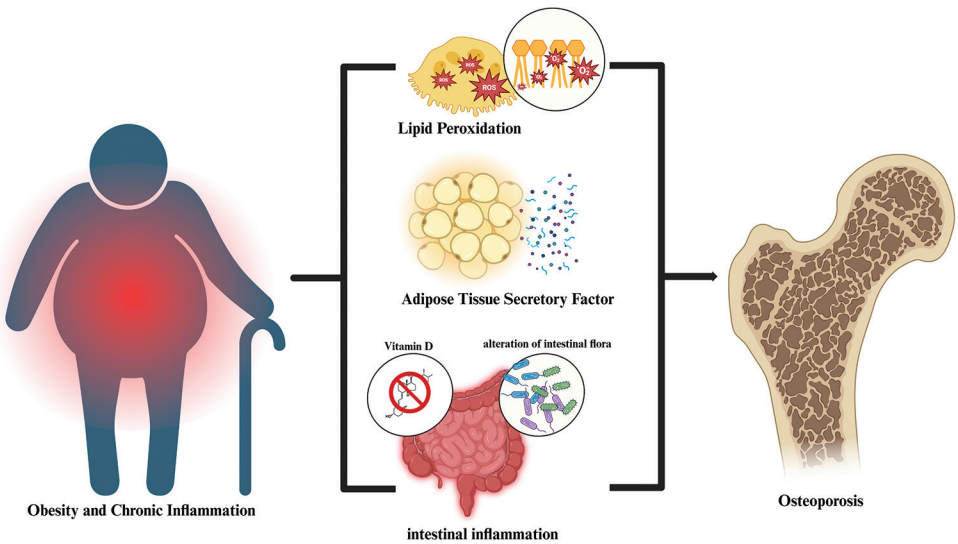

Figure 6. Mechanism of osteoporosis induced by abnormal lipid metabolism

4.1. Detrimental effects of lipid peroxidation on bone health

Lipid peroxidation, a process in which lipid molecules react with oxygen to form peroxides, is often catalysed by pro-oxidant reactions such as the Fenton reaction.[91,92] This cascade reaction leads to cellular membrane damage, dysfunction, and ultimately cell death.[93] In the context of osteoporosis, ROS generated by lipid peroxidation induce oxidative stress, impairing the function of osteoblasts and osteoclasts.[33] ROS not only disrupt cellular membranes, but also perturb mitochondrial structure, alter membrane potential, and affect adenosine triphosphate (ATP) synthesis, while also disrupting intracellular signalling pathways, thus impacting bone metabolism. Moreover, lipid peroxidation diminishes the activity of antioxidant enzymes, leading to ROS accumulation and oxidative stress.[94,95] A study has shown that serum total antioxidant capacity and SOD levels are decreased in mice on a high-fat diet, and SOD is intricately linked with ROS scavenging.[96] Lipid peroxidation damages the cell membrane and mitochondria of osteoblasts, thus reducing bone formation function. Studies have indicated that overexpression of ROS can inhibit the Wnt/β-catenin pathway, thereby reducing the expression of bone morphogenetic protein 2 (BMP2) and Runt-related transcription factor 2 (Runx2) in osteoblasts.[97] The effect of lipid peroxidation on osteoblasts is also evident in the reduction of bone matrix synthesis and the limitation of cell proliferation and differentiation. Moreover, lipid peroxidation has been identified as key modulators in the regulation of cellular metabolism. Specifically, they facilitate the process of lipogenesis through the activation of peroxisome proliferator-activated receptor γ, while concurrently exerting an inhibitory effect on bone formation by impeding the β-catenin signalling cascade. This dual action underscores the intricate interplay between lipid metabolism and skeletal development.[98,99] Lipid peroxidation also enhances the activity of osteoclasts by activating osteoclast signalling pathways (e.g., NF-κB and mitogen-activated protein kinase (MAPK)), reducing the ratio of glutathione to glutathione oxide, and increasing the expression of bone resorption markers, thus promoting osteoclast generation and bone matrix degradation.[100,101] It is posited that lipid peroxidation affects bone metabolism through multiple mechanisms, which not only destroys osteoblasts but also enhances the activity of osteoclasts, resulting in bone loss. Therefore, in the treatment of osteoporosis, the intervention of lipid peroxidation can effectively prevent the occurrence of osteoporosis and alleviate the progression of osteoporosis.

