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The Warburg effect in osteoporosis: Cellular signaling and epigenetic regulation of energy metabolic events to targeting the osteocalcin for phenotypic alteration

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ABSTRACT

Osteoporosis is a silent disease of skeletal morphology that induces fragility and fracture risk in aged persons irrespective of gender. Juvenile secondary osteoporosis is rare and is influenced by familial genetic abnormalities. Despite the currently available therapeutic options, more-acute treatments are in need. Women suffer from osteoporosis after menopause, which is characterized by a decline in the secretion of sex hormones in the later phase of life. Several studies in the past two decades emphasized hormone-related pathways to combat osteoporosis. Some studies partially examined energy-related pathways, but achieving a more vivid picture of metabolism and bone remodeling in terms of the Warburg phenomenon is still warranted. Each cell requires sufficient energy for cellular propagation and growth; in particular, osteoporosis is an energy-dependent mechanism affected by a decreased cellular mass of the bone morphology. Energy utilization is the actual propagation of such diseases, and narrowing down these criteria will hopefully provide clues to formulate better therapeutic strategies. Oxidative glycolysis is a particular type of energy metabolic pathway in cancer cells that influences cellular proliferation. Therefore, the prospect of utilizing collective glucose metabolism by inducing the Warburg effect may improve cell propagation. The benefits of utilizing the energy from the Warburg effect may be a difficult task. However, it seems to improve their effectiveness in the osteoblast phenotype by connecting the selected pathways such as WNT, Notch, AKT, and Insulin signaling by targeting osteocalcin resulting in phenotypic alteration. Osteocalcin directs ATP utilization through the sclerostin SOST gene in the bone microenvironment. Thus, selective activation of ATP production involved in osteoblast maturation remains a prime strategy to fight osteoporosis.

Abbreviations: AKT, Protein kinase B; AMP, Adenosine monophosphate; AR, Androgen receptor; ATP, Adenosine triphosphate; BAD, BCL2 associated agonist of cell death; BCL2, B-cell lymphoma 2; BCL-x, B-cell lymphoma-extra large; BMPs, Bone Morphogenetic protein; ER, Endoplasmic reticulum; ERK2, Extracellular signal-regulated kinase 2; FADH, Semiquinone; FKBP12, FKBP prolyl isomerase like; GC, Glucocorticoid; Glut1, Glucose transporter 1; Glut4, Glucose transporter type 4; GTP, Guanosine triphosphate; Hex-A, Hexokinase A; Hh, Hedgehog; IGF1, Insulin-like growth factor – 1; IR, Insulin resistance; MSC, Bone marrow mesenchymal stem cells; mTOR, The mechanistic target of rapamycin; NADH, Nicotinamide adenine dinucleotide; NDP52, Nuclear domain 10 protein 52; OC, Osteocalcin; OxPhos, Oxidative phosphorylation; PI3K, phosphoinositide 3-kinase; PKC, Protein kinase C; PKM2, Pyruvate kinase isozymes M2; PPARγ, Peroxisome proliferator activated receptor-γ; PTH, Parathyroid hormone; Runx2, Runt related transcription factor – 2; S6K, Ribosomal protein S6 kinase; SGK, Serine/threonine-protein kinases; TRIM16, Tripartite motif-containing protein 16.

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1. Introduction

Osteoporosis is a significant bone ailment in all races, but commonly manifests in people aged 50 years and above and can remain unnoticed in many cases until complicated by a fracture [83]. It greatly increases the probability of the risk of a fracture in prime areas like the hip, spine, and wrist, and also includes other regions in the body which reflect overall bone health and growth [65]. Kinsela and Velkroff [44] projected that in the next 30 years, the percentage of the population aged ≥65 years will exponentially increase in most countries. Ironically, osteoporosis can also affect children and adolescents due to activities that cause diseases in their bones or treatments they may receive. Specific and rare forms of primary osteoporosis are infantile and aged idiopathic osteoporosis, innate osteoporosis, and localized osteoporosis [57]. Although several factors are responsible for the onset of osteoporosis, significant reasons for secondary osteoporosis include immobility, certain diseases, treatments for leukemia, inflammatory conditions, glucocorticoid (GC) therapy, hypogonadism, and also inadequate dietary supplementation [89]. Several factors like systemic diseases, hormone imbalances, malignant neoplasms, chronic use of glucocorticoids and other drugs, lifestyle factors, and depression are underlying causes of secondary osteoporosis [57].

