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REVIEW

The Role of Sirtuins in Bone Repair From the Perspective of Glucose Metabolism

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Abstract: Impaired clinical fracture healing remains a major challenge, with surgical treatment often insufficient in patients with metabolic disorders or comorbidities such as diabetes and osteoporosis. Recent advances in metabolomics have brought the Sirtuin protein family to the forefront of bone regeneration research. These NAD^+-dependent deacetylases exhibit cell-specific expression and regulate critical processes in osteoblasts and osteoclasts, linking glucose metabolism with bone remodeling. Sirtuins influence key pathways such as Wnt/β-catenin, AMPK, and mTOR, offering novel insights into the mechanisms of fracture healing. Emerging pharmacological strategies targeting Sirtuins show promising results in preclinical models. This review highlights the potential of Sirtuin-based interventions as therapeutic targets in the metabolic regulation of bone repair.

Keywords: Sirtuins, bone repair, osteoblasts, osteoclasts, glucose metabolism

Introduction

Bone possesses an intrinsic ability to regenerate and restore its original structure and function after injury. This complex repair process is orchestrated by a tightly regulated interplay between osteoblasts, which mediate bone formation, and osteoclasts, which drive bone resorption. While this balance is maintained under normal physiological conditions, various metabolic and pathological states—such as aging, diabetes, or osteoporosis—can disrupt the repair mechanism, leading to delayed healing or nonunion.[1] In the United States alone, approximately 100,000 fracture patients experience nonunion annually, accounting for 10–15% of all fractures.[2,3]

Among emerging regulators of bone metabolism, the Sirtuin (silent information regulatory proteins, SIRTs) family has garnered significant attention. These nicotinamide adenine dinucleotide $(NAD)^+$-dependent enzymes (SIRT1–SIRT7), homologous to the yeast silent information regulator 2 (Sir2) gene, are expressed across various tissues and function as histone deacetylases or Adenosine Diphosphate (ADP)-ribosyltransferases.[4,5] Beyond their canonical role in epigenetic regulation, Sirtuins modulate key aspects of cellular energy metabolism, oxidative stress response, and signaling pathways involved in bone remodeling.

Recent advances in metabolomics have highlighted the importance of glucose metabolism in osteoblast and osteoclast function. Both cell types exhibit high metabolic demands throughout differentiation and activation, with glucose serving as the primary energy substrate. Disruptions in glucose metabolism can impair bone cell activity, disturb the osteoblast–osteoclast balance, and ultimately hinder bone regeneration.

This review aims to explore the role of Sirtuins in bone repair, with a particular focus on how they influence glucose metabolic pathways and energy signaling in osteoblasts and osteoclasts. Understanding these regulatory mechanisms may inform the development of targeted therapies for metabolically impaired fracture healing.

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Search Strategy

We systematically reviewed literature from PubMed, Web of Science, Embase, Scopus, Cochrane Library, and Google Scholar and additionally included China National Knowledge Infrastructure (CNKI) and Wanfang Database to capture relevant Chinese-language publications. The search covered the period from January 2000 to March 2025. A comprehensive search strategy was employed using a combination of controlled vocabulary (eg, MeSH terms) and free-text keywords. Core search terms included: SIRT1, SIRT3, SIRT6, bone metabolism, fracture healing, osteoblasts, osteoclasts, mesenchymal stem cells, glucose metabolism, Wnt signaling pathway, NF-κB, AMPK, and mTOR. Boolean logic (AND, OR) was used to ensure precise filtering, and language was restricted to English and Chinese. A sample PubMed query is provided below:

((SIRT1 OR SIRT3 OR SIRT6) AND ("Bone Metabolism"[Mesh] OR "Fracture Healing"[Mesh]) AND ("Osteoblasts"[Mesh] OR "Osteoclasts"[Mesh] OR "Mesenchymal Stem Cells"[Mesh]) AND ("Glucose Metabolism"[Mesh] OR "Energy Metabolism"[Mesh]) AND ("Wnt Signaling Pathway"[Mesh] OR "NF-kappa B"[Mesh] OR "AMP-Activated Protein Kinases"[Mesh] OR "mTOR protein"[Mesh])). Search strategy section Supplementary Materials.

A PRISMA flow diagram (Figure 1) was constructed to illustrate the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final synthesis.

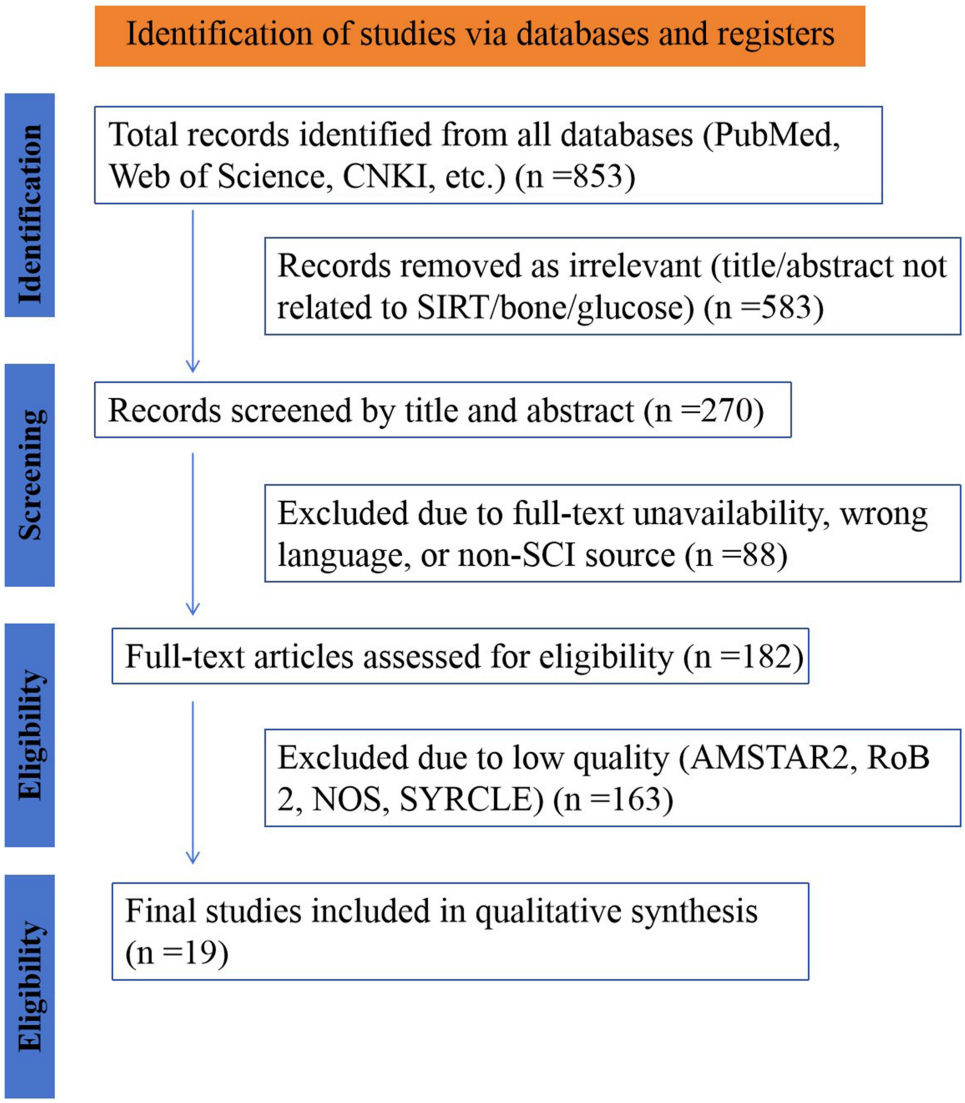

Figure 1 PRISMA flowchart.

Inclusion criteria were as follows: (1) Original studies (eg, basic research, animal models, clinical studies, or systematic reviews) involving the interaction of SIRT1, SIRT3, or SIRT6 with bone metabolism and glucose-related pathways; (2) Studies published in peer-reviewed journals; (3) Focus on skeletal tissues or bone-relevant cell types [osteoblasts, osteoclasts, Mesenchymal Stem Cells (MSCs)].

Exclusion criteria included:

(1) Studies unrelated to SIRT1/3/6 or not involving skeletal systems;

(2) Articles without original data (eg, narrative reviews);

(3) Preprints or non–peer-reviewed literature.