4.2. Impact of secreted factors from adipose tissue on bone metabolism

Adipose tissue not only serves as a reservoir for energy storage but also secretes a variety of factors, such as leptin, adiponectin, and TNF-α.[102,103] Leptin, secreted by adipose tissue, primarily regulates appetite and energy balance but also influences bone metabolism by promoting the generation of osteoblasts and inhibiting bone resorption.[104,105] Martin *et al.*[106] found that leptin can reduce bone marrow adipogenesis, prevent disuse-induced bone loss, and inhibit bone resorption. Elefteriou *et al.*[107] found that the sympathetic nervous system can promote bone resorption by increasing the expression of osteoclast differentiation factor RANKL, while leptin can reduce bone resorption by regulating the sympathetic nerves. Some novel adipokines, such as lipocalin-2 (LCN-2), nesfatin-1, and apelin, have the potential to be transformed into therapeutic targets. LCN-2 has been recognised as an osteokine involved in bone development and homeostasis. One study has found that LCN-2 is associated with early-onset osteoporosis caused by *Wnt1* and *Pls3* mutations, and it is related to iron status in abnormal WNT1 signalling.[108] A prospective study on a cohort of elderly women indicated that elevated levels of circulating LCN-2 could predict the risk of future osteoporotic fractures requiring hospitalisation.[109] Nesfatin-1, an adipokine composed of 82 amino acids, is closely associated with diabetes and skeletal disorders. Puzio *et al.*[110] revealed that nesfatin-1 treatment in ovariectomised rats with osteopenia resulted in the preservation of bone structure and an increase in bone strength. Similar studies have shown that, Nesfatin-1 administration led to significant increases in serum osteocalcin and bone alkaline phosphatase, as well as in trabecular volumetric mineral density and trabecular bone mineral density in the metaphysis of long bones as revealed by peripheral quantitative computed tomography, compared with the control group. Apelin, which is expressed in various tissues including bone marrow, is an adipokine secreted by adipocytes. Apelin-13 has been shown to have protective effects in conditions such as heart disease, diabetes, pulmonary fibrosis, and osteoporosis. Chen *et al.*[111] found that apelin-13 treatment can improve mitochondrial dysfunction and apoptosis induced by intracellular oxidative stress through the AMPK-α-mediated mitotic pathway, thereby reducing the occurrence of osteoporosis in ovariectomy rats. The expression of apelin in human osteoblasts can promote osteoblast proliferation and inhibit apoptosis via the APJ (a G protein-coupled receptor)/phosphoinositide 3-kinase/Akt (serine/threonine kinase 1) pathway.[112] The secreted factors from adipose tissue plays a complex role in bone metabolism, which usually possesses anti-inflammatory and antioxidant effects that aid in bone protection. However, under certain circumstances, it can also exert opposite effects. Wang *et al.*[113] found that the absence of adiponectin had a protective effect against oophorectomy-induced osteoporosis in mice. These factors secreted by adipose tissue have a significant impact on bone, such as inducing inflammation and altering bone metabolism. It has been shown that high-fat diet-fed mice exhibit elevated serum lipid levels, decreased bone mineral density, and increased levels of serum inflammatory factors, including IL-1 and TNF-α. IL-1 can promote osteoclast generation by stimulating TNF receptor-associated factor 6 and activating NF-κB and MAPK pathways with the assistance of the RANKL.[114] TNF-α secreted by adipose tissue can slow down osteoblast differentiation and enhance osteoclast activity by recruiting TNF receptor-associated factor and activating NF-κB/c-Fos in the nuclear factor of activated T cells cytoplasmic 1 (NFATc1) pathway.[115,116] Therefore, it is believed that adipose tissue can activate osteoclast signalling pathways by secreting such factors as NF-κB to enhance bone resorption and inhibit bone formation. Interventions targeting such factors, such as regulating the action of leptin or employing anti-inflammatory drugs, may aid in improving osteoporosis. Further research in this field is anticipated to yield more effective treatment options for osteoporosis. In recent years, studies have also found that the skeleton itself secretes related factors to affect systemic metabolism in order to resist obesity. Osteoblasts in the bone are also believed to influence adipose tissue and systemic energy metabolism by secreting bone-derived hormones or bone-motility factors.[117] Schnurri-3 (also known as Hivep3) is an adapter protein that inhibits the osteogenic activity of osteoblasts in a cell-intrinsic manner and regulates the expression of multiple secreted factors.[118] Li *et al.*[119] used Schnurri-3 knockout mice to explore the general relationship between bone formation and metabolic syndrome. Schnurri-3 knockout mice exhibited resistance to high-fat diet-induced obesity, improved glucose homeostasis, enhanced insulin sensitivity, and browning of white adipose tissue (**Figure** 7).