In osteoporosis, both physical and molecular mechanisms are provoked, and the skeletal remodeling unit emits a tremendous amount of energy during the processes of both resorption and formation. In parallel, molecular mechanisms related to glucose intolerance at the osteoblastic, osteoclastic, and osteocytic levels are elucidated [46]. Glycolysis promotes osteoblast differentiation, which is under research for future purposes, but it may alter levels of significant intermediate metabolites that regulate gene expressions [25]. The progression of significant energy production in bone cells has been widely studied by many biologists to understand its purpose. The earlier literature underlined glucose as a primary nutrient and lactate as an end product [9,17,70]. In aerobic glycolysis, the level of glucose metabolism is higher in cells as the production of lactate from glucose occurs 10–100-times quicker than the complete oxidation of glucose in mitochondria. The sum of ATP synthesized for a given period is similar when either form of glucose metabolism is utilized [79]. Two major pathways that regulate energy production in the bone cells are glycolysis and oxidative phosphorylation. At the end of these mechanisms, overall energy or ATP production was reported in different forms such as Glycolysis: ATP-2 and NADH-2(3-5ATP); Pyruvate oxidation: NADH-2(5ATP); Citric acid cycle: 2ATP/GTP (2ATP), 6 NADH (15 ATP) and 2 $FADH_2$ (3ATP), the total number of ATPs generated lie between 30 and 36 [104]. But, another mode of energy production in the cancerous cell is being identified as the *Warburg effect*. Warburg [91] stated that cancer cells utilize glucose through glycolysis over oxidative phosphorylation despite the availability of abundant oxygen (i.e., the Warburg effect). Another important facet of the Warburg effect implies cancer cells can also control cellular mechanisms by conserving redox homeostasis throughout the oscillation and reinstate the NADH through translocation of the electrons in the glycolysis events [52]. Therefore, ATP synthesis can be altered to meet certain needs [50], and further investigations are obligatory to discern the exact mechanism for the role of aerobic glycolysis [52,56].

Leberti and Locasale [50] suggested that the Warburg effect supports the growth and proliferation of cells through rapid biosynthesis in a metabolic environment. Further, this evidence can be utilized to affect bone remodeling processes, which may provide an alternative way to find a solution for energy utilization. The consecutive approaches of osteogenesis are explained in Fig. 1, which is focused on three (2 + 1) major pathways responding to produce ATP in the bone. The regular process of energy supply during cell metabolism is connected between OxPhos and glycolysis with end products such as glucose - pyruvate – lactate. The proposed mechanism provides additional sources of energy supply, which directly supply ATP as glucose - lactate. Overall representation of Fig. 1 denotes the energy differences between the regular glucose metabolism (light blue color) and the Warburg effect (dark blue color). The Warburg effect provides more energy supply during bone differentiation. This mechanism will be suitable for improving energy production during osteoblast differentiation in the osteoporotic condition. The influence of bone fragility originates from many sources, such as genetics, medical history, improper energy utilization, intoxication behaviors, etc. Hence, bone remodeling is a significant task that may pose remedies for osteoporosis-related diseases, keeping in mind that this conceptual review is framed based on utilizing energy metabolism in bone remodeling through the Warburg effect to affect osteoblast maturation.

2. Roles of energy metabolism and utilization in bone diseases

Osteoblast cells are leading centers for accomplishing insulin in the bone, while osteoblasts and adipocytes have a common mesenchymal progenitor; therefore mutual signaling between them and within the bone marrow microenvironment has a critical role in bone remodeling. In addition, osteocalcin is produced by bone but controls carbohydrate

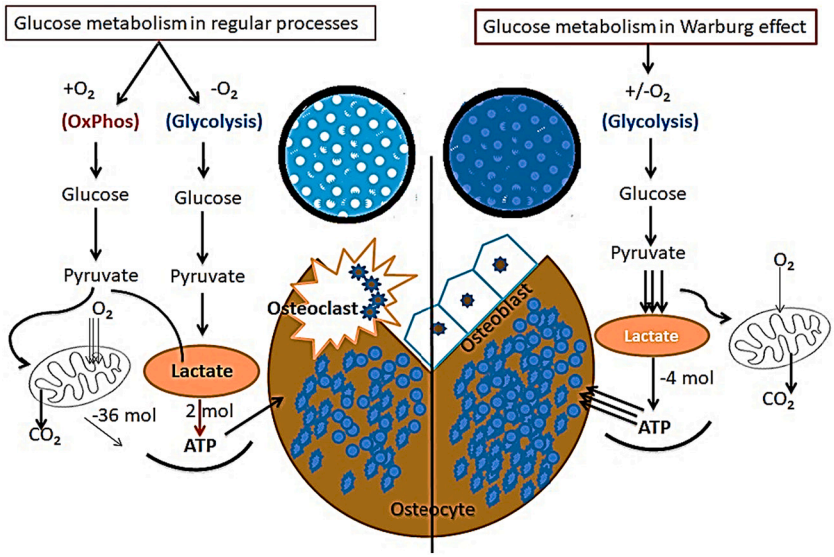

Fig. 1. Activation of cell propagation in osteoporotic condition- Illustration of energy production pathway in bone cells and induction of glucose metabolism through the Warburg effect. The energy production processes in the normal cells are associated with Glycolysis and Oxidative-phosphorylation (OXPHOS) with ATPs as the end products of pyruvate. These function as energy resources of OXPHOS which activates the processes in the mitochondria under an aerobic state to produce 36 ATPs. While under, osteoporotic conditions, there is lower energy production which subsequently results in fewer ATPs. Utilization of excess energy through the Warburg effect provides an alternate source for energy conception during bone differentiation and remodeling.

