Current Osteoporosis Reports (2023) 21:1–10
https://doi.org/10.1007/s11914-022-00763-6

BIOMECHANICS (JS NYMAN AND V FERGUSON, SECTION EDITORS)

The Role of Bone Cell Energetics in Altering Bone Quality and Strength in Health and Disease

Carolyn Chlebek[1] · Clifford J. Rosen[1]

Accepted: 26 October 2022 / Published online: 26 November 2022

Abstract

Purpose of Review Bone quality and strength are diminished with age and disease but can be improved by clinical intervention. Energetic pathways are essential for cellular function and drive osteogenic signaling within bone cells. Altered bone quality is associated with changes in the energetic activity of bone cells following diet-based or therapeutic interventions. Energetic pathways may directly or indirectly contribute to changes in bone quality. The goal of this review is to highlight tissue-level and bioenergetic changes in bone health and disease.

Recent Findings Bone cell energetics are an expanding field of research. Early literature primarily focused on defining energetic activation throughout the lifespan of bone cells. Recent studies have begun to connect bone energetic activity to health and disease. In this review, we highlight bone cell energetic demands, the effect of substrate availability on bone quality, altered bioenergetics associated with disease treatment and development, and additional biological factors influencing bone cell energetics.

Summary Bone cells use several energetic pathways during differentiation and maturity. The orchestration of bioenergetic pathways is critical for healthy cell function. Systemic changes in substrate availability alter bone quality, potentially due to the direct effects of altered bone cell bioenergetic activity. Bone cell bioenergetics may also contribute directly to the development and treatment of skeletal diseases. Understanding the role of energetic pathways in the cellular response to disease will improve patient treatment.

Keywords Bioenergetics · Bone quality · Substrate availability · Glycolysis · Oxidative phosphorylation

Introduction

Cellular mechanisms such as collagen deposition, mineralization, and bone resorption rely on cellular energy to effectively produce changes in bone quality. Examinations of bone quality often focus on altered bone composition and morphology, neglecting the bioenergetic pathways necessary for tissue-level changes. Mammalian cells generate reservoirs of energy in the form of adenosine 5'-triphosphate (ATP) via several pathways. Glycolysis produces two units of ATP per glucose input and can take place anywhere in the cytosol of the cell. Oxidative phosphorylation is more energy efficient and produces 32 ATP molecules per input glucose; however, the bioenergetic advantage of this pathway is limited due to the reliance on oxygen availability, confinement to the mitochondria, and extended length of time required for ATP generation. Converted glucose molecules are the primary oxidative input in most cells, but mitochondrial respiration can also be fueled by fatty acids and amino acids [1] (Fig. 1).

Across all cell types, energetic pathways can both activate or be activated by other biological processes. Glycolysis initiates downstream signaling pathways, such as Wnt signaling [2]. Oxidative phosphorylation produces reactive oxygen species, which have established roles in inducing DNA damage and cell death but can also act as signaling molecules through various pathways such as differentiation, proliferation, and antioxidant production [3, 4]. The extent of glycolytic and oxidative activity within cells also are altered by numerous upstream signaling pathways. Energetic pathway activity is critical for healthy bone cell function, influencing bone remodeling activities and regulating organ-level bone quality.

This article is part of the Topical Collection on *Biomechanics*

✉ Clifford J. Rosen
Clifford.Rosen@mainehealth.org

[1] Maine Medical Center Research Institute, 81 Research Drive, Scarborough, ME, USA