To ensure methodological rigor, we applied standardized quality assessment tools based on study type: A MeaSurement Tool to Assess the methodological Quality of Systematic Reviews (AMSTAR) 2 for systematic reviews, risk of bias (RoB) 2 for randomized trials, Newcastle-Ottawa Scale for observational studies, and SYRCLE's tool for animal studies (Table 1). All terminology referring to key biological components—such as osteoblasts, osteoclasts, mesenchymal stem cells, glycolysis, and oxidative phosphorylation—was standardized across sections. Definitions and functional roles were consistently described in relation to their metabolic context in bone tissue.

To ensure the relevance and scientific rigor of the included studies, our keyword selection focused on Sirtuin isoforms with well-established roles in bone metabolism, particularly SIRT1, SIRT3, and SIRT6. SIRT1 is extensively studied for its dual regulatory role in osteoblast and osteoclast differentiation, as well as in maintaining bone remodeling dynamics. SIRT3 is primarily involved in regulating mitochondrial energy metabolism in bone cells, supporting bone homeostasis. SIRT6 exerts a bidirectional influence on the osteogenic differentiation of MSCs and contributes to the maintenance of bone mass.

We further refined our search by including key signaling pathways mechanistically linked to Sirtuin activity and glucose metabolism:

(1) Wnt/β-catenin pathway, this pathway is essential for promoting glycolysis in osteoblasts. SIRT1 enhances this effect by activating RUNX2 through deacetylation and forming a SIRT1–FoxO3a complex, thereby stimulating Wnt/β-catenin signaling and upregulating glycolysis-related genes required for osteoblast differentiation and bone formation.

(2) Nuclear factor-kappaB (NF-kappaB) signaling, this inflammatory pathway plays a crucial role in osteoclast differentiation and activation. SIRT1 inhibits NF-κB signaling, thereby suppressing osteoclastogenesis and contributing to the balance between bone resorption and formation. Given NF-κB's involvement in inflammation-induced metabolic dysregulation, its modulation by SIRT1 may also affect glucose metabolism in the bone microenvironment.

(3) AMPK pathway, as a key cellular energy sensor, AMPK is activated through the SIRT3–PGC-1α/MnSOD axis, promoting mitochondrial biogenesis and oxidative metabolism in bone cells. This supports energy-demanding processes such as bone remodeling and regulates the differentiation of osteoblasts and osteoclasts under glucose-restricted conditions.

(4) mTOR signaling, this pathway is central to cell growth, protein synthesis, and glucose uptake. SIRT1 promotes osteoblast differentiation via mTOR activation, whereas SIRT3 may modulate mTOR-mediated osteoclast differentiation. Both actions implicate the mTOR pathway in the Sirtuin-dependent regulation of glucose-utilization during bone repair.

Although non–peer-reviewed sources (eg, preprints) were considered during the initial search phase, they were excluded from final analysis due to the absence of peer-review validation. Peer review is a critical quality-control process that ensures the reliability of data interpretation, methodological soundness, and reproducibility of results. Including non-reviewed work risks incorporating flawed study designs or unverified conclusions, potentially biasing the synthesis. For example, unvetted preprints may neglect confounding factors or overstate mechanistic findings, thereby undermining the credibility of the review.

Bone Repair Is the Result of the Joint Action of Osteoblasts and Osteoclasts

Osteoblasts originate from MSCs and skeletal stem cells (SSCs) with multi-lineage differentiation potential. The differentiation of stem cells into mature osteoblasts requires many complex steps. First, MSCs derived from the periosteum and bone marrow are recruited to the fracture site under the action of *SDF1* and *CXCR4*, differentiate into α-SMA9^{+} osteochondral precursor cells, and then invade the fracture site. The former rapidly amplifies through secreting

Table 1 Study Quality Scores

Study Type	Quality Assessment Tool	Example Study Quality Scores (Selected Studies)	Score Explanation	Impact on Data Synthesis
Randomized Controlled Trials (RCTs)	Cochrane Risk of Bias Assessment Tool (RoB 2)	Study A: Low risk of bias Study B: High risk of bias	RoB 2 assesses bias risks in multiple domains such as randomization process, deviation from intended interventions, and completeness of outcome data. A low - risk score indicates a more reliable study in design, implementation, and reporting. A high - risk score suggests potential flaws that may affect the credibility of the results.	Low - risk RCTs carry more weight in data synthesis. Their results are more influential in shaping the overall conclusion. High - risk studies are treated with caution. They may contribute less to the combined result or even be excluded in extreme cases to avoid misleading the overall outcome.
Observational Studies	Newcastle - Ottawa Scale (NOS)	Study C: 7 points (out of 9) Study D: 4 points	NOS evaluates studies based on selection of study participants, comparability of groups, and outcome assessment. Higher scores indicate better - quality studies. For example, clear inclusion and exclusion criteria, representative samples in participant selection, control of confounding factors in group comparability, and reliable outcome measurement methods can all earn points.	Higher - scoring observational studies are more emphasized in data synthesis. Their data is more likely to be considered in drawing conclusions. Lower - scoring studies like Study D have less influence. They may be used as supplementary information or need to be combined with high - quality studies for a comprehensive analysis.
Systematic Reviews	AMSTAR 2 Assessment Tool	Study E: High - quality (meeting most key items) Study F: Low - quality (failing to meet multiple key items)	AMSTAR 2 assesses aspects such as clarity of research questions, rationality of inclusion study selection and data collection, and appropriateness of methodological quality assessment. A high - quality systematic review meets most key items, indicating a more rigorous and reliable synthesis of existing research evidence.	High - quality systematic reviews like Study E serve as important references in data synthesis, providing a solid foundation for integrating other research findings. Low - quality systematic reviews may have methodological flaws, so their reference value is limited. They may not be included in data synthesis to ensure the reliability of the overall result.
Animal Experiments	SYRCLE's Risk of Bias Tool	Study G: Low risk of bias Study H: High risk of bias	SYRCLE's tool evaluates bias risks in animal experiments in areas such as random sequence generation, allocation concealment, blinding implementation, and completeness of outcome data. A low - risk score implies a more standardized experimental design and implementation, leading to more reliable results. A high - risk score indicates potential loopholes that may affect the accuracy	

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factors such as Gremlin, LepR, and Prx1.[6–11] Through the regulation of transcription factors *RUNX2* and *SOX9*, which differentiate into osteoblasts and chondrocytes respectively, WNT/β-catenin and bone morphogentic protein (BMP) signaling act on preosteoblasts (high expression of RUNX2) to induce osterix (OSX, also known as SP7), and ultimately the expression of RUNX2 and OSX marks the formation of mature osteoblasts.[12] Chondrocytes become hypertrophic chondrocytes (a key state of endochondral ossification) under the joint regulation of *SOX9* and the transcriptional cofactors *SOX5* and *SOX6*. With decreased expression of SOX9, the inhibition of *RUNX2* and β-catenin is released, and the cartilage cells gradually calcify and transdifferentiate into osteoblasts. Human skeletal stem cells (hSSCs) were recently isolated and identified by Michael T. Longaker et al. Unlike MSCs, hSSCs do not have the potential for adipogenic differentiation.[13] After fracture, hSSCs immediately undergo a regenerative response. hSSCs composed of podoplanin (PDPN), CD146, CD73 and CD164 signature proteins accumulate significantly at the fracture site and gradually differentiate into chondrocytes, osteoblasts and stromal cells.[13]

Osteoclasts are derived from hematopoietic stem cell lineage, specifically differentiating from tissue-resident monocytes/macrophages. The proliferation of osteoclast precursors is regulated by the interaction between macrophage colony-stimulating factor (M-CSF) and its receptor, c-FMS. Subsequent differentiation is initiated by the binding of receptor activator of nuclear factor-κB (RANK) to its ligand, RANKL, leading to the sequential development of mononuclear osteoclasts, multinucleated osteoclasts through cell fusion, and ultimately, mature osteoclasts. Mature osteoclasts attach to the bone surface, where they form a specialized structure known as the ruffled border. This structure facilitates efficient bone resorption through the secretion of protons (H+) to acidify the extracellular environment and proteolytic enzymes, such as cathepsin K (CTSK) and matrix metalloproteinases (MMPs), which degrade the organic components of bone matrix.[14]

Bone repair is a complex process involving the coordinated participation of multiple cell types. Inflammatory cells, mesenchymal stem cells, endothelial cells, chondrocytes, and osteocytes all play critical roles, ultimately regulating osteoblast and/or osteoclast activity to drive and complete the bone repair process.[3] During the initial inflammatory phase of bone repair, osteoclasts are recruited to resorb small bone fragments at the fracture site, which are subsequently incorporated into the forming callus.[15] Bone remodeling, a fundamental process in the later stages of repair, encompasses bone resorption, formation, quiescence, and subsequent resorption. This cyclical process is mediated by the coupling of osteoclasts and osteoblasts, ultimately resulting in the complete replacement of damaged or aged bone with new bone tissue.