disposal and insulin secretion [20]. Generally, skeletal development is purely dependent upon energy derived from fat cells, indeed by fat cells stimulated by the hypothalamus that regulate the bone mass by regulating energy utilization and insulin secretion [43]. Wei et al. [93] highlighted that the skeleton is one of the most substantial glucose-ingesting organs next to the liver, fat, and skeletal muscles. In contrast to the surfeit of literature on energy metabolism in muscles and adipose tissues, only a few works focused on understanding the bioenergetics of bone metabolism. Meanwhile, Munoz et al. [64] stated that adipose tissue store major nutrients necessary for fuel consumption, whereas the skeleton consumes energy for growth and remodeling. The sheer size of the skeleton implies that its energy supplies are related to global metabolic demands throughout bone growth and remodeling [81]. Reid [72] stated that interactions among bone mass and body mass are initial perceptions of the decisive role of adiposity in bone strength, and it has been widely epidemiologically studied.

This review focuses on the significance of energy metabolism in bone diseases, as it is a unique concept that underlies energy-related metabolic pathways for regulating bone diseases and remodeling. Brun et al. [13] revealed that bone remodeling occurs every day, in multiple localities and over prolonged surfaces, which suggests high energy requirements by bone cells. Ironically, Goudy et al. [34] postulated that high energy metabolism possibly creates bone-related diseases like osteonecrosis to control infection after a surgical operation, improve blood circulation and energy metabolism, support bone cellular energy, and overcome bone imperfections. It is clearly understood that enormous energy is needed to carry out bone metabolism, which in parallel creates an energy-deficient environment for other physiological functions including basal metabolism, menstrual function, bone health, immunity, protein synthesis, and cardiovascular and psychological health [63]. A recent study proposed that osteoblast-induced insulin signaling is concerned with regulating glucose homeostasis in the entire body by indirectly endorsing osteocalcin (OC) decarboxylation through osteoclasts [27,30]. In the OC osteoblast cell line, $OC^{-/-}$ cells showed an abnormal quantity of visceral fat during experimental observation [47], revealing deficient proteins for osteoblasts leading to the response between hormones by osteoblasts that regulates glucose metabolism. Comprehensive knowledge of skeletal physiology in controlling these intermediary metabolisms and knowledge of its energy utilization is required to understand bone-fat interactions. The integrative role of bone metabolic homeostasis is a potential provocative data feature in bone biology.

Bone cells require a vast and incessant stream of energy for remodeling [42]. According to Karsenty and Oury [41], bone and energy metabolic processes have to be regulated to cover the considerable energy for bone remodeling. The same authors also stated that managing energy and glucose in the body has a significant role in bone remodeling. Our opinion is that utilizing the lactate end product of different energy cycles can provide sufficient energy for skeletal remodeling to improve osteoblast phenotypes. Perhaps glucose metabolism that occurs in osteoblasts can generate lactate as a significant end product irrespective of oxygen conditions [25]. Fundamentally, we need to understand the complete mechanism for elucidating whether to encourage the osteoblast phenotype by aerobic glycolysis [48].

2.1. Factors affecting energy/glucose metabolism in osteoblast differentiation and remodeling

Generally, the skeletal cell population consists of higher amounts of osteoblasts and long-standing osteocytes. They require a perpetual energy stream for fuel synthesis to be used for mineralization mediated by bone remodeling [102]. At the same time, in the processes of bone remodeling, osteoblasts and osteoclasts are directly associated with bone cells and MSCs, which are osteoblast precursors. They differentiate into osteoblasts and support osteoclast formation [51,76]. In the recent literature, [93] all through primary osteoblast culture, glucose transporter 1 (Glut1) is known as a major transporter that suppresses adenosine 5′-monophosphate kinase and blocks ubiquitination of Runx2 by selective deletion of Glut1 in precursor osteoblasts to suppress its differentiation in both in vitro and in vivo culture models. Similarly, another possibility of increasing osteoblast cell lineages is connected to anabolic WNT and aerobic glycolysis [24]. The concentration of OC in serum was correlated with osteoblast numbers and bone formation, and studies confirmed in human and rodent models that OC is also used as a serum marker of bone formation [12,35]. Bone has a significant role in energy metabolism. Wei et al. [93] appraised the disadvantages of osteoblast-specific inhibition by loss of insulin resistance (IR) in mice fed a high-fat diet. From that study, we can understand that decreasing osteocalcin levels by IR in the bone influences whole-body glucose homeostasis in mice fed a high-fat diet. In connection with that, SMURF1-mediated IR ubiquitination contributes to the development of osteoblast IR. Gonadotropin hormones are essential in osteoblasts and bone remodeling; in particular, loss of the androgen receptor (AR) may decrease the trabecular bone mass, and this leads to separation of trabecular bone with no effect on cortical bone [15,67,87]. This review proposes that osteoblast testosterone signaling through the AR is important in trabecular bone but has no effect on cortical bone formation [32]. ARs in osteoblasts promote trabecular bone formation and inhibit age-related resorption of trabecular bone. Several factors promote bone remodeling through osteoblast maturation under physiological and hormonal or anabolic and metabolic processes. Acclimatizing these mechanisms and connecting them with energy-based anabolic activity may accelerate osteoblast numbers in an osteoporotic condition.