4.3. Complexity of the relationship between obesity and bone health

Obesity, a metabolic disorder characterised by excessive fat accumulation, has a complex and multifaceted relationship

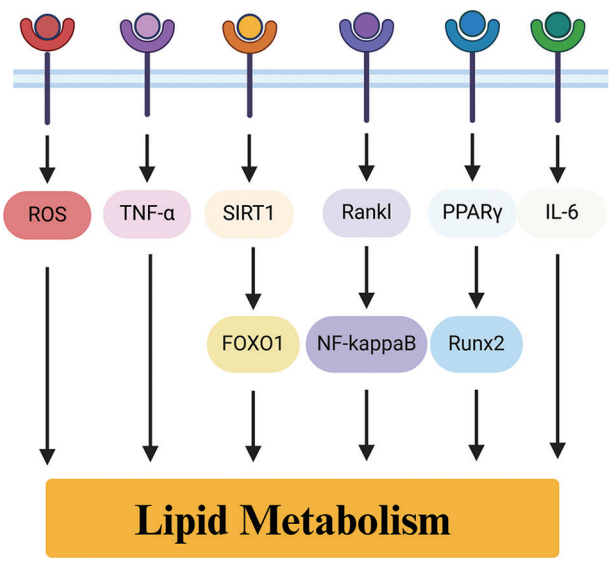

Figure 7. Signalling pathways involved in lipid metabolism of osteoporosis

Abbreviations: FOXO1: Forkhead box O1; IL-6: Interleukin 6; NF-κB: Nuclear factor kappa B; PPARγ: Peroxisome proliferator-activated receptor gamma; Rankl: Receptor activator of nuclear factor kappa-B ligand; ROS: Reactive oxygen species; Runx2: Runt-related transcription factor 2; SIRT1: Sirtuin 1; TNF-α: Tumour necrosis factor alpha.