The remodeling of the callus is an essential and integral component of the bone repair process. However, the ability of bone-resorbing osteoclasts to resorb cartilage has been a subject of debate. Previous studies have identified the presence of osteoclasts, sometimes referred to as chondroclasts, within tissue sections of the endochondral callus,[16] suggesting their potential role in cartilage resorption during callus remodeling.

Some studies have also shown that inhibiting the function of osteoclasts does not significantly affect the size of cartilage callus, but only delays the remodeling of hard callus. Studies using fracture models of *TRPV1* knockout mouse have shown that osteoclasts play a crucial role in the formation and remodeling of cartilage callus.[17] The reduced number of osteoclasts in *TRPV1* knockout mice leads to abnormal callus growth, large and persistent nonunions, and the reduced expression of RUNX2 and Alkaline phosphatase (ALP) in Bone mesenchymal stem cell (BMSC). Studies by Adams et al have shown that the cartilage resorption process is mediated by a small number of cells derived from mesenchymal stem cells (not from hematopoietic stem cells) expressing fatty acid binding protein 5 (FABP5), which are called septal cells (Septoclasts).[18] Septoclasts appear with the formation of blood vessels in the chondrocyte region during the long bone fracture healing process, and play the role of cartilage resorption and endochondral osteogenesis.

Maintaining the dynamic balance of osteoblasts and osteoclasts is the key to successful bone remodeling and is crucial to the final completion of bone repair. The site of bone remodeling activity is called the basic multicellular unit (BMU), which includes the following four consecutive stages: 1) recruitment and activation of osteoclast precursor cells to the damaged bone surface; 2) resorption of damaged bones by mature osteoclasts; 3) osteoclasts undergo apoptosis while recruiting osteoblast precursor cells; 4) mature osteoblasts produce new bone (the formed osteoid is mineralized). During the above process, the coupling between the two cells directly interacts through bidirectional signal transduction of EFNB2-EphB4, FASL-Fas or SEMA3A-NRP1[19–21] (Figure 2A). On the other hand, osteoblasts promote or inhibit the differentiation and activation of osteoclasts by secreting a series of active factors, such as M-CSF, RANKL, OPG,

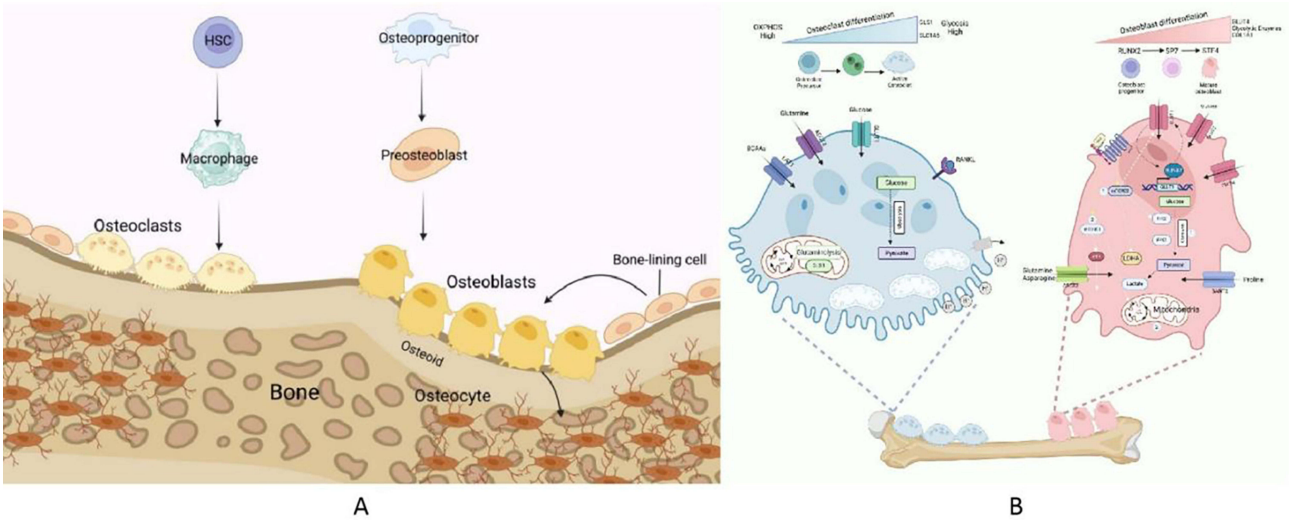

Figure 2 Bone Development, Repair Mechanisms and the Role of Energy Metabolism in Osteoblasts and Osteoclasts.
Notes: (**A**) Bone development and repair mechanisms; (**B**). Energy metabolism in osteoblast and osteoclast.

WNT5A, and WNT16. Osteoclasts also affect osteoblast differentiation through secretion of Sphingosine-1-Phosphate (S1P), collagen triple helix repeat containing-1 (CTHRC1) and C3.[22]

Overview of Bone Metabolism and Glucose Utilization

Bone metabolism is a dynamic and highly regulated process involving osteoblasts, which form new bone, and osteoclasts, which resorb bone. These two cell types work in a coordinated manner to maintain skeletal integrity. Their activity is tightly linked to energy metabolism, particularly glucose metabolism, which provides the necessary energy for bone remodeling[23–25] (Figure 2B). Recent studies suggest that glucose metabolism plays a crucial role in osteoblast and osteoclast function, influencing their differentiation, proliferation, and activity.[26–28]

Osteoblasts and Glucose Metabolism

Osteoblasts, derived from mesenchymal stem cells, predominantly rely on glycolysis rather than oxidative phosphorylation (OXPHOS), even in oxygen-rich conditions—a phenomenon similar to the Warburg effect in cancer cells.[29–31] This metabolic preference supports the biosynthetic demands of collagen production and extracellular matrix mineralization.[32,33] Glucose uptake in osteoblasts is primarily mediated by Glucose transporter type 1 (GLUT1), and its expression is crucial for osteoblast differentiation and function.[34–36] Inhibition of glycolysis has been shown to impair osteoblast differentiation, underscoring its importance in bone formation.[37]

Wnt/β-catenin and IGF1 signaling pathways have been implicated in enhancing glycolysis in osteoblasts.[38,39] IGF1 signaling, for instance, promotes glucose uptake through GLUT1 and enhances glycolytic enzyme expression.[40] Additionally, PTH signaling has been reported to shift osteoblast metabolism towards aerobic glycolysis, further promoting bone anabolism.[41,42] Conversely, Notch signaling suppresses glucose metabolism and osteoblast differentiation by activating AMPK, demonstrating the complexity of metabolic regulation in bone cells.[43]

Osteoclasts and Glucose Metabolism

Osteoclasts, derived from hematopoietic stem cells, require a significant amount of energy for bone resorption. Unlike osteoblasts, early osteoclast precursors depend on mitochondrial respiration, while mature osteoclasts shift towards glycolysis to meet their energy demands.[24,44,45] Studies have shown that inhibiting glycolysis impairs osteoclast differentiation and reduces their bone-resorbing activity.[46,47] This reliance on glycolysis is supported by increased GLUT1 expression during osteoclast differentiation.[48]

The RANKL/RANK signaling pathway, essential for osteoclastogenesis, upregulates glycolytic enzyme expression, including lactate dehydrogenase (LDH), which facilitates ATP production via glycolysis.[49,50] Additionally, the hypoxia-inducible factor-1α (HIF-1α) pathway enhances glycolytic metabolism in osteoclasts, thereby promoting bone resorption.[51,52] Interestingly, the metabolic shift towards glycolysis also increases lactate production, which contributes to the acidification of the resorption lacuna, further facilitating bone degradation.[53,54]

Energy Balance and Bone Remodeling

The balance between osteoblast and osteoclast activity is crucial for maintaining bone homeostasis, and metabolic pathways play a central role in this process.[55–57] AMPK and mTOR serve as metabolic sensors that regulate energy availability in bone cells.[58] While AMPK activation promotes catabolic processes and inhibits osteoclastogenesis, mTOR activation supports osteoblast differentiation and function.[59] The intricate interplay between energy metabolism and bone remodeling suggests that targeting glucose metabolism may provide new therapeutic strategies for metabolic bone diseases.