2.2. Factors for energy/glucose metabolism in osteoclast differentiation and remodeling

Likewise, osteoclasts have augmented demand for adenosine triphosphate (ATP) during bone resorption and differentiation processes [36]. A model proposed by Fernandes et al. [26] suggests that osteoclasts are associated with the dynamic endocrine part, which affects glucose metabolism by regulating osteoclast numbers. Osteoclast secretion and osteoblast bone matrix deposition are specific cellular function acquisitions, and these features are meaningful for cell differentiation. These features are specifically auxiliary to bio-energetic cell-specific physiology activity [48]. Park-Min [69] reported that bone resorption and osteoclast formation are active metabolic reprogramming and are correspondingly focused energy-intensive steps. Even though it is important to focus on osteoclast energy metabolism, it has not been widely explored. Ferron et al. [27] revealed that gene-associated osteoprotegerin-dependent osteoclasts' events influence the link between bone and energy metabolism. Coherent with that, insulin signaling in osteoblasts induces osteoclast acidification and bone resorption through dwindling expression of osteoprotegerin [68]. According to Park-Min, [69] in mature osteoclasts, metabolic reprogramming triggers energy, strengthening phenotypic changes that facilitate bone resorption. Edwards and Weicada [21] and Sobacchi et al. [82] stated that osteoclast resorptive activity occurs in osteopetrosis patients through mutations rather than differentiation. This occurs in different forms as a mutation in CLCN7 or TCIRG1, exposing diverse osteoclast numbers and perpetuating the rate of bone formation, and these severe events lead to a weakening in osteopetrosis. A recently discovered endocrine function of bone that is mediated by Lipocalin-2 is the regulation of food intake (LCN2). LCN2, which is released by osteoblasts, enhances glucose metabolism while suppressing appetite and reducing fat mass [105]. Phosphoethanolamine/phosphocholine phosphatase 1 (PHOSPHO1), a particular form of the enzyme, may have a role in energy metabolism, according to recent research [106]. According to Weivoda et al. [96] further elucidation clarifies the mechanism through which osteoclasts promote bone formation could benefit further therapeutic approaches promoting bone formation even in the absence of osteoclasts.

2.3. Osteocytes coordinate bone remodeling by regulating osteoblasts and osteoclasts

Examining the levels of circulating hormones in osteocytes is the best way to understand bone remodeling and resorption [8]. Osteocytes are former osteoblasts that mineralize bone matrix by entombing it during bone deposition and are regularly distributed throughout bones [7]. *SOST* genes are expressed in osteocytes and regulate mechanical loading in cells, and their progression improves cell numbers in bone and provides strength to establish bone surfaces that can withstand high strain [97]. In connection with that, it was reported that decreasing *SOST* gene expression in humans causes high bone-mass disorders like Van Buchem's disease and sclerosteosis [5]; perhaps this occurs through regulating Wnt and bone morphometric protein (BMP) signaling during osteoblastogenesis and bone mass acquisition. Sclerostin is the product of *SOST* genes which are expressed by osteocytes, and it is involved in preventing Wnt signaling and interacts with BMPs through the specific receptor low-density lipoprotein receptor-related protein 5 (LRP5)/LRP6 [88,98]. According to Bellido, [7] sclerostin derived from osteocytes provides a negative response to osteoblast generation and activity in the osteoblastic pathway. In the course of *SOST* expression, transcripts of the *SOST* and sclerostin proteins are abridged through mechanical loading with the considerable mechanical strain being associated with more substantial reductions [74]. Similarly, Brun et al. [13] suggested, that peroxisome proliferator-activated receptor-γ (PPARγ) in late osteoblasts and osteocytes contributes to bone remodeling associated with a critical function in glucose metabolism through enhanced energy uptake by bone cells and directing vital organs such as the pancreas, adipose tissues, and the liver by secreting osteokines instead of osteocalcin-like BMP7 [13]. Another type of mechanism in osteocytes is the endoplasmic reticulum (ER)-mediated mitochondrial transfer between osteocytes to coordinate their energy metabolism. These exchanges of mitochondrial transmission may be initiated from ER-donor osteocytes to ER recipients [31]. In Fig. 2, we represent osteocytes that play vital roles in bone remodeling in multiple ways, regulating osteoblasts and osteoclasts through the SOST gene via sclerostin, and controlling glucose metabolism in bone remodeling through PPARγ expression. Skeletal homeostasis is regulated through several genetic factors. SOST gene is vital in communication between osteoblast and osteoclast to provide a favorable osteoblast differentiation condition by enhancing the BMP and WNT signaling by down-regulating the sclerostin expressions.