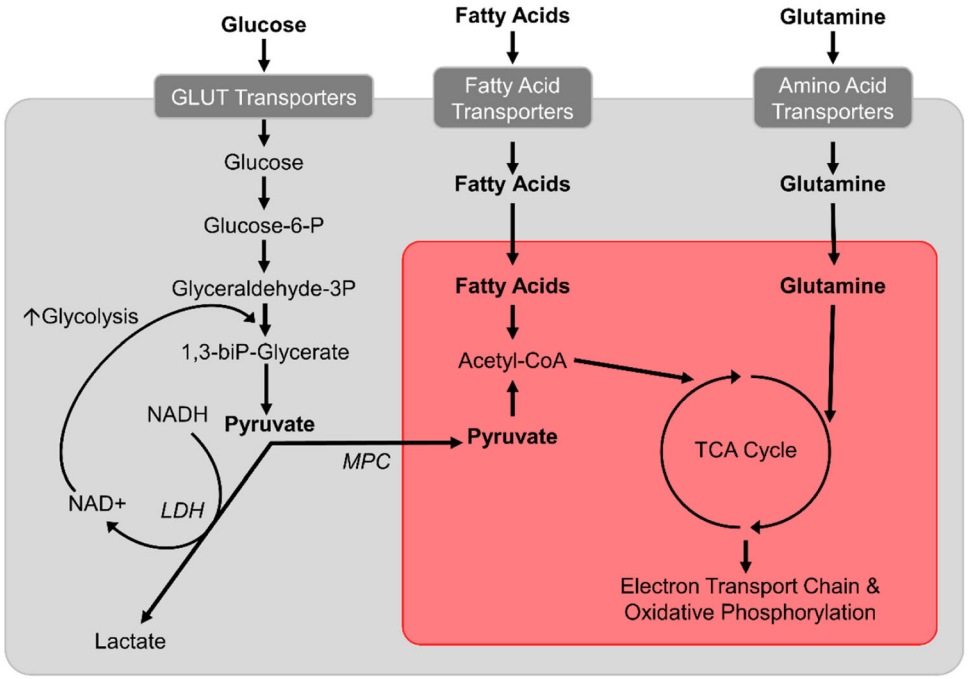

Fig. 1 Cells derive energy from glucose, fatty acids, and amino acids such as glutamine

Many bone diseases and their treatments can alter bioenergetic activity within bone cells, highlighting the complex interactions between osteogenic signaling and energetic pathways.

Bone Cell Energetic Demands

Osteoclasts, osteoblasts, and osteocytes each play unique roles in bone growth, maintenance, and repair. The energetic pathways supporting bone cell function remain underexplored. Osteoclasts participate in bone remodeling by resorbing mineralized tissue, and the release of minerals during this process contributes to whole-body calcium homeostasis [5]. During osteoclast differentiation, cells produce more energy via oxidative phosphorylation compared to glycolysis, but both energetic pathways are necessary [6–8]. Disruption of mitochondrial function during differentiation negatively affected osteoclasts; inhibition of *Mfn2*, a gene encoding mitochondrial outer membrane protein Mitofusin 2, decreased osteoclast number [9] and global deletion of mitochondrial complex I decreased osteoclast differentiation and subsequent resorption [10].

Osteoclastic resorptive activities rely on the influx of glucose as the primary substrate, and lactate or pyruvate supplementation can support resorptive activities in the absence of glycolysis [11]. Although serum-level fatty acid oxidation was associated with systemic bone resorption marker CTX [12], fatty acids and amino acids have relatively small contributions to the bioenergetic programs driving resorption [13]. Compared to progenitors, mature osteoclasts have diminished glycolytic efficiency and elevated intracellular ATP [14]; however, inhibition of glycolysis prevented resorptive activity [11]. Both osteoclastogenesis and resorption were suppressed in mouse models lacking *Pdk2* [7], a positive regulator of aerobic glycolysis. Osteoclasts have more abundant mitochondria compared to most other cell types [15, 16], yet the resorptive process relies on both oxidative phosphorylation [9] and glycolysis [11, 13, 14].

Osteoblasts, cells that deposit mineralized matrix that forms bone tissue, differentiate from mesenchymal stromal cells. As osteoblastic differentiation progresses, oxidative phosphorylation and glycolysis are elevated simultaneously [17–19, 20•, 21•]. Mitochondrial size [18, 22], volume [18, 22], and number [17] increase over the course of osteoblastic differentiation. Despite osteoblastic reliance on increased oxidative phosphorylation during differentiation [23], mature osteoblasts use both oxidative phosphorylation and glycolysis [17, 19, 21•, 22, 24]. Compared to progenitors, mature osteoblasts generate a greater portion of ATP via glycolysis over oxidative phosphorylation [19, 21•, 25••, 26]. Although osteoblastic oxidative phosphorylation is likely primarily fueled by pyruvate [25••], amino acid consumption also plays a role. Reduction in amino acids via inhibition of *Eif2ak4* led to decreased proliferation of precursors, diminishing osteoblast function *in vivo* [27]. Inhibition of *Slc7a*, an amino acid transporter responsible for rapid increases in glutamine, reduced Wnt signaling-induced osteoblast differentiation [28]. Systemic bone formation marker P1NP was associated with metabolic activity related to the TCA cycle and pyruvate metabolism in healthy adults [12].