In summary, glucose metabolism is essential for both osteoblast and osteoclast function, influencing their differentiation and activity. Understanding the metabolic dependencies of bone cells can help identify new approaches for treating bone disorders such as osteoporosis and fracture healing deficiencies.

Sirtuins Participate in Glucose Metabolism of Bone Cells

Sirtuins (SIRTs), a highly conserved protein family known as class III histone deacetylases (HDACAs), are divided into four types: type I (SIRT 1–3), type II (SIRT4), type III (SIRT5), and type IV (SIRT6 - 7). Their distinct sub - cellular localizations, including the nucleus (SIRT1, 6, 7), cytoplasm (SIRT2), and mitochondria (SIRT3-5), endow them with diverse catalytic activities, thereby regulating various cellular functions such as energy homeostasis, oxidative stress response, and cell differentiation. In the context of bone tissue's complex energy metabolism, the interaction between SIRTs and bone cell glucose metabolism is of great significance.

SIRT1

SIRT1 (Table 2) was originally described as a histone deacetylase due to its NAD+-dependent deacetylation of lysine residues. Later studies found that it can also deacetylate non-histone proteins, such as p53, PGC-1α, and FoxO1. Its main roles in metabolism are mitochondrial biogenesis, glycolysis, response to hypoxia and angiogenesis[60] SIRT1 is related to insulin secretion and sensitivity and can be regarded as an insulin sensitizer. SIRT1 inhibits HIF-1α through insulin signaling, which can reduce the glycolysis rate and promote OXPHOS; at the same time, SIRT1 can also deacetylate and reduce the catalytic activity Phosphoglycerate mutase 1 (PGAM-1), thereby inhibiting the glycolysis process.[61] The inhibitory effect of SIRT1 on glycolysis helps reduce glucose consumption during conditions of fasting or energy deficiency.

A large number of studies have shown that the *Sirt1* gene was specifically knocked out in different bone lineage cells, proving that SIRT1 has a direct effect on bone lineage cells. Zainabadi et al established Sirt1-deficient mice in osteoblasts and osteoclasts, and found that these two mice models showed a phenotype of low bone mass in trabecular bone after Sirt1 knockout.[62] However, osteoblasts and osteoclasts Sirt1 double deficiency does not lead to a more severe bone loss phenotype. Mechanistic studies have shown that the bone loss phenotype of osteoblast Sirt1 deficiency is related to the reduced number of osteoblasts and reduced bone formation rate, while the phenotype of bone loss of osteoclast Sirt1 deficiency is associated only with increased osteoclast formation. At different differentiation stages of osteoblasts, SIRT1 has the potential to regulate osteoblast differentiation in early and late osteoblast lineages through different mechanisms, thereby increasing bone mass and protecting bone cortex and trabecular bone. Mice with osteoblast-specific knockout of SIRT1 (ObKO) showed osteopenia at 4 months, while mice with osteoclast-specific knockout of SIRT1 (OcKO) showed low bone mass at both 1 and 4 months.[62] In addition, pharmacological activation of SIRT1 has a protective effect against osteoporosis, and 12-month-old male mice treated with the SIRT1 agonist SRT1720 (100 mg/kg/day) for 5 months showed a significant increase in bone mass (approximately 30%).[62] Overexpression of Sirt1 in MSCs can increase the number of osteoblasts and decrease the number of osteoclasts to increase bone mass, and this phenotype can be observed even in aged mice.

Table 2 Sirtuins Participate in Glucose Metabolism of Bone Cells

SIRT Type	Location	Main Functions	Effects on Osteoblasts	Effects on Osteoclasts	References
SIRT1	Nucleus	Regulates glycolysis, mitochondrial biogenesis, oxidative stress response, and insulin sensitivity by deacetylating PGC-1α, FOXO1, and HIF-1α.	Enhances differentiation, increases bone formation, and reduces oxidative stress-induced apoptosis.	Suppresses osteoclast formation via NF-B inhibition and FOXO activation.	[60–66]
SIRT2	Cytoplasm	Involved in gluconeogenesis, insulin sensitivity, and fatty acid metabolism through deacetylation of PEPCK-C.	Limited direct impact; little research available.	May promote osteoclast differentiation through NFATc1 modulation.	[67,68]
SIRT3	Mitochondria	Enhances mitochondrial energy metabolism, protects against oxidative stress via SOD2 activation, and maintains cellular homeostasis.	Protects osteoblasts from oxidative stress, maintains mitochondrial function, and supports bone formation.	Regulates osteoclast activity via mTOR and ROS signaling.	[69,70]
SIRT4	Mitochondria	Inhibits insulin secretion via interaction with ANT2/3 and IDE in pancreatic β-cells, potentially affecting osteoblast differentiation.	Potentially affects differentiation through insulin signaling.	Influences bone resorption through insulin-mediated pathways.	[71,72]
SIRT5	Mitochondria	Regulates glycolysis, TCA cycle, and oxidative phosphorylation through desuccinylation and deglutarylation of metabolic enzymes.	Possibly impacts osteoblast function via mitochondrial metabolism regulation.	Potential effects through oxidative stress modulation in osteoclasts.	[73]
SIRT6	Nucleus	Reduces glycolysis by inhibiting HIF-1α and GLUT1, regulates mitochondrial respiration, and modulates osteoblast differentiation via RUNX2 and OSX.	Promotes differentiation, maintains bone homeostasis via RUNX2 and β-catenin interaction.	Reduces osteoclast numbers and inhibits FasL-mediated activation.	[74–76]
SIRT7	Nucleus	Regulates osteoblast differentiation by deacetylating OSX, interacts with WNT/β-catenin signaling.	Enhances osteoblast differentiation through OSX deacetylation and WNT/β-catenin signaling.	Effects on osteoclasts remain unclear.	[77,78]

SIRT1 plays an important role in regulating bone metabolism in both the skull and long bones, but there are certain differences in the mechanism and extent of its influence (Table 3). In the skull, SIRT1 mainly increases bone density by promoting osteoblast differentiation, and under calorie restriction (CR) conditions, SIRT1 expression is significantly upregulated, thereby improving bone quality.[62] In SIRT1 knockout mice, skull bone formation is inhibited, indicating that it has a positive regulatory effect on skull bone metabolism.[62] It is worth noting that the expression level of SIRT1 in the skull is relatively stable during aging.[62] In contrast, SIRT1 in long bones (such as femur and tibia) not only promotes osteoblast differentiation, but also reduces osteoclast activity and bone resorption by inhibiting the NF-κB signaling

Table 3 Comparison of SIRT1 Action in Skull and Long Bones

Comparison Criteria	Skull (Calvaria)	Long Bones (Femur, Tibia)
Effect of SIRT1 on Bone Density	SIRT1 promotes bone formation, increasing bone mass	SIRT1 promotes bone formation and reduces bone resorption
Cell Types Affected by SIRT1	Primarily affects osteoblasts	Affects both osteoblasts and osteoclasts
Impact of SIRT1 Knockout	Reduced bone mass, but less severe	Significant reduction in bone mass, more severe impact
Effect of Aging on SIRT1 Expression	SIRT1 expression remains relatively stable	SIRT1 expression may decline with age
Effect of SIRT1 Activation	Bone density can be enhanced by CR or SRT1720	Bone mass increases and bone resorption decreases with SRT1720 treatment

pathway, thereby maintaining bone homeostasis. In SIRT1 knockout mice, the bone density of long bones decreased particularly significantly, and osteoblast-specific knockout of SIRT1 also led to impaired bone formation in long bones,[79] indicating that SIRT1 has a stronger regulatory effect on long bones. In addition, SIRT1 overexpression mice showed an increased bone formation rate and a significant increase in bone density, further demonstrating the importance of SIRT1 in long bones.[79] Compared with the two, the effect of SIRT1 on long bones is more obvious than that on the skull. Bone loss in long bones is more severe when SIRT1 is missing, and SIRT1 overexpression has a stronger promoting effect on long bones.[62,79] At the same time, during the aging process, SIRT1 expression in long bones may decrease, while that in the skull is relatively stable, which may explain why long bones are more affected in elderly osteoporosis.[62,79]

In osteoclasts, SIRT1 inhibits differentiation by negatively regulating the NF - κB signaling pathway and positively regulating FoxO. This dual - regulatory effect on osteoblast and osteoclast differentiation helps maintain bone homeostasis. It is also worth noting that SIRT1 has different regulatory mechanisms and extents in the skull and long bones. In the skull, it mainly promotes osteoblast differentiation to increase bone density, and its expression is upregulated under calorie restriction, improving bone quality. In long bones, SIRT1 not only promotes osteoblast differentiation but also reduces osteoclast activity and bone resorption by inhibiting the NF - κB signaling pathway. The differential response of SIRT1 in different bone types may be related to the distinct microenvironments and cellular compositions.