3. Energy aids in bone differentiation and remodeling

Generally, cells require energy for propagation, and energy synthesis that can be from a wide array of sources and pathways. Similarly, bone cells have specific metabolic pathways for acquiring energy. Motyl et al. [62] postulated that metabolic pathways control gene expressions through epigenetic modifications of substrates and cofactors generated through bioenergetic pathways. Female athletes with either low energy or reproductive disorders or both develop a deficiency in bone mineral density that brings about structural changes in the bone and is likely to reduce bone strength [2,3]. Osteoporosis and osteoporotic fractures can increase during or after the end of their professions [6,55]. Surprisingly, due to the nature of bone formation and functions, it was hypothesized that bone act as an endocrine organ [47]. Feedback responses of the skeleton with pancreatic beta-cells, adipose tissues, and the brain are associated with energy homeostasis and glucose metabolism, and it is intriguing to think of bone as an endocrine organ. It is perplexing that osteocalcin has thrown light on the interactions of bone with specialized tissues [100].

On the other hand, Riddle and Clemens [73] emphasized the role of leptin in bone and energy metabolism. Its role was primarily investigated in the context of anorexia nervosa and hypothalamic amenorrhea. A clear understanding of skeletal energy metabolism could provide clues

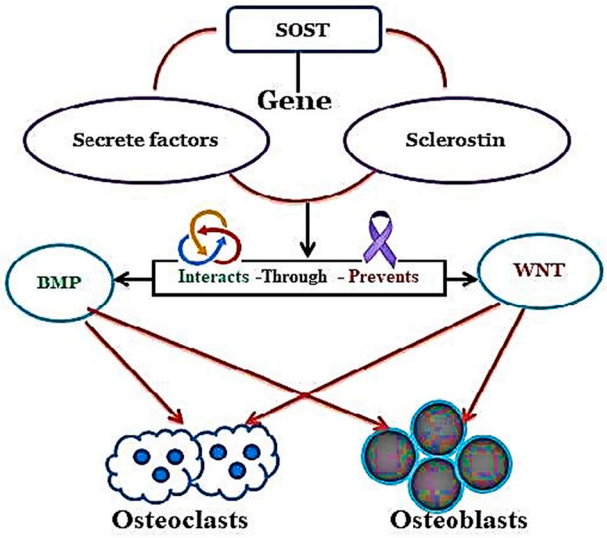

Fig. 2. Controlled mechanisms of osteoblast and osteoclast during bone remodeling. Illustration of SOST gene control on osteoblasts and osteoclasts through sclerostin through BMP and WNT signaling by preventing the secrete factor's interaction with sclerostin.

to innovative regimens for treatment and therapeutics with better efficacy and fewer side effects [62]. In this context, lineage tracing adds significant knowledge to the production and characteristic features of osteoblasts. The progenitors of osteoblasts are skeletal stem cells that function to secrete and synthesize type I collagen to maintain the extracellular matrix and control osteoclast differentiation [61]. Lee et al. [48] outlined that cells like osteoblasts and osteoclasts form bone and are reported to be involved in remodeling. Osteoblasts originate from mesenchymal progenitors, which in turn give rise to bone lining cells or osteocytes, while the latter lineage includes both mature osteoclasts and their macrophage precursors.

Adipose tissue stores cellular nutrients for fuel consumption necessary for utilization in bone growth and remodeling processes [20]. An integral component of osteoblasts is glucose. A plethora of studies has confirmed that lactate is a product that is abundantly secreted by most glucose carbons through oxygen present in bone or osteoblasts [9,17,71]. Hence, these clearly show a novel, pH-dependent mechanism of activation for a hormone, and insulin signaling in osteoblasts acts as a critical link between bone remodeling and energy metabolism [27]. It is certain that human osteoclasts increase the mitochondrial mass and produce high OxPhos during osteoclastogenesis. Lemma et al. [49] proved that osteoclast activity is determined by glycolysis, and the subcellular level is localized in an adjacent sealing zone. The coherence between metabolic pathways allows a perfect balance from mature osteoclast formation to the acquisition of a bone resorption capacity. Generally, in all metazoans, cells have the potential to generate ATP through glycolysis and oxidative phosphorylation. As a theoretical study [59] reported earlier, glycolysis generates six times more H+ than OxPhos per ATP molecule created. A cluster of factors, including PPARγ co-activator 1β (PGC1β), phosphorylated PPARγ, and estrogen-related receptor α (ERRα) were shown to play fundamental roles in osteoclast differentiation and function.