with osteoporosis.[120,121] Obesity leads to hypertrophy and hyperplasia of adipose tissue. Although this process often results in increased bone density, it does not imply an improvement in bone mass. Thus, the notion that fat accumulation plays a protective role in bone has been questioned and challenged.[102] A study has indicated an inverted U-shaped relationship between lumbar bone density and body mass index (BMI), suggesting that a moderate increase in BMI is beneficial for enhancing bone density. However, a high BMI can still be detrimental to bone health.[122] Furthermore, both the expansion of adipose tissue in bone marrow and the increase in blood fat content can lead to reduced bone formation, resulting in a significant decrease in bone mineral density and an increased risk of fractures.[123,124] A cohort study demonstrated that obesity is associated with an increased risk of all-cause fractures and vertebral fractures in postmenopausal women, which, however, is considered a protective factor against pelvic fractures.[125] Therefore, a moderate BMI and adipose tissue are conducive to increasing bone density, while a high BMI will increase the likelihood of osteoporotic fractures. The redistribution of adipose tissue also plays a significant role in the pathogenesis of osteoporosis. Excessive fat accumulation can lead to greater loads on the joints and bones of obese individuals, resulting in the occurrence of osteoporosis.[126] What's more, obesity may put extra stress on bone tissue through fat accumulation, causing structural changes in bones and increasing the risk of fractures.[127] Calcium deficiency and poor calcium deposition are the primary causes of obesity-induced osteoporosis. Obese individuals tend to have difficulty absorbing vitamin B12 and vitamin D effectively, which is detrimental to bone tissue remodelling.[128] A previous study has shown that 86.2% of obese women have difficulty absorbing calcium effectively due to vitamin D deficiency.[129] Vitamin D deficiency affects the adipogenesis and lipolysis and thus contributes to obesity.[130] The vicious cycle between obesity and vitamin D deficiency accelerates bone loss. Vitamin D deficiency may also occur during weight loss.[131] Inflammation is considered to be a crucial mediator of obesity-induced osteoporosis, and adipocytes can directly release a variety of inflammatory factors, including TNF-α, IL-6, and C-reactive protein.[132] The accumulation of adipose tissue induces chronic inflammation, which may be due to the fact that the increased metabolic activity of adipocytes in obese individuals necessitates the synthesis of large amounts of protein. When the endoplasmic reticulum cannot meet the demand for protein synthesis, endoplasmic reticulum stress will occur, which further activates the inflammatory response and leads to the imbalance of hormone and adipokine release, thus accelerating the progression of osteoporosis.[133] Macrophages and lymphocytes are also activated to release inflammatory factors in adipose tissue.[134] Furthermore, the number of fatty acid-producing bacteria in the intestine of obese individuals increases, leading to intestinal mucosal damage and inflammatory response, which promotes systemic chronic inflammation and further triggers the release of inflammatory factors.[135] Therefore, the effect of obesity on bone density is not simply "protective" or "destructive", but depends on the interaction of multiple factors, including fat distribution, nutrient absorption, inflammatory status, etc. Osteoporosis interventions for obese patients need to consider these factors to develop more effective treatment strategies.

Abnormal lipid metabolism affects bone mass through multiple mechanisms, including lipid peroxidation, secreted factors from adipose tissue, and obesity (**Table 3**). Oxidative

Table 3. Relationship between lipid metabolism and osteoporosis

Cell/model	Intervention	Mechanism	Effect	References
BMSCs, high-fat-diet mice	Asiatic acid	SIRT1/FOXO1 pathway	Inhibited oxidative stress and promoted osteogenic differentiation	101
12-month-old female mice	High fat	TNF-α, IL-6	1. Decreased BMD with age in obese mice 2. Increased bone marrow adiposity and proinflammatory cytokines	103
Rats	High cholesterol or vitamin C	Rankl-NF-κB pathway	1. Increased the number of TRAP-positive osteoclasts 2. Suppressed osteoclast differentiation by decreasing serum lipid peroxidation	105
Male Wistar rats	Vanadium, magnesium	SOD, GPx	Disturbed the balance between osteoblastic and osteoclastic cells	106
Tail-suspended female rats	Leptin	Rankl-NF-kappaB pathway	Prevented disuse-induced bone loss through a strong inhibitory effect on bone resorption and a delayed effect preventing the decrease in bone formation	111
Adrb2-deficient mice	Leptin	Rankl	Leptin-regulated neural pathways inhibit bone resorption by modulating Rankl expression	112
Ovariectomised mice	Adiponectin	Complex cross-talk between fat mass and bone	APN deficiency protected against OVX-induced osteoporosis in mice	118
Young mice	High fat	Rankl, TNF, and PPAR-γ	HFD-induced bone loss was mainly due to increased osteoclast bone resorption by affecting the bone marrow microenvironment	119
BMSCs, high-fat diet mice	TNF-α	PPAR-γ, Runx2	TNF-α knockout retained HFD-induced femoral trabecular bone loss mainly by suppressing adipogenesis, osteoclastogenesis, and enhancing osteoblastogenesis	120