Age significantly influences SIRT1 function. With aging, the expression of SIRT1 in long bones tends to decline, which may explain the more severe bone loss in long bones of the elderly. Gender differences also exist, although not fully elucidated. Given the hormonal differences between men and women, especially the role of estrogen in bone metabolism, further research is needed to clarify how gender affects SIRT1 - mediated bone metabolism. In terms of cell types, SIRT1 exhibits cell - specific functions. For example, its regulatory effect on MSCs during differentiation into osteoblasts is distinct from that on mature osteoblasts, highlighting the importance of considering cell - type specificity in SIRT1 - targeted therapies.

The mechanisms of SIRT1's effect on osteoblast lineage may be as follows: 1) SIRT1 activates RUNX2 through direct deacetylation of RUNX2, or promotes osteogenic differentiation of MSCs by forming SIRT1-FoxO3A complex and inhibiting the indirect regulatory effect of PPARγ; 2) SIRT1 upregulates β-catenin expression through direct deacetylation, or blocks the binding of FoxO to β-catenin through FoxO deacetylation, thereby stimulating WNT signaling to enhance osteoblast activity; 3) SIRT1 reduces osteosclerostin (SOST) expression to promote bone formation; 4) SIRT1 induces mitochondrial biogenesis and antioxidant enzyme production by activating PGC-1α transcriptional activity, thereby inhibiting ROS production and protecting cells; 5) In mature osteoblasts, SIRT1 inhibits p53-p21, NF-κB signaling, and the FoxO1/β-catenin pathway inhibit ROS to delay osteoblast apoptosis.[63–65] In addition, SIRT1 can inhibit osteoclast differentiation through negative regulation of NF-κB signaling and positive regulation of FoxO.[66] In summary, SIRT1 can promote osteoblast differentiation and inhibit osteoclast differentiation (Figure 3).

SIRT2

SIRT2 (Table 2) regulates spindle dynamics by deacetylation of tubulin during cell mitosis, ensuring the correct separation of chromosomes, while deacetylation of H4K16 promotes chromatin condensation and maintains genome stability.[4,5] In addition, SIRT2 also affects cell cycle progression by regulating the activity of mitotic checkpoint-related proteins (such as BubR1) and the APC/C complex, and participates in DNA replication stress response by deacetylation of CDK9 to ensure the accuracy of cell division.[4,5] Currently, research on SIRT2 is mainly focused on oncology, where it is regarded as a potential target for tumor treatment. Evidence-based studies have shown that its inactivation may lead to tumorigenesis. SIRT2 mediates phosphoenolpyruvate carboxykinase (PEPCK-C), thus stabilizing and reducing its ubiquitination.[67] As a glucose level sensor, SIRT2 also maintains insulin sensitivity and promotes gluconeogenesis or inhibits lipogenesis (mediated by PPARγ) through its deacetylation activity.

There are currently few reports on the effects of SIRT2 on bone cells. Studies have found that SIRT2 plays an important role in bone metabolism, especially in the age-related bone loss process. In vivo studies of SIRT2 knockout (SIRT2-KO) rats found that compared with wild-type (WT) rats, 36-week-old SIRT2-KO rats had significantly increased trabecular bone mineral density (Tb. BMD), bone volume fraction (BV/TV), and trabecular number (Tb. N), while no significant difference was found in 12-week-old rats. In addition, the serum bone resorption marker β-CTX level was reduced in SIRT2-KO rats, indicating that SIRT2 deficiency inhibited bone resorption.[68] In vitro experiments further

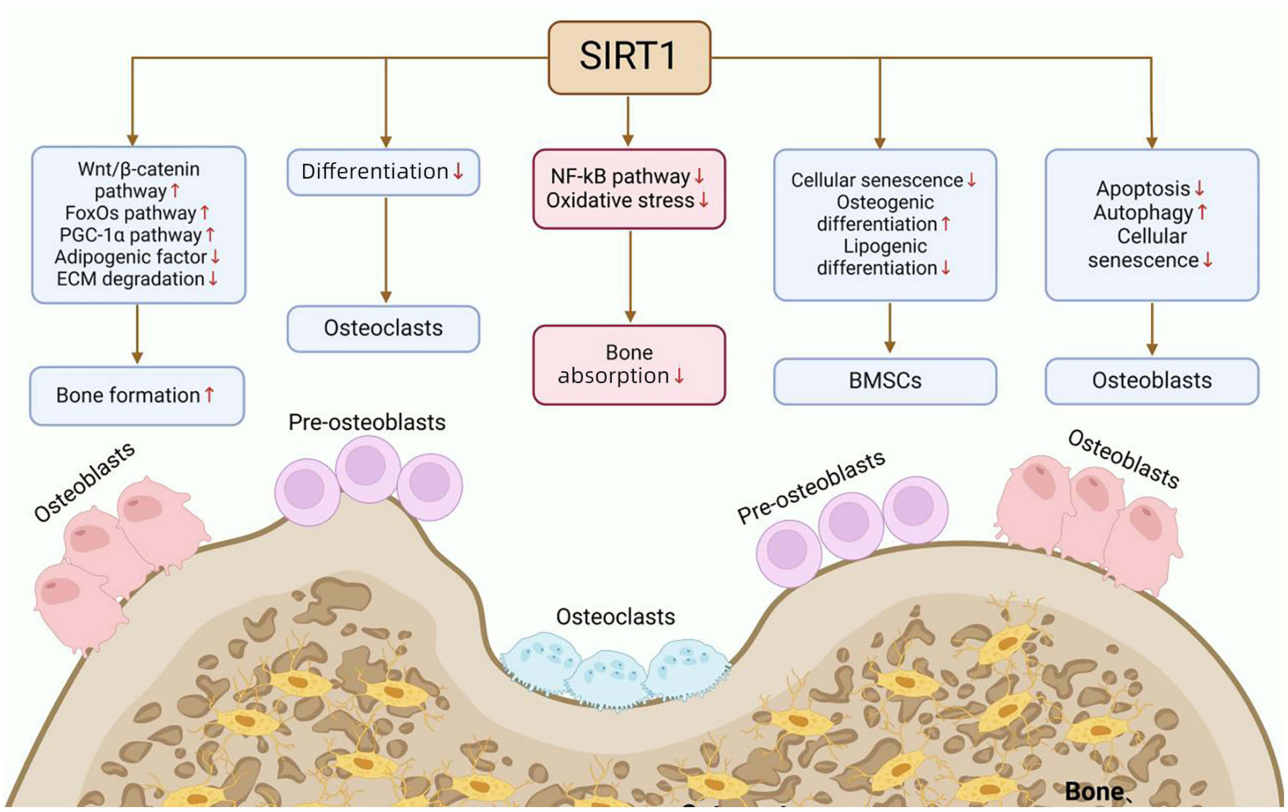

Figure 3 SIRT1 maintains bone homeostasis by targeting a series of downstream signaling pathways.
Notes: ↑ = Increase in the specified outcome. ↓ = Decrease in the specified outcome.

confirmed that the SIRT2 inhibitor AGK2 could significantly inhibit the differentiation of bone marrow-derived mononuclear cells (BMMs) into osteoclasts and reduce osteoclast formation by downregulating c-Fos and NFATc1 expression.[68] It can be speculated that SIRT2, mediated through NFATc1, has the potential to maintain or promote osteoclast differentiation. This suggests that SIRT2 may affect bone metabolism by regulating osteoclastogenesis.