Consequently, in bone remodeling, osteoblast differentiation is accepted to play a significant role via transcriptional regulation of distinct metabolic genes [37,90,94,95]. Generally, osteocytes are formed as the end lineage of mature osteoblasts that produce their energy through glycolytic processes [62]. These cells were shown to generate protons, acidify their microenvironment, and be located in a hypoxic environment [39], although there is scant literature on osteocyte energy metabolism. Glucose consumption has always been seen to

be driven by osteoblast [10] and osteoclast [38] activity. Still, osteocytes control these two bone cells, which regulate bone remodeling and calcium homeostasis [1]. Similarly, PPARγ expression by osteocytes regulates osteoblast differentiation and osteoclast resorption [13]. According to Tatsumi et al. [84] to avoid bone loss in typical conditions or emergencies, osteocytes must send their signals, and it is crucial that they trigger a bone loss in response to unloading. Thus, osteocytes also represent an attractive target for the development of diagnostics and therapeutics for bone diseases, such as osteoporosis.

4. Warburg effect on glucose metabolism and bone remodeling

The critical point in an organism's survival is the control systems required to monitor aberrant individual cell proliferation when nutrient availability exceeds levels needed to support cell division [89]. Recently, it was depicted that osteoporosis is a disease with an improper energy supply for bone cell growth. Ironically, cancer is abnormal cell division which is the reverse of osteoporosis. This review's principal aim was to address the causes and inculcate mainstay research to overcome osteoporosis disease in young people. Adequate literature is available on the research of bone remodeling and the utilization of energy pathways for cell growth in aerobic and anaerobic systems. Therefore, our review's central aim was to address energy utilization in cell propagation through the Warburg effect, which is an efficient way to generate sufficient energy for bone cell division and growth. A wide array of cells, including cancer cells, frequently exhibit high glycolysis rates even in the presence of average oxygen concentrations, often called aerobic glycolysis, and the same is described as the Warburg effect in cancer [22,91]. In addition, Liberti and Locasale [50] postulated that in tumors and other proliferating or developing cells, the rate of glucose uptake dramatically increases, and lactate is produced, even in the presence of oxygen and fully functioning mitochondria. This process, known as the Warburg effect, has also been extensively studied. Aerobic glycolysis by cancer cells is due to a permanent impairment of mitochondrial OxPhos [103]. The sum of these phenomenal actions perhaps helps to meet the need for surplus energy in bone cell remodeling to provide maximum cell confluence. Homeostasis or balance to cover these enormous energy costs needs to be co-regulated between energy metabolism and bone.

In other words, bone remodeling may play a significant role in the management of glucose and energy needs in the body [41]. The massive input of excess carbon as lactate is sufficient because it allows faster incorporation of carbon into biomass, facilitating rapid cell division [89]. While Epstein et al. [23] sorted additional evidence by inducing changes in the cellular environment, tremendous increase in the ATP demand by altering the ATP-dependent membrane pumps and aerobic glycolysis rapidly increased while oxidative phosphorylation remained constant. Another proposed mechanism to account for the Warburg effect's biosynthetic function is the regeneration of NAD+ from NADH in the pyruvate-to-lactate step that completes aerobic glycolysis [50]. Among the perplexing processes, Epstein et al. [23] proposed the idea of developing an alternative model of glucose metabolism in which the two metabolic pathways serve as complementary mechanisms for meeting ATP demands. Despite the decrease in energy yields due to the "glycolytic phenotype", this seems to allow for an increase in the cell proliferation rate and may apply to other rapidly growing cells [11]. In other words, glycolysis is a process that takes place in the cytoplasm by converting glucose into pyruvate, lactate, and hydrogen ions through nine enzymatic reaction steps, and several glycolytic enzymes are involved in different steps of glycolysis and play essential roles in the phenomenon of the Warburg effect [45]. Henceforth based on all the above-discussed research reports, aerobic glycolysis or the Warburg effect is an efficient way to accelerate osteoporosis treatment. In Fig. 3, significant structures of bioenergetic sources involved in utilizing bone homeostasis is depicted. We proposed utilizing this hormonal resource to accelerate the Warburg effect to target cellular signaling to produce maximum energy during osteoporosis.