Bioenergetic programs affect downstream signaling in osteoblasts and their precursors; glucose availability is required for Runx2-mediated osteoblastic differentiation and

deposition of collagen by osteoblasts [29]. Wnt signaling, a canonical pathway associated with bone formation, has differential effects on osteoblasts and their precursors; Wnt signaling stimulates glutamine catabolism through the TCA cycle in osteoblastic precursors [30] but increases aerobic glycolysis in mature osteoblasts [31]. Downstream effects of Wnt-Lrp5 signaling influence whole-body fatty acid levels [32]. Mitochondria may be enhanced by Wnt signaling; Wnt3a treatment increases mitochondrial biogenesis in osteoblasts and their progenitors [33]. Molecules in the Wnt signaling pathway may serve as promising targets for future therapeutics to treat bone disease [34], but the connection between Wnt and bioenergetic function highlights a new set of pharmaceutical opportunities.

As osteoblasts deposit new bone, they can further differentiate into bone resident cells, osteocytes. Early studies reported that osteocytes have fewer mitochondria than osteoblasts, suggesting an energetic shift from oxidative phosphorylation to glycolysis [15]. However, more recent evidence indicates that mitochondrial respiration is greater in osteocytes compared to osteoblasts [20•, 35]. Mitochondrial number within osteocytes varies within cortical bone tissue as a function of cell distance from the bone surface, suggesting spatial differences in bioenergetic activity [35, 36]. Mitochondria can be transferred between osteocytes in response to metabolic stress [37]. Osteocyte signaling can control the bone remodeling unit, affecting both bone resorption and formation [38]. Energetic pathways affect osteocyte signaling, and osteocytic production of RANKL and osteocalcin is dependent on glucose uptake by Glut1 [39].

Biological Factors Influencing Bone Metabolism

Aging

Osteogenic metabolism reflects the unique aspects of bone and varies across health conditions and between sexes. Within many organ systems, aging is associated with increased mitochondrial dysfunction and accumulation of mitochondrial DNA (mtDNA) mutations. In bone, mitochondria become more porous with age and produce reactive oxygen species [40]. Age-related mitochondrial swelling has been recorded in osteocytes but not osteoblasts [41]. Murine models containing genetic modifications that increase the rate of mtDNA mutations are associated with early-onset osteoporosis following the accumulation of peak bone mass [42].

The reliance on glycolysis or oxidative phosphorylation likely shifts with age. Whole bone metabolites were altered with age; compared to young animals, older mice have elevated glycolytic intermediates but similar TCA cycle metabolites, suggesting dysfunctional mitochondrial activity that is compensated for with glycolysis [41]. Old animals also had reduced energy demand compared to young animals [41, 43]. The number of mitochondria located in osteocytic dendrites decreased with age [37]. Bone research pursuing age as a variable should consider the age-related differences in bioenergetic function.

Sex

Bioenergetic profiles in bone likely differ by sex; in skeletally mature mice, the bones of males had greater metabolites associated with amino acid metabolism (cysteine, methionine, arginine, proline), glycolysis, and TCA cycle whereas lipid metabolism and fatty acid biosynthesis were upregulated in females [44•]. Clinically, energetic fuel can be altered by diet; patients may be advised to reduce caloric intake to improve overall health. However, following weight loss in obese patients, bone mineral density increased in males but decreased in females [45], suggesting sex-dependent effects on bone quality.

Mechanical Stimuli

The beneficial effects of mechanical loading are dependent on age and sex. In men, mechanical loading enhances bone morphology throughout life [46] whereas load-induced improvements in bone quality occur in women pre-menopause [47–49], but female mechanoresponsiveness is reduced with age [50, 51]. In murine loading models, bioenergetic pathways are transcriptionally activated in whole bone samples [52, 53] and vary spatially across the cortex [54]. Load-induced metabolic changes also were altered with age. Old female mice had reduced metabolic transcriptional activity following mechanical loading compared to younger animals [52]. Mesenchymal stromal cells isolated from adult rats produced more reactive oxygen species following loading compared to younger animals [55].