Although research on the effect of SIRT2 on bone cells is limited, emerging evidence indicates its significance in bone metabolism, particularly in age - related bone loss. In a study of SIRT2 - knockout (SIRT2 - KO) rats, 36 - week - old SIRT2 - KO rats showed a significant increase in trabecular bone mineral density (Tb.BMD), bone volume fraction (BV/TV), and trabecular number (Tb.N) compared to wild - type rats, while no significant difference was observed in 12 - week - old rats. This suggests that the role of SIRT2 in bone metabolism becomes more prominent with age. The underlying mechanism may be related to its regulation of osteoclastogenesis. In vitro experiments have shown that the SIRT2 inhibitor AGK2 can significantly inhibit the differentiation of bone marrow - derived mononuclear cells (BMMs) into osteoclasts by down-regulating the expression of c - Fos and NFATc1.

The age - dependent effect of SIRT2 on bone metabolism implies that as the body ages, the balance of bone remodeling is disrupted, and SIRT2 may play a role in this process. Regarding gender, due to the different patterns of bone aging between men and women, future research should explore whether SIRT2 functions differently in male and female bone cells. In different cell types, SIRT2 seems to have a more direct impact on osteoclasts. However, considering the complex interactions between osteoblasts and osteoclasts, the indirect effect of SIRT2 on osteoblasts through osteoclast regulation also requires in - depth investigation.

SIRT3

SIRT3 (Table 2) is the main deacetylase in mitochondria. It has been found that it can target long-chain acyl-CoA dehydrogenase (LCAD), 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2), isocitrate dehydrogenase 2 (IDH2)

and glutamate dehydrogenase (GDH) promote energy metabolism.[69] In addition, SIRT3 can also protect cells from oxidative stress damage by ROS through activating superoxide dismutase 2 (SOD2). In response to changes in cellular energy, SIRT3 binds to the substrate acetyl-CoA synthase (AceCS2) and activates the enzyme activity of AceCS2 through deacetylation of AceCS2. In addition, SIRT3 can deacetylate Lys413 through IDH2, completely restoring the activity of the key TCA enzyme IDH2.[69]

Huh et al reported 8-week-old Sirt3-deficient mice showed a phenotype of premature skeletal aging (lower trabecular bone mass). SIRT3 deacetylates and activates SOD2, thereby improving mitochondrial antioxidant capacity, reducing the accumulation of reactive oxygen species (ROS), protecting osteoblasts from oxidative damage, and promoting osteogenic differentiation.[69] In addition, SIRT3 deacetylates isocitrate dehydrogenase 2 (IDH2) and glutamate dehydrogenase (GDH), enhancing the tricarboxylic acid cycle (TCA) and NADPH production, improving mitochondrial energy metabolism, ensuring the energy supply required for osteoblast differentiation and mineralization, and promoting new bone formation.[69] On the other hand, SIRT3 deacetylates and activates FoxO3a, regulating the expression of osteoblast antioxidant genes, improving cell survival rate, and maintaining osteoblast energy homeostasis through the AMPK signaling pathway, thereby enhancing osteogenic capacity.[80] In addition, SIRT3 also regulates the RANKL-OPG axis to reduce the formation of osteoclasts, thereby reducing bone resorption and maintaining bone homeostasis, ultimately promoting bone formation and protecting bone tissue.[80] Therefore, SIRT3 has protective effect on bone formation.

The role of SIRT3 in osteoclasts remains controversial. Studies have shown that SIRT3 can promote osteoclastogenesis by activating the mTOR pathway, and knocking out Sirt3 in BMMs promotes osteoclast differentiation and activation due to enhanced ROS expression.[70] This contradiction may be attributed to multiple factors. Firstly, different experimental models, such as the use of BMMs versus RAW 264.7 cells or in - vivo versus in - vitro experiments, can lead to inconsistent results. Secondly, the metabolic state of cells also affects SIRT3 function. When ATP production is impaired after Sirt3 deficiency, cells may shift to glycolysis to meet energy demands, which in turn affects osteoclast differentiation. Thirdly, the different stages of osteoclast differentiation and the balance of ROS levels play important roles. SIRT3 can both reduce ROS to inhibit excessive oxidative damage and promote osteoclast differentiation by regulating an appropriate amount of ROS.

Age may influence SIRT3 function in bone cells. As the body ages, mitochondrial function declines, which may affect the activity and expression of SIRT3. Gender differences also need to be considered, as estrogen levels can impact bone metabolism, and the relationship between SIRT3 and estrogen remains unclear. In different cell types, SIRT3 shows distinct functions in osteoblasts and osteoclasts, and its effect may vary depending on the differentiation stage of bone cells, adding complexity to the understanding of its role in bone metabolism.

SIRT4

SIRT4 (Table 2) in the mitochondrial matrix has ADP ribosyltransferase activity. Studies have found that under energy-sufficient conditions, SIRT4, which is highly expressed in pancreatic β-cells, can interact with adenine nucleotide transporter 2/3 (ANT2/3) and insulin-degrading enzyme (IDE) to inhibit insulin secretion. SIRT4 inhibits the transport function of ANT2/3 by binding to it, limiting the output of mitochondrial ATP to the cytoplasm, and reducing the ATP/ADP ratio, thereby indirectly inhibiting the closure of ATP-dependent K^+ channels, reducing membrane depolarization and insulin release.[81] In addition, SIRT4 can also interact with IDE, enhancing its ability to degrade insulin, reducing the storage and secretion level of insulin in cells.[82] In a state of sufficient energy (high sugar), SIRT4 is highly expressed, inhibiting the activity of GDH, reducing glutamate metabolism, limiting TCA cycle activity, further reducing ATP generation, and ultimately reducing insulin secretion.[83]

There is an insulin receptor (IR) on the surface of osteoblasts, and IR-deficient mice will exhibit reduced osteoblast differentiation caused by inhibition of RUNX2. Therefore, when insulin signaling is lacking, the level of osteoblast differentiation will be reduced. IR activates RUNX2 through the PI3K/AKT signaling pathway to promote osteoblast differentiation, while IR deficiency leads to weakened PI3K/AKT signaling, which prevents RUNX2 from being effectively activated, thereby inhibiting osteogenic differentiation.[71] At the same time, IR deficiency leads to decreased AKT activity, which prevents FoxO1 from being phosphorylated and retained in the nucleus, thereby inhibiting the expression and activity of RUNX2.[71] Overactive FoxO1 also promotes the expression of osteogenic inhibitory genes,

further reducing osteogenic differentiation.[71] In addition, insulin can promote the expression of osteocalcin and collagen type I through IR, while IR deficiency reduces the expression of these genes, affecting bone formation, and the lack of insulin signaling also affects the activity of the Wnt/β-catenin signaling pathway, further weakening RUNX2-mediated osteogenic differentiation.[71] Kumar et al found that insulin signaling can stimulate bone resorption.[72] This phenomenon may be related to the activation and secretion of osteocalcin induced by insulin signaling, which maintains a relative balance between bone resorption and bone formation.

Age can affect insulin sensitivity and SIRT4 expression, which may in turn influence bone metabolism. During the aging process, the increase in insulin resistance and the potential change in SIRT4 expression may disrupt the normal differentiation and function of osteoblasts. Regarding gender, the post - menopausal decrease in estrogen levels in women affects insulin sensitivity and bone metabolism. Whether SIRT4 functions differently in men and women in this context requires further study. In different cell types, SIRT4 mainly acts on osteoblasts through insulin - signaling regulation, but its potential impact on osteoclasts and the underlying mechanisms remain to be explored.