Abbreviations: APN: Adiponectin; BMD: Bone mineral density; BMSC: Bone marrow mesenchymal stem cell; FOXO1: Forkhead box O1; GPx: Glutathione peroxidase; HFD: High-fat diet; IL-6: Interleukin 6; NF-κB: Nuclear factor kappa B; OVX: Ovariectomy; PPAR-γ: Peroxisome proliferator-activated receptor gamma; Rankl: Receptor activator of nuclear factor kappa-B ligand; Runx2: Runt-related transcription factor 2; SIRT1: Sirtuin 1; SOD: Superoxide dismutase; TNF: Tumour necrosis factor; TRAP: Tartrate-resistant acid phosphatase.

stress and cellular membrane damage caused by lipid peroxidation adversely impact the function of osteoblasts and osteoclasts, thereby regulating bone formation and resorption. The relationship between obesity and osteoporosis involves the endocrine function of adipose tissue and the regulation of secreted factors on bone metabolism. An in-depth understanding of these mechanisms is crucial for developing new treatment options to alleviate the symptoms of osteoporosis.

5. Interactions between cuproptosis, ferroptosis, and lipid metabolism

5.1. Key roles of copper and iron in lipid metabolism

Copper, as an essential trace element, serves as a cofactor for numerous enzymes, including ceruloplasmin and tyrosinase, which play significant roles in the oxidation and transformation of lipids.[136,137] Both copper deficiency and excess can impact lipid metabolism.[138] Zhong *et al.*[139] found that copper induces changes in lipid metabolism through oxidative stress-mediated autophagy and the Nrf2/peroxisome proliferator-activated receptor γ pathway, leading to non-alcoholic fatty liver disease. Copper-induced oxidative stress can promote the recruitment of Nrf2 to the peroxisome proliferator-activated receptor γ promoter, thereby inducing target gene transcription and adipogenesis, which may indirectly affect the function of osteoblasts and consequently bone formation. Iron is a key cofactor in cellular respiration and DNA synthesis, which also plays a crucial role in lipid metabolism. Both iron overload and deficiency can affect lipid metabolism, leading to lipid accumulation or increased oxidative stress.[140] Li *et al.*[141] confirmed that chronic alcohol consumption can induce hepatic steatosis, inflammation, and oxidative stress through receptor for advanced glycation end products (RAGE). Interestingly, during this process, liver iron metabolism also changes significantly, such as increased iron uptake and storage and decreased iron output, suggesting that chronic alcohol consumption may affect iron metabolism and thus regulate lipid metabolism, mediating disease. In a Mendelian randomisation study, higher blood iron and copper levels were associated with lipid metabolism disorder and its two subclasses, hyperlipidaemia, and hypercholesterolaemia.[142] Therefore, both copper and iron play significant roles in lipid metabolism. Moreover, copper and iron metabolism are intertwined in the body, and they exert synergistic effects in maintaining bone metabolic balance. When there is insufficient iron reserve in the body, copper is redistributed to tissues crucial for regulating iron balance, including the upper intestinal cells, liver, and blood.[143] Copper in intestinal cells may also positively affect iron transport, which in turn affects bone metabolism. For example, copper in the liver may promote the biosynthesis of circulating ferroxidase-ceruloplasmin, thereby facilitating the release of stored iron.[144] At the same time, in cases of iron deficiency, many intestinal genes associated with iron absorption are reversely activated by the hypoxia-inducible transcription factor, hypoxia-inducible factor 2α. Copper also affects the DNA-binding activity of hypoxia-inducible factors.[145] Therefore, in cases of iron deficiency, copper can promote iron metabolic homeostasis. However, copper deficiency occurs in iron overload diseases (such as hereditary haemochromatosis), and high doses of iron supplementation may lead to copper consumption and interfere with copper utilisation.[146] To sum up, the interaction between copper and iron in lipid metabolism is complex and subtle, and keeping a balance between the two is essential for maintaining normal metabolic function. Further research on this point may provide new perspectives and strategies for the prevention and treatment of related diseases.