Diminished gravitational loading via spaceflight reduces bone quality. In mesenchymal stromal cells, decreases in osteogenic differentiation and oxygen consumption rate induced by simulated microgravity were recovered with upregulation of *Sirt1* [56], a molecule that protects against oxidative stress, highlighting the connection between oxidative phosphorylation and mechanical loading. The greatest transcriptional changes in osteocyte-like cells exposed to microgravity via spaceflight or the ISS included activation of bioenergetic pathways and upregulated glycolytic genes [57•], suggesting that mechanical loading is an essential regulator of energetic pathways. The direct effects of load-induced changes in bioenergetic function on bone quality warrant further investigation.

Tissue Envelope: Cortical and Cancellous Bone

Bone can be classified as distinct tissue types; cortical and cancellous bone have different morphological structures and unique

transcriptional profiles [58]. The bioenergetic profiles of each tissue envelope also may differ; cortical bone is presumed to have more variability in oxygen and glucose availability across the cortex due to its compact structure compared to cancellous bone. The increased surface area of cancellous bone likely facilitates more frequent nutrient acquisition. Therapeutic inhibition of glycolysis improved cortical bone architecture and increased bone strength in both young and adult male mice, but had limited effects on cancellous bone in young animals [59]. In this study, glycolytic inhibition prevented further trabecular bone loss in aged animals. Cortical and cancellous bone may employ unique bioenergetic programs that facilitate the different responses to aging and therapeutic or external stimuli.

Substrate Availability Affects Bone Quality

Activation of energetic pathways by bone cells is dependent on substrate availability. Changes in substrate availability are linked to altered bone quality, which may be a downstream effect of bone cell bioenergetic activity (Fig. 2). Compared to other organs in the body, bone takes up a large proportion of glucose [43, 60], highlighting the role of bone in global energy metabolism. Both preclinical and clinical examinations of bone quality should take past dieting patterns and therapeutic manipulation of substrate availability into account.

If an excess of glucose is available within the body, in cases like obesity or diabetes, bone quality is diminished [61, 62]. In high-fat diet-fed mice, cancellous bone morphology is negatively altered; bone volume fraction was decreased, trabecular number reduced, and trabecular spacing increased [63–67]. Cortical bone quality also was reduced following induction of obesity, with fewer morphological changes than cancellous bone [65–67]. The reduced bone quality following obesity is related to the cellular activities within bone. High glucose availability can lead to mitochondrial dysfunction and altered activation of oxidative phosphorylation in some cell types [68] and may have similar effects in bone cells. Following high glucose culture conditions, the ability of osteoblast-like MC3T3 cells to mineralize during differentiation was diminished [69•]. Bone marrow mesenchymal stromal cells cultured in high glucose media had reduced cell viability and osteogenesis compared to cells cultured in normal glucose conditions [70•].

Glucose can be restricted by dietary intake or therapeutic intervention. If calories are restricted, available glucose within the body is diminished. Patients with anorexia nervosa have diminished bone quality and increased fracture risk [71–73].