SIRT5

SIRT5 (Table 2) can specifically recognize negatively charged acylated lysine structures. Because of its larger lysine acyl binding pocket in its structure, SIRT5 has significant desuccinylation, demalonylation and deglutarylation activities compared with other members of the Sirtuins family. Through protein post-translational modification, it participates in the regulation of important physiological processes such as glycolysis, tricarboxylic acid cycle, electron transport chain, oxidative stress, and cell apoptosis, and plays an important role in physiological functions such as antioxidant, regulating mitochondrial apoptosis and inflammatory response.[4]

Mass spectrometry analysis showed that most of SIRT5's substrates are key enzymes involved in metabolic regulation. As a protein deacetylase with deacetylation activity, SIRT5 regulates the activity of multiple metabolic enzymes through de-modification. Among them, SIRT5 acts on the rate-limiting enzyme of sugar metabolism through desuccinylation and deglutarylation, thereby affecting the level of glucose metabolism in cells. It has been reported that SIRT5 promotes IDH desuccinylation and glucose-6-phosphate dehydrogenase (G6PD) deglutarylation respectively to regulate intracellular NADPH homeostasis and redox potential. Sirt5 deficiency will lead to high levels of intracellular ROS, causing oxidative damage to cells.[73] In addition, SIRT5 activates PMK2 through desuccinylation, enhancing its ability to catalyze the terminal reaction of glycolysis, thereby increasing ATP production and biomass synthesis, and promoting cellular metabolic adaptation. The upregulation of PMK2 activity not only increases glycolytic flux, but may also affect oxidative phosphorylation and ROS balance by regulating the function of the mitochondrial electron transport chain (ETC).

At present, there are few reports on the effect of SIRT5 on bone cells. However, considering that bone cells play an important role in the metabolic process and are regulated by relevant signals in metabolic pathways, SIRT5 in mitochondria, which are metabolic centers, is involved in a variety of metabolisms. The regulation of enzymes and mitochondrial biological functions may affect the differentiation and function of bone cells through direct or indirect effects.

Although there are limited reports on the effect of SIRT5 on bone cells, considering the importance of bone cells in metabolism and the central role of mitochondria in cellular metabolism, SIRT5 may affect bone cell differentiation and function. Given that bone remodeling requires a large amount of energy, the regulation of metabolic enzymes by SIRT5 in mitochondria may directly or indirectly influence the energy supply for bone cell activities. Future research should focus on clarifying the specific mechanisms through which SIRT5 affects bone cells, such as its impact on osteoblast differentiation and osteoclast activity.

SIRT6

SIRT 6 (Table 2) is regarded as an ADP-ribosylase and acts as an NAD^+-dependent deacylase of acetyl and long-chain fatty acyl groups, mainly deacetylating histones H3Lys9 and H3Lys56.[5] Therefore, SIRT 6 affects cellular homeostasis by regulating DNA repair, DNA telomere stability, and glucose and lipid metabolism. SIRT6 can inhibit multiple key regulators of glycolysis to reduce glycolytic flux, such as HIF-1α, GLUT1, and also inhibit insulin and AKT signal transduction. SIRT6 deficiency exhibits increased HIF-1α activity and glucose uptake, as well as reduced mitochondrial respiration.[74]

Sirt6 deficiency mice in MSCs showed an impaired bone formation phenotype with significantly reduced trabecular bone density and cortical bone volume; however, overexpression of Sirt6 hinders the osteoblast differentiation of MSCs.[75] This indicates that SIRT6 has a dual regulatory role in MSC osteogenic differentiation. Its deficiency leads to decreased RUNX2 expression, inhibiting MSC differentiation into osteoblasts, and accelerates MSC transdifferentiation into adipocytes by impairing the Wnt/β-catenin signaling pathway, thereby weakening bone formation ability.[75] At the same time, SIRT6 maintains mitochondrial homeostasis. Its deficiency leads to impaired mitochondrial energy metabolism, affecting the ATP supply of osteoblasts and reducing osteogenic activity.[75] On the other hand, SIRT6 overexpression negatively regulates c-Myc by deacetylation of H3K56, inhibits ribosome biogenesis, and reduces cell proliferation, thereby hindering MSC differentiation into osteoblasts.[75] In addition, SIRT6 overexpression also inhibits HIF-1α activity and reduces the expression of glycolytic enzymes, limiting energy supply during MSC differentiation, thereby limiting osteogenic differentiation.[75]

Some studies have found that SIRT6 promotes osteoblast activity through direct interaction with RUNX2 and OSX, mainly by deacetylation of H3K9 promoter and interaction of SIRT6 with RUNX2 and OSX.[76] Specific knockout of Sirt6 in hematopoietic stem cells reduces the number of osteoclasts through increased OPG expression. Loss of SIRT6 expression in osteoclast precursor cells will inhibit transcription in osteoclast precursors FasL to induce osteoclast activation, resulting in an increase in the number of osteoclasts.

In bone metabolism, SIRT6 has a dual - regulatory role in MSC osteogenic differentiation. Sirt6 - deficient mice in MSCs show an impaired bone - formation phenotype with reduced trabecular bone density and cortical bone volume. The deficiency of SIRT6 leads to decreased RUNX2 expression, inhibiting MSC differentiation into osteoblasts and promoting their trans - differentiation into adipocytes through the impairment of the Wnt/β - catenin signaling pathway. On the other hand, SIRT6 overexpression in MSCs also hinders osteoblast differentiation. It negatively regulates c - Myc by deacetylating H3K56, inhibits ribosome biogenesis, and reduces cell proliferation.

In osteoclasts, specific knockout of Sirt6 in hematopoietic stem cells reduces the number of osteoclasts through increased OPG expression. However, the loss of SIRT6 expression in osteoclast precursor cells inhibits the transcription of FasL in osteoclast precursors, leading to an increase in the number of osteoclasts. The complex role of SIRT6 in bone cells may be related to its regulation of multiple signaling pathways, and further research is needed to fully understand its mechanism of action.

SIRT7

SIRT7 (Table 2) is a widely expressed nuclear protein that interacts with RNA polymerase I and histones and is a positive regulator of RNA polymerase transcription, making it closely related to activated rRNA genes (rDNA). Therefore, it is important for cell survival and is essential nuclear protein for DNA damage response.[4,5] Studies have reported that SIRT7 can interact with HIF-1α and HIF-2α, resulting in the inhibition of HIF-1α/2α transcription and reduced protein levels.[77] SIRT7 deacetylates HIF-1α and HIF-2α, weakening their ability to bind to target gene promoters, thereby inhibiting their transcriptional activity and reducing their stability, making them more susceptible to degradation and reducing protein levels. In addition, SIRT7-mediated deacetylation enhances the binding of HIF-1α/2α to the von Hippel-Lindau (VHL) complex, which acts as an E3 ubiquitin ligase to promote the ubiquitination of HIF-1α/2α and degradation through the proteasome pathway, thereby further reducing its protein content. Since HIF-1α/2α is a key transcription factor that regulates glucose metabolism and angiogenesis under hypoxic conditions, SIRT7 reduces the expression of downstream genes such as VEGF and GLUT1 by inhibiting its activity, thereby reducing the ability of cells to adapt to hypoxic environments.

Adult female Sirt7-deficient mice showed significantly reduced trabecular and cortical bone mass, and specific deletion of Sirt7 in osteoblasts also showed reduced trabecular bone mass and cortical bone thickness, which was related to osteoblast number and bone formation defects.[78] The current study did not report the effect of SIRT7 on osteoclasts, so it cannot be ruled out that it may indirectly affect bone mass by regulating osteoclast activity. For example, SIRT7 may affect osteoclast activity by regulating the RANKL/OPG ratio or the NF-κB pathway, and future studies should further verify its role in osteoclasts. The mechanism of action of SIRT7 on osteoblasts may be that SIRT7 deacetylates OCX C-terminal Lys368 and promotes the depropionylation of OSX by SIRT1, which is related to the positive regulation of OSX transactivation activity Studies have shown that SIRT7 knockdown can accelerate bone formation of BMSCs

through the WNT/β-catenin pathway to a certain extent.[76] However, this seems to contradict the conclusion that SIRT7 deficiency leads to bone loss. This may be related to different cell types or experimental conditions. For example, in BMSCs (bone marrow mesenchymal stem cells), SIRT7 knockdown may promote their differentiation into osteoblasts, while in mature osteoblasts, SIRT7 may promote osteogenic activity by regulating OSX through deacetylation. Therefore, the specific effect of SIRT7 on osteogenesis may depend on the interaction of cell type, differentiation stage and signaling pathway, and future studies need to clarify its spatiotemporal specific effects.

The mechanism of SIRT7 on osteoblasts may involve the deacetylation of OCX C - terminal Lys368 and the promotion of OSX depropionylation by SIRT1, which is related to the positive regulation of OSX transactivation activity. However, the seemingly contradictory results between SIRT7 knockdown promoting bone formation in BMSCs and Sirt7 deficiency leading to bone loss may be due to differences in cell types or experimental conditions. Future studies are required to clarify the spatiotemporal - specific effects of SIRT7 on osteogenesis.