Ferroptosis, a form of iron-dependent lipid peroxidation-driven cell death, is characterised by the inactivation of GPX4 and the accumulation of lipid ROS. In osteoporosis, the imbalance between bone resorption and bone formation, which may be related to enhanced osteoclast activity leading to bone loss, can be exacerbated by iron overload. The latter can intensify oxidative stress through Fenton reactions, promoting lipid peroxidation in the bone microenvironment and thus accelerating osteocyte damage. Cuproptosis, another form of cell death triggered by the accumulation of copper ions in mitochondria, involves mitochondrial respiratory chain dysfunction and protein toxic stress. Although abnormal copper metabolism may affect skeletal health, its role in bone metabolism is still in the exploratory stage. Therefore, in the current pathogenesis of osteoporosis, prioritising the regulation of ferroptosis is warranted. This can be achieved through dietary and lifestyle changes, such as an iron-restricted diet and the supplementation of antioxidants (e.g., vitamin C and vitamin E, which can neutralise lipid ROS and reduce oxidative stress), as well as pharmacological treatments including iron chelators, GPX4 activators, and bisphosphonates. Although current evidence is insufficient, abnormal copper metabolism may be associated with certain secondary osteoporosis conditions, such as Wilson's disease. Future research could explore the application of copper chelators (e.g., penicillamine) or mitochondrial protectants in specific populations.

5.2. Impairment of cellular function by cuproptosis and ferroptosis through joint promotion of lipid peroxidation

Copper ions can catalyse the oxidation of lipids and thus result in lipid peroxidation. Additionally, copper ions directly affect lipid peroxidation levels through their redox reaction capabilities, which can cause cellular membrane damage and dysfunction.[147,148] Excessive accumulation of copper inhibits the function of antioxidant enzymes (e.g., GPX), resulting in decreased antioxidant defences and an increased risk of lipid peroxidation.[149] Iron ions generate hydroxyl radicals through the Fenton reaction, catalyse lipid peroxidation, and subsequently lead to cellular membrane destruction and dysfunction. Lipid peroxides produced during lipid peroxidation can affect bone formation and mineralisation.[34] Lipid peroxidation induced by copper and iron can injure osteoblasts, and diminished osteoblast function will lead to decreased bone formation and bone density. Lipid peroxidation caused by abnormal metabolism of copper and iron can also upregulate bone resorption-related signalling pathways in osteoclasts to increase bone resorption, thus leading to bone

loss. Therefore, exploring ways to regulate the levels of these metal ions and improve the antioxidant defence mechanism to reduce the effects of lipid peroxidation will not only help to understand the pathological mechanisms of osteoporosis, but also provide valuable guidance for clinical practice.

The interactions between copper, iron, and lipid metabolism and the relationship between metal ions and lipid peroxidation in cells have profound effects on bone health (**Figure 8**). Excessive accumulation of copper and iron ions can injure osteocytes through lipid peroxidation mechanism and affect bone formation and resorption. Oxidative stress and cellular membrane damage caused by lipid peroxidation can lead to bone loss and increase the risk of fractures. Understanding these mechanisms helps shed light on the pathological processes of osteoporosis and provides a theoretical basis for developing new treatment strategies.

6. Summary and outlook

Osteoporosis is a prevalent bone disease characterised by reduced bone density and deteriorated bone structure, leading to an increased risk of fractures. The occurrence of osteoporosis is not only related to the imbalance of bone metabolism but also closely associated with abnormal metabolism of trace elements and lipids in the body. Iron is an essential mineral involved in a variety of physiological functions, including oxygen transport and cellular metabolism. However, excess iron can promote free radical production, leading to ferroptosis, a type of iron-mediated programmed cell death. The role of ferroptosis in osteoporosis has received increasing attention. Excessive accumulation of iron can interfere with bone formation and remodelling by promoting the overactivity of bone resorption cells and inhibiting the function of osteoblasts, ultimately leading to osteoporosis. Copper is an essential trace element involved in a variety of physiological processes, including iron metabolism, antioxidant defence, and collagen synthesis. Cuproptosis, as a novel cell death modality, has been increasingly recognised for its relationship with osteoporosis. Copper ions, in excess, can generate free radicals that cause oxidative stress and toxicity to osteocytes, thereby affecting bone formation and remodelling. Excessive accumulation of copper may cause dysfunction of osteoblasts and bone resorption cells, thus interfering with the normal process of bone metabolism. Moreover, copper may play a pivotal role in the regulation of bone mass and bone quality by influencing the synthesis and mineralisation of bone matrix. Abnormal lipid metabolism plays a significant role in the pathogenesis of osteoporosis. Lipids are not only an important source of energy reserves, but also play a key regulatory role in bone metabolism. Increased adipose tissue, particularly visceral fat accumulation, is strongly associated with decreased bone density and an increased risk of osteoporosis. Adipose tissue affects bone metabolism by secreting a variety of bioactive substances, such as adipokines and cytokines. Cuproptosis, ferroptosis, and abnormal lipid metabolism play significant roles in the pathogenesis of osteoporosis.