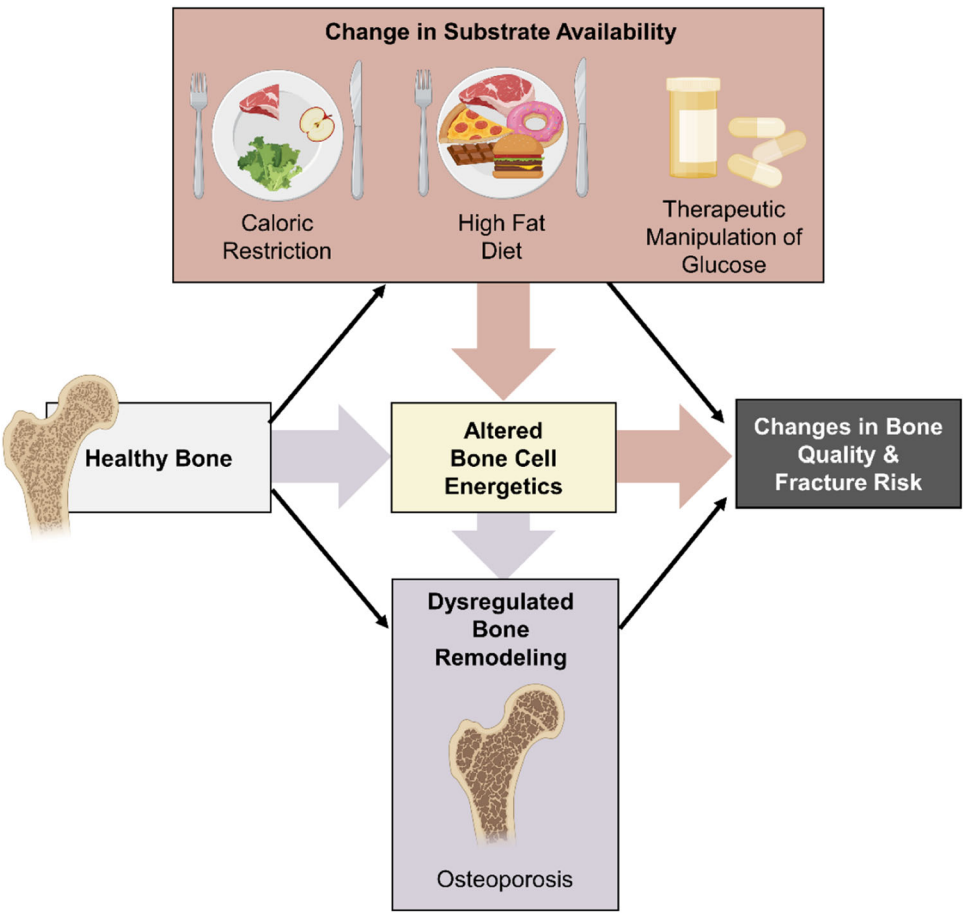

Fig. 2 Altered bone cell energetics are associated with changes in bone quality. Substrate availability influences the metabolic capabilities of cells; altered bone cell energetics may account for differences in bone morphology following changes in available glucose. Bone cell energetic activity also may play a role in the reduced bone quality of osteoporotic patients. Created with Biorender.com

Caloric restriction in humans is associated with decreased bone mineral density [74, 75]. Following caloric restriction in the mouse, bone quality is diminished in the cortical envelope [76–80]. The effect of calorie restriction on cancellous bone is less clear; some studies report that cancellous bone is negatively affected by caloric restriction [76, 77] whereas other researchers report improved cancellous bone morphology [78–80]. Caloric restriction also leads to increased adipogenesis in bone marrow stromal cells [76].

Canagliflozin, a therapeutic used to treat patients with type 2 diabetes mellitus and cardiovascular disease [81, 82], reduces available glucose by inhibiting SGLT2, the transporter responsible for the reabsorption of glucose from urine. Although glycemic control and cardiovascular health improve with canagliflozin treatment, SGLT2 inhibitors are associated with greater fracture risk [83], despite the lack of *Sglt2* expression in bone tissue. In mouse models, lifelong loss-of-function of *Sglt2* reduced bone mineralization with no significant changes to bone strength [84]. Long-term treatment with canagliflozin reduced cancellous bone quality in non-diabetic mice [85]. The negative effects associated with SGLT2 inhibition in bone are most likely due to the systemic decrease in available glucose following canagliflozin treatment.

Bone Cell Energetic Changes in Disease Progression and Treatment

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is a disease directly related to the regulation and processing of glucose. Patients diagnosed with T2DM are initially insulin resistant but ultimately produce insufficient amounts of insulin, a hormone regulating cellular sugar intake, resulting in excess circulating glucose. In addition to challenges with glycemic control, diabetic patients have increased fracture risk, highlighting the connection between T2DM and bone [62]. Hyperglycemia and T2DM lead to the accumulation of advanced glycation endproducts (AGE's), which are associated with decreased bone quality. In mouse models, diabetes may be induced with high-fat diet feeding or drugs. Therapeutic initiation of T2DM reduced both cortical and cancellous bone quality, resulting in diminished bone strength [85, 86].

Bone cells are directly affected by diabetes. Insulin signaling in osteoblasts leads to osteocalcin expression that in turn upregulates glucose metabolism [87]. Tissue composition is altered in T2DM patients, with increased AGE's and greater mineral content compared to non-diabetic controls [88]. Following AGE accumulation, mitochondrial oxidative metabolism is reduced and reactive oxygen species accumulate [22]. Mesenchymal stromal cell viability and differentiation potential were reduced following treatment with AGE's [89]. Further, osteocyte apoptosis has been associated with AGE accumulation [90].