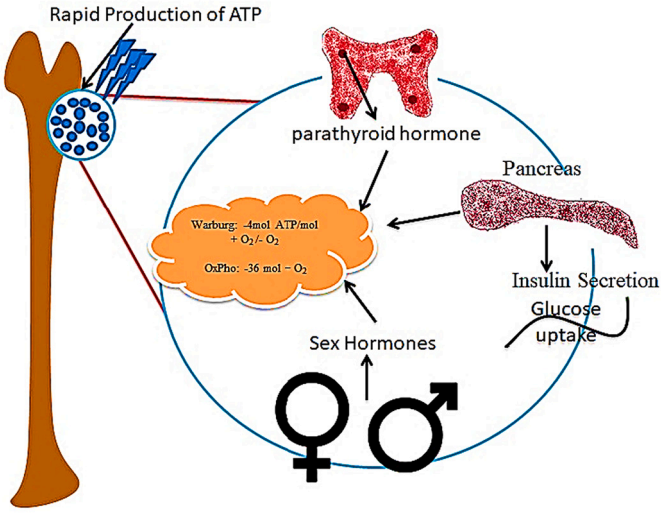

Fig. 3. Possible resources for energy uptake in osteoblast maturation associated with the Warburg phenomenon. Osteoblast differentiation involves energy utilization and regulation of mechanisms such as insulin metabolism in bone and oxidative phosphorylation realting to glycolysis in bone cells. Bone cells under osteoporotic conditions will exhibit the down-regulation of these energy resources. Contrastingly, Warburg's effects lead to an improved number of ATPs and proper utilization of energy flow to replace osteoporosis.

5. A prospective link between signaling stimulation and the Warburg effect for osteoblast maturation

The proposed idea is based on energy stimulation during osteoblast maturation through the Warburg effect. It emphasizes increasing cell numbers in bone morphology and remodeling. In addition to stimulation of energy to osteoblasts, another possible way to enhance energy is to interconnect with aerobic glycolysis. Some literature exists based on the

Table 1
Represent possible links and mechanisms which are targeting the energy-related pathway inhibitor mechanisms to emphasize the Warburg effect.

Mechanism	Target	References
mTORC1 inhibitor	(a) FKBP12 (b) mTOR	Cooper [18]
OxPhos inhibitor	(a) Citric acid cycle (b) Fatty acid oxidation (c) Amino acid oxidation	Schemidt et al. [78]
PKB or Akt inhibitor	(a) BAD- Bcl-2/Bcl-X (b) IκB kinase (c) Glucose transporter 4 (GLUT4) (d) Wnt pathway	Lodish et al. [53]
Autophagy inhibitor	(a) AMP-activated protein kinase (b) (acetyl-CoA carboxylase) kinase (c) TRIM16 (d) NDP52	Thurston et al. [86] Chauhan et al. [14]
PDK1 inhibitor	(a) PI3K/AKT signaling pathway (b) AGC kinases: PKC, S6K, SGK. (c) Insulin signaling	Mora et al. [60] Frodin et al. [29]
Proton pump or HK inhibitor	(a) H+/K+ ATPase	Sakai, et al. [77]
GLUTI inhibitor	(b) Vitamin C (c) Glucose	Montel-Hagen et al. [58]
PKM2 inhibitor	(d) glucose flux (e) ERK2	Christofk et al. [16] Prakasam et al. [71]
PFKFB3 inhibitor	(a) Glycolysis pathway	Atsumi et al. [4]

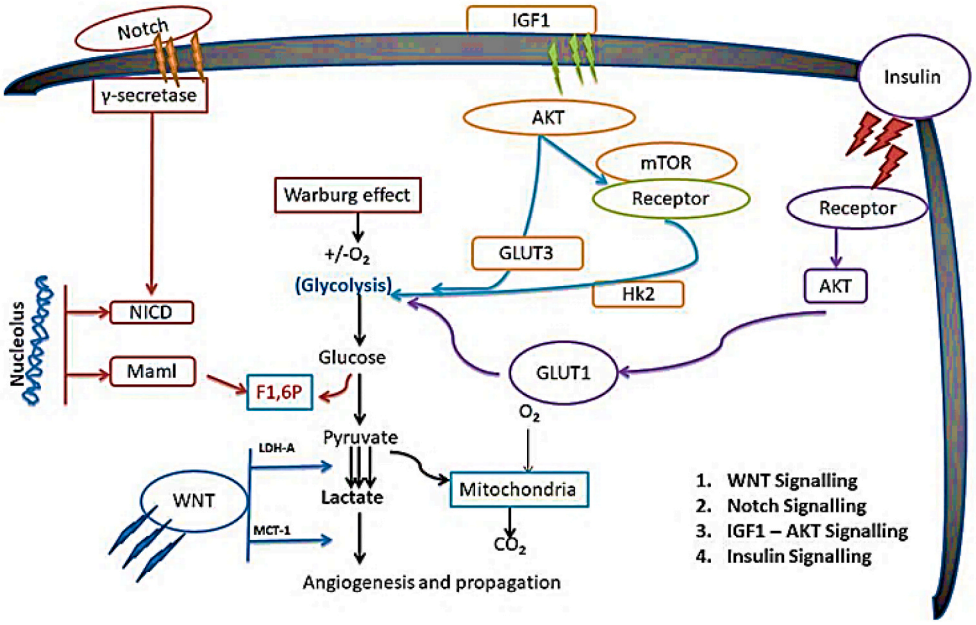

Fig. 4. Proposed links between energy pathways, which are highlighted in stimulating the Warburg phenomenon. The above pictorial representation suggested four signaling and transducing events such as WNT, Notch, IGF1 - AKT, and Insulin which are identified to stimulate energy flow to bone cells differentiation for improved angiogenesis. WNT signaling will target the pyruvate to lactate regulation; Notch signaling will target the glucose regulation; IGF1 and Insulin signaling will target the glycolysis regulation. Warburg mechanism regulates these four transducing signals within different stages and improves the energy flow for replacing osteoporosis.