Research on ferroptosis in osteoporosis is relatively novel and primarily focuses on the cellular level; however, clinical applications are still limited, and the specific mechanisms of action and signalling pathways have not been fully elucidated. Treatments for ferroptosis in osteoporosis are not yet mature, and further research is needed to discover new therapeutic approaches. Due to the recent emergence of research on cuproptosis in osteoporosis, the current research is relatively limited, and more studies are needed to explore the specific link between cuproptosis and osteoporosis. Lipid metabolism is closely related to osteoporosis, but current therapies targeting lipid metabolism disorders are not widely used in osteoporosis, and more clinical studies are needed to verify their effects. At present, most studies on these three topics in osteoporosis are still in their infancy. Overall, research in these fields provides a new perspective for understanding the complex mechanisms of osteoporosis, but more studies should be carried out in order to overcome the current limitations and shortcomings. Future studies should consider the interaction of these factors to gain a more comprehensive understanding of the pathological mechanisms of osteoporosis. Intensifying research in these fields will not only help shed light on the pathogenesis of osteoporosis, but may also lead to the development of novel

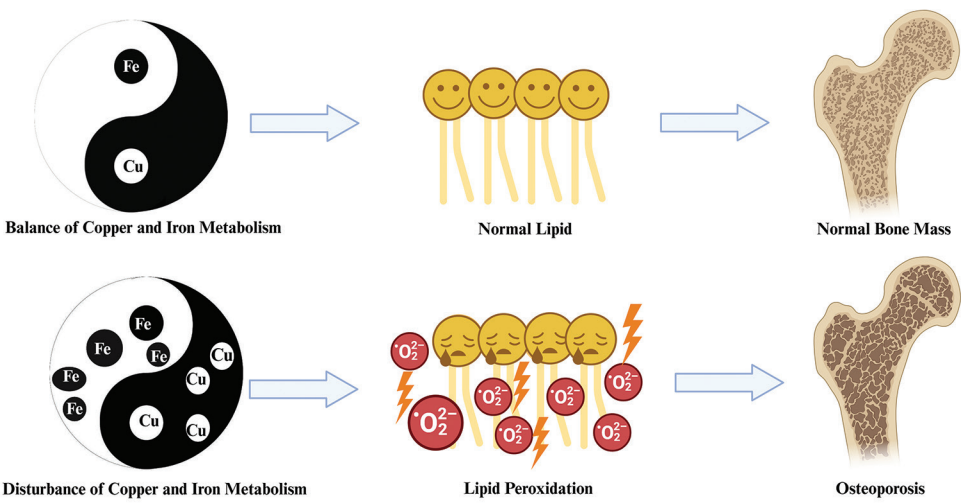

Figure 8. Ferroptosis and cuproptosis cause osteoporosis by promoting lipid peroxidation
Abbreviations: Cu: copper; Fe: iron; $\cdot O_2^{2-}$: superoxide anion radical.

diagnostics and treatments that will improve the quality of life of individuals with osteoporosis.

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Author contributions
Conceptualization: HZ, KR, and FY; *Writing - original draft:* HZ and JD; *Writing - review & editing:* JC, XZ, LW, and TQ. All authors approved the final version of the manuscript.
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Not applicable.
Availability of data
Not applicable.
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