Therapeutic treatment of T2DM improves glycemic control for patients and affects bone quality. Metformin treatment is associated with reduced fracture risk in humans [91, 92]. Alternatively, treatment with thiazolidinediones reduced bone mineral content, bone formation, and trabecular bone volume [92, 93]. Metformin and thiazolidinedione treatments may have direct or indirect effects on bone quality through their regulation of energetic pathways; both therapeutics reduce oxidative phosphorylation [94, 95] but in a dual, independent manner, metformin also may reduce oxidative stress and mitochondrial-mediated apoptosis [94]. Given the effects of diabetes and therapeutic treatment on bone cell energetics, evaluation of patients' diabetic history and pharmaceutical usage is critical when evaluating the current and potential future bone quality.

Fracture Healing

Following bone fracture, the healing cascade includes an early influx of immune cells. The increase in total cell number within the fracture space decreases available oxygen, causing cells to shift towards glycolytic metabolism [96]. The increase in lactate production produces signaling cascades that attract mesenchymal stromal cells, increase extracellular matrix synthesis, and enhance angiogenesis. The revascularization following fracture enables the delivery of more oxygen and therefore enhanced oxidative phosphorylation, which initiates stromal cell differentiation [96]. Protection of mitochondria via inhibition of the mitochondrial permeability transition pore improves fracture repair, highlighting the important role of bioenergetic processes [97]. The coordinated cascade of healing during fracture healing relies on the efficient bioenergetic function of immune and osteogenic cells.

Local delivery of bone morphogenic protein-2 (BMP-2) to the fracture site is clinically used to promote fracture healing. BMP-2 induces SMAD signaling, and initiates cartilage and bone formation. Following BMP-2 treatment, markers of glycolysis and the TCA cycle are increased in bone areas that are Alp+, suggesting increased energetic activity by osteoblasts [98]. BMP-2 signaling in the pancreas and adipose tissue similarly alters cellular energetics [99]. Therefore, BMP-2 may directly or indirectly alter the bioenergetic function of osteoblasts to improve fracture healing.

Osteoporosis

Osteoporosis is a disease of low bone mass that leads to an increased risk of fracture [100–103]. Morbidity and mortality are positively correlated with the incidence of osteoporotic fracture [104]. In addition to reduced bone quality, osteoporosis may be associated with altered bioenergetic function of