Quantitative Synthesis of Sirtuin-Related Effects

While a meta-analysis was not conducted due to heterogeneity in study design and outcome measures, several key studies report quantitative findings that support the magnitude of Sirtuin-related effects in bone metabolism (Table 4).

Progress in Therapeutic Research

In recent years, there has been an increasing number of targeted therapeutic studies on Sirtuins, which are mainly divided into two categories: Sirtuin activating compounds (SACs) and Sirtuin inhibitors. Sirtuins play a key role in fracture repair and bone metabolism, making them potential therapeutic targets.

SACs

SACs mainly act on SIRT1, and their representative drugs include resveratrol and its derivative SRT1720. Studies have shown that SRT1720 can significantly enhance bone formation, reduce bone resorption, and increase bone density, which is expected to improve the clinical problems of osteoporosis and poor fracture healing.[84] In addition, SIRT3 activators such as nicotinamide riboside (NR) enhance the deacetylation activity of SIRT3, improve mitochondrial function, reduce osteocyte oxidative stress, and promote mitochondrial homeostasis through the AMPK-PGC-1α/MnSOD pathway, thereby increasing osteoblast activity, inhibiting osteoclastogenesis, and ultimately promoting bone repair and maintaining bone homeostasis.[85] However, this type of compound still faces limitations such as poor stability, low bioavailability, and potential nonspecific effects in clinical settings.[86]

Sirtuin Inhibitors

Sirtuin inhibitors are mainly used to reduce the adverse effects caused by overactive Sirtuins.[87] The SIRT2 inhibitor AGK2 reduces osteoclastogenesis and bone resorption by inhibiting the deacetylation of SIRT2. Studies have found that SIRT2 activity is closely related to osteoclast differentiation, and its inhibitor AGK2 can block the activation of NF-κB and Akt signaling pathways, thereby reducing osteoclast formation and bone loss. In addition, AGK2 can also inhibit oxidative stress levels and reduce the expression of inflammatory factors, thereby effectively preventing age-related bone

Table 4 Summary Of Sirtuin Isoforms And Bone Metabolism Effects

Sirtuin Isoform	Reference	Model System	Reported Outcome	Effect Size Estimate
SIRT1	Zainabadi et al[62]	OVX mice (osteoporosis model)	↑ Trabecular bone volume (~25%)	~25% increase
SIRT1	Yao et al[64]	MC3T3-E1 osteoblasts (oxidative stress)	↓ Apoptosis by 40% via FoxO1/β-catenin	~40% reduction in apoptosis
SIRT1	Gu et al[65]	MC3T3-E1 osteoblasts (fluoride exposure)	↑ Apoptosis via p53 acetylation (knockdown)	Qualitative increase (no % given)
SIRT2	Jing et al[68]	Rats (age-related bone loss)	↓ Osteoclastogenesis by 50%	~50% reduction
SIRT3	Li et al[70]	Mice (estrogen deficiency model)	↓ Osteoclast number (30–40%), ↑ bone density	30–40% reduction in osteoclasts
SIRT6	Sugatani et al[74]	SIRT6 knockout mice	↓ Bone turnover markers, osteopenia	Significant reduction (qualitative)
SIRT6	Kim et al[76]	SIRT6-deficient osteoblast lineage cells	↑ Osteoclast activity, osteopenia	Increased osteoclast activity (qualitative)

Notes: ↑ = Increase in the specified outcome. ↓ = Decrease in the specified outcome.

loss, showing potential value in the prevention and treatment of osteoporosis.[88] In addition, SIRT6 inhibitors can increase osteoblast activity and promote bone formation,[89] and its mechanism involves multiple signaling pathways. SIRT6 mainly regulates the Wnt/β-catenin and NF-κB signaling pathways by deacetylation of H3K56 and H3K9.[89] During osteogenesis, SIRT6 inhibits the Wnt signaling pathway, reduces the accumulation of β-catenin, and thus inhibits osteoblast differentiation.[89] In addition, SIRT6 inhibits NF-κB signaling, reduces the expression of inflammatory factors, and maintains bone homeostasis. The loss or inhibition of SIRT6 can enhance the expression of osteoblast-related genes such as Runx2 and Osx, thereby promoting osteoblast differentiation and increasing bone formation.[89] However, such inhibitors may have adverse effects on other tissues or systems, such as increasing cancer risk or interfering with normal cell cycle regulation, which limits their clinical application.[90]

Current Status and Challenges of Clinical Trials

Although targeted drugs for Sirtuins have clear therapeutic potential, related clinical research is still in the early stages, and long-term safety and effectiveness need to be further verified. At present, most studies are still focused on animal models and cell experiments, with a limited number of clinical trials and small sample sizes. In addition, due to the complexity and tissue specificity of the functions of members of the Sirtuins family, unexpected side effects and selectivity challenges may be faced during drug development. For example, SIRT1 promotes bone formation in bone tissue, but may regulate inflammation or affect metabolic processes in other tissues, so SACs may have multiple effects.

Future Development Direction

This review has several limitations that should be acknowledged. Firstly, although we intended to conduct a meta - analysis to synthesize the data, challenges in data compatibility and availability among the included studies prevented us from performing a comprehensive meta - analysis. As a result, we were unable to report meta - analysis parameters such as the number of included studies, the I^2 statistic for heterogeneity, and combined effect values (eg, OR, RR, MD). This lack of meta - analysis means that we could not quantitatively summarize the overall effect of Sirtuins on bone metabolism and fracture healing, potentially limiting the strength of our conclusions. Secondly, due to the absence of a meta - analysis, we did not perform a funnel plot or Egger's test to assess publication bias. Publication bias can significantly affect the reliability of research findings, as studies with positive or significant results are more likely to be published. Without evaluating this bias, we cannot be certain that our review is free from the influence of unpublished studies, which may have different outcomes and could potentially change our understanding of the role of Sirtuins in bone - related processes. The third notable limitations of this review is the potential language bias inherent in the literature search. By restricting the language of included studies to English and Chinese, there is a risk of overlooking valuable research conducted in other languages. This may lead to an incomplete understanding of the role of Sirtuins in bone metabolism, as studies published in languages other than English and Chinese could potentially offer unique insights, novel findings, or different perspectives on the subject matter.

In future research, we plan to address these limitations. We will focus on improving data collection methods to ensure better compatibility among studies, enabling a more robust meta - analysis. This will involve standardizing data reporting in future studies and using more advanced statistical techniques to account for heterogeneity. Additionally, we will conduct a thorough funnel plot and Egger's test to accurately assess publication bias. By doing so, we aim to provide a more comprehensive and reliable understanding of the role of Sirtuins in bone metabolism and their potential as therapeutic targets for fracture healing and other bone - related diseases. To mitigate this limitation, future research could consider the use of translation tools for critical non - English studies.

In the future, the research on Sirtuins targeted therapy needs to be further promoted from multiple aspects. First, drug design should be optimized to improve the tissue specificity of SACs and inhibitors to reduce unnecessary side effects and enhance the therapeutic effect. Secondly, the mechanism of action of Sirtuins in fracture repair and bone metabolism needs to be studied in depth to further reveal its specific function in bone physiological regulation in order to develop more precise intervention strategies. In addition, the advancement of clinical trials is crucial, and large-scale, multi-center clinical trials should be accelerated to systematically evaluate the long-term efficacy and safety of Sirtuins targeted therapy to provide solid evidence support for future clinical applications. Finally, the combined application of Sirtuins

targeted drugs with other bone repair therapies can be explored, such as combined with stem cell therapy, tissue engineering and other strategies to improve the overall therapeutic effect and promote bone tissue regeneration and functional recovery. Comprehensive consideration of the research progress in these aspects will help promote the clinical transformation and application of Sirtuins targeted therapy in the treatment of bone-related diseases.

Summary and Outlook

Sirtuin proteins are differentially expressed in bone metabolism-related cells and play a role at the intersection of bone and energy metabolism, offering a potential pathway to explore bone repair mechanisms. Currently, research on targeted drugs based on Sirtuins is continuously emerging. Elucidating the mechanism of Sirtuins on important signaling molecules in the bone repair mechanism may provide new targets for the clinical treatment of poor fracture healing.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study is a literature review and does not require the informed consent of patients, and does not require ethical approval.

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