energy cycle in metabolism, with existing shreds of evidence, we propose an accelerating alternative approach for osteoporosis treatment. We proposed herewith those prospective links associated with specific signaling pathways that utilize the Warburg effect towards bone remodeling. According to the Warburg effect [52], the control of cellular mechanisms happens by translocating the electrons during the fluctuation of NADH in the cells, through glycolysis processes. Table 1 and Fig. 4 show that the target mechanism and regulating gene are associated with signaling pathways for bone turnover or remodeling during osteoporosis treatment. We also listed the transducing signals for the possible links to utilizing the bone remodeling.

Rewiring of cellular metabolism in osteoblast differentiation is a recently reported phenomenon, while Wnt/Lrp5 signaling promotes bone formation in both mice and humans. In parallel, it stimulated aerobic glycolysis and glutamine catabolism as well as fatty acid oxidation during osteoblastogenesis [24,28,40]. Slaninova et al. [80] promoted that Notch induces the transcription of Glut1, hexokinase A (Hex-A), and Impl3 (Ldha homolog) in *Drosophila* cells, resulting in a Warburg-like effect. In comparison, long-term evidence suggests that parathyroid hormone (PTH) signaling harnesses bone formation in osteoporotic patients and stimulates glucose consumption and lactate production in bone explants [9,66,75]. Significantly, Wnt3a-Lrp5 signaling increases Glut1, Hk2, Ldha, and Pdk1 downstream of mTORC2 Akt activation, while inducing osteoblast differentiation by the ST2 bone marrow mesenchymal progenitor cell line [24]. On the other hand, Hedgehog (Hh) signaling, a critical inducer of the early steps of osteoblast differentiation, was reported to stimulate aerobic glycolysis in both muscles and brown adipose tissues through a non-canonical mechanism [54,85]. Notably, an insulin resistance (IR) signaling deficiency in osteoblasts is likely relevant to both types of diabetes, as emerging evidence supports IR in osteoblasts in models of type II diabetes [27,93,]. Several studies emphasized that the insulin-like growth factor 1 (IGF1) receptor (IGF1R) directly stimulates osteoblast differentiation, matrix production, and mineralization, while its deficiency contributes to bone formation deficits in diabetes [19,99,101]. Several signaling pathways influence cellular energy cycles, and we likely concentrated on specific pathways associated with aerobic glycolysis. As per this review, we discuss how targeting OC can improve osteoblast differentiation. Its unique secretion by osteoblasts can improve several metabolic activities in the human body such as calcium deposition, hormonal actions, pancreatic signaling for regulating insulin secretion and sensitivity, etc. In bone remodeling, OC regulates energy expenditure with insulin sensitivity of the bone to regulate excess energy during stimulation of the Warburg effects in osteoblasts. The lack of OC secretion by osteoclasts and osteocytes should be avoided in this strategy, which may lead to an adverse effect of producing a cancerous effect. This review reflects why we proposed to use osteoblasts for bone remodeling. Conditions associated with osteoporosis may act as a regulator of energy homeostasis in the differentiation of bone. Accelerating the energy flow during bone remodeling may be possible by targeting the WNT, Notch, AKT, and Insulin signaling pathways. Different checkpoints were explicitly presented for our hypothesis in order to preserve energy balance throughout the remodeling of bone cells.

6. Expert opinions

ATP synthesis is a dynamic process for cell homeostasis and growth. It can be regulated by transducing signals with metabolic substrate and enzyme activity. To the best of our knowledge, osteoporosis factors are well described and it is purely based on energy and enzymatic alterations to osteoblast differentiation and osteoclast resorption. The Warburg effect is an organized transducing signal, to provide surplus energy for cell propagation. This review highlights possible transducing signals associated with oxidative glycolysis to improve ATPs during osteoblast differentiation.

7. Conclusions

We concluded that further studies are needed to access the Warburg phenomenon for osteoporosis treatment. Energy utilization is a significant task for bone cell propagation and differentiation. To the best of our knowledge, osteoporosis maintains its state by utilizing minimal energy to reduce the cell mass in skeletal morphology. Through this review, we proposed that collective glucose metabolism induction through the Warburg effect can improve cell propagation. Many metabolic pathways are linked with energy utilization and bone remodeling, and the Warburg effect could pave the way for a better understanding of alternative therapeutic approaches for osteoporosis. The selective activation of ATP production with osteoblast differentiation remains the principal component of fighting osteoporosis, and we suggest that extensive studies are required to identify more-effective mechanisms of energy utilization in osteoblast differentiation.

Declaration of Competing Interest

All authors of this paper declare that they have no conflict of interest.

Data availability

No data was used for the research described in the article.

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