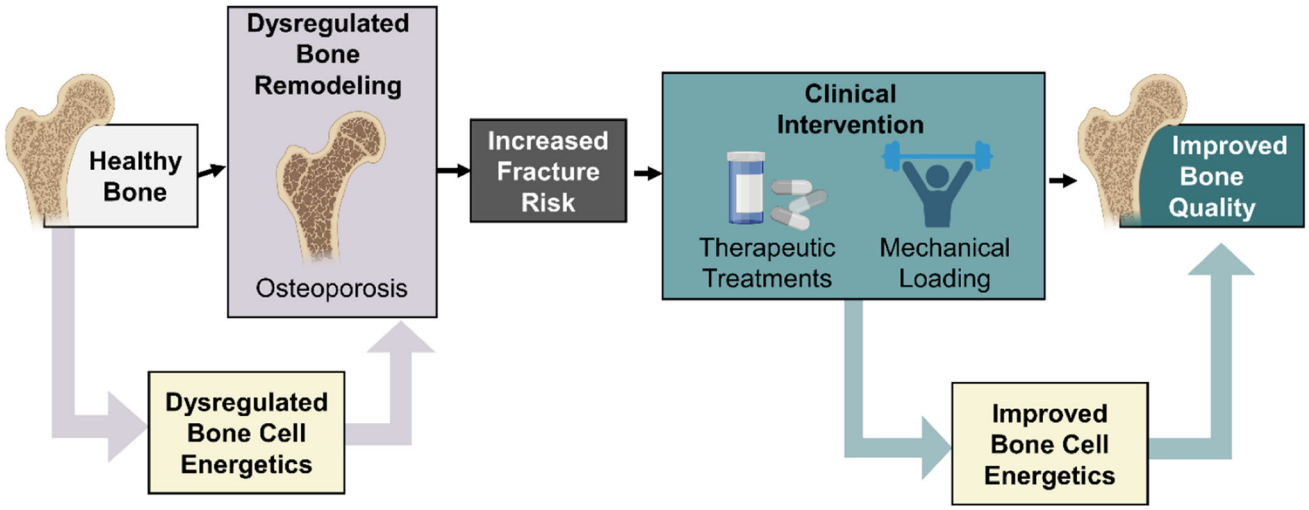

Fig. 3 Bone cell energetics likely play a key role in the development and treatment of osteoporosis. Created with Biorender.com

bone cells. Low bone mass at the spine is associated with activation of both fatty acid oxidation and glycolysis in patient plasma [105•], but further investigation is required to determine if systemic bioenergetic changes are linked directly to bone cell activity (Fig. 2). Osteoporosis disproportionally affects postmenopausal women, due to reduced estrogen signaling [103, 106]. The anabolic effects of estrogen could be partially attributed to altered bioenergetic programs of osteoclasts; mitochondrial function was reduced during osteoclast differentiation following *in vitro* estrogen delivery [107•]. Reactive oxygen species are increased following the decline of estrogen and negatively impact the survival and differentiation of osteogenic progenitor cells [108]. In mice, osteoporosis can be modeled with ovariectomy surgery. Following ovariectomy, TNF-α production increased in mesenchymal stromal cells [109]. MicroRNA-705 expression was increased downstream of TNF-α, eventually leading to heightened reactive oxygen species accumulation [109].

Clinical treatment of osteoporosis has been associated with enhanced bone cell energetics, which may play a role in the improvement of bone quality (Fig. 3). Several osteoporotic therapeutic interventions target osteoclasts to reduce bone resorption. Denosumab is a monoclonal antibody that inhibits bone resorption by reducing RANKL-mediated signaling between osteoclasts and osteoblasts. Patients treated with denosumab have increased bone mineral density and reduced fracture risk [110]. Transcriptional analyses of skeletal tissue revealed that in both osteoclasts and bone marrow plasma, denosumab treatment reduced *DPP4* expression, a gene whose protein product is involved in systemic glucose homeostasis [111••]. Although denosumab-treated patients also had decreased circulating DPP4, their glucose levels were similar to the control group. Further studies will be required to determine the potential contributions of altered bone cell energetics to the clinical success of denosumab.

Anabolic, bone-forming therapeutics for osteoporosis treatment are limited. Parathyroid hormone increases both cortical and cancellous bone in patients by stimulating the bone remodeling unit [112]. In bone, both aerobic glycolysis and glutamine uptake increase with PTH treatment [113, 114•]. Further supporting the glycolytic effects of PTH, the mitochondrial membrane potential in osteoblasts is diminished following PTH treatment [115]. Overall, energetic output of osteocytes may be improved with PTH; respiration and glucose utilization increased in PTH-treated osteocyte-like OCY454 cells [116].

Resveratrol, a dietary supplement with some evidence for improving bone health [117], is an antioxidant that upregulates *Sirt1* to improve mitochondrial activity [118]. Haplo-insufficient *Sirt1* female mice have reduced bone mass and decreased bone formation [119]. *In situ* delivery of resveratrol increased *Sirt1* expression and improved bone morphology in the tibia, following *in vivo* caloric restriction [76]. *In vitro* delivery of resveratrol to mesenchymal stromal cells increased osteogenic differentiation and decreased adipogenesis [120]. The energetic changes in bone cells following denosumab, PTH, and resveratrol treatments suggest a direct role of bioenergetic processes in the improvement of bone quality.

Conclusion

Bioenergetic pathways are critical to the maintenance of bone health and the treatment of bone diseases. Substrate availability influences bone quality and should be considered in patient settings; diet history and prescribed medications may influence bone health. Many established therapeutics and osteogenic processes are interconnected with bioenergetic pathways, highlighting the role of energetics in bone. Further, this connection underscores the potential for energetic pathways as therapeutic targets. Future work should examine the

potential of bioenergetics as direct therapeutic targets to improve bone quality.

Declarations

Competing Interest The authors did not receive support from any organization for the submitted work.

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- •• Of major importance

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