The nuclear receptor peroxisome proliferator-activated receptor (PPARγ) is a crucial cellular and metabolic switch that regulates many physiologic and disease processes. Emerging evidence reveals that PPARγ is also a key modulator of skeletal remodeling. Long-term use of rosiglitazone, a synthetic PPARγ agonist and a drug to treat insulin resistance, increases fracture rates among patients with diabetes. Recent studies have revealed that PPARγ activation not only suppresses osteoblastogenesis, but also activates osteoclastogenesis, thereby decreasing bone formation while sustaining or increasing bone resorption. The pro-osteoclastogenic effect of rosiglitazone is mediated by a transcriptional network comprised of PPARγ, PPAR-gamma coactivator 1β and estrogen-related receptor α, which promotes both osteoclast differentiation and mitochondrial activation. Therefore, PPARγ plays dual roles in bone homeostasis by regulating both mesenchymal and hematopoietic lineages.

PPARγ is a crucial cellular and metabolic switch
Peroxisome proliferator-activated receptor (PPARγ) is a member of the nuclear hormone receptor superfamily of ligand-responsive transcription factors [1]. Ligand-activated PPARγ forms functional heterodimers with the retinoid X receptor (RXR)α and recruits cofactors to activate the transcription of target genes. Several synthetic and natural lipophilic compounds have been identified as PPARγ agonists, including thiazolidinediones (TZDs) [2], 15-deoxyΔ12,14-prostaglandin J2 [3,4], polyunsaturated fatty acids [5] and components of oxidized low density lipoprotein particles such as 13-hydroxyoctadecadienoic acid and 15-hydroxyeicosatetraenoic acid [6].

PPARγ regulates a diverse array of physiologic processes including adipogenesis [7], lipid metabolism [8,9], insulin sensitivity [10–12] and inflammation [13–15], and is also involved in diseases such as diabetes, obesity and atherosclerosis [1]. Its importance is accentuated by the widespread use of TZDs, including rosiglitazone (BRL 49653 or Avandia; GlaxoSmithKline) and pioglitazone (Actos or Glustin; Takeda Pharmaceuticals), which are synthetic PPARγ ligands, as drugs for insulin resistance and type 2 diabetes mellitus (T2DM) [1,2,16].

Furthermore, PPARγ is a metabolic switch for stem cell fate in both mesenchymal and hematopoietic lineages (Figure 1). Initial studies have shown that activation of PPARγ shifts the balance of mesenchymal stem cell fate by favoring adipocyte differentiation and inhibiting osteoblast differentiation [17,18]. Recent studies have revealed an independent role of PPARγ in hematopoietic lineage determination [19,20]. Activation of PPARγ shifts the balance of the myeloid progenitor cell fate by favoring osteoclast differentiation and inhibiting mature macrophage differentiation [19]. Therefore, PPARγ is a transcriptional sensor that translates increased local concentration of ligands into an orchestrated set of cellular and metabolic responses.

Osteoblasts and osteoclasts: two key cell types controlling skeletal homeostasis
The skeleton is a dynamic tissue that constantly remodels by balancing osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Under physiologic conditions, resorption and formation are tightly coupled, thereby maintaining bone mass. However, under pathologic conditions such as osteoporosis, resorption outpaces formation, leading to the uncoupling of bone remodeling and a net loss of bone [21].

The two main cell types in bone are of distinct developmental origins; osteoblasts are of mesenchymal lineage [22] whereas osteoclasts are of hematopoietic lineage [23]. The osteoblast is responsible for building both the organic and inorganic components of bone. It is derived from mesenchymal progenitors and differentiates in response to growth factors such as bone morphogenetic proteins [24]. Osteoblast differentiation requires an orchestrated series of events to activate osteoblastogenic transcription factors (including Runx2, Osterix, activating transcription factor 4 and β-catenin) and to inhibit adipogenic transcription factors (including PPARγ and CCAAT-enhancer-binding protein (CEBPα)) [25,26]. By contrast, the osteoclast is responsible for removing both the organic and inorganic components of bone. It is derived from hematopoietic progenitors in the monocyte/macrophage lineage [27,28] and differentiates in response to the tumor necrosis factor (TNF) family cytokine RANKL [receptor activator of nuclear factor (NF)κB ligand] [29,30]. Osteoclast differentiation requires the concerted activation of transcription factors including c-fos, c-jun, NFATc1 (nuclear factor of activated T-cells, cytoplasmic 1) and NFκB [31].

The functions of osteoblasts and osteoclasts are regulated by nutritional, hormonal, mechanical and immunologic cues, and by drugs such as glucocorticoids, TZDs, statins and bisphosphonates. Decreased osteoblast function, whether genetic or pharmacologic, can lead to osteopenia or osteoporosis with a low bone mass and a high fracture risk, while pathologic increases in osteoblast proliferation can cause bone cancers such as osteosarcoma. Defects in osteoclast function, whether genetic or pharmacologic, can lead to osteopetrosis, a disease characterized by increased bone mass but poor bone quality due to the formation of ‘woven bone’, characterized by an irregular bone structure, rather than the normal ‘lamellar bone’, characterized by a uniform

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layered structure with parallel collagen fibers. Pathologic stimulation of bone resorption occurs in postmenopausal osteoporosis, inflammatory arthritis, and metastasis of tumors to bone. In these diseases, elevated osteoclast activity and/or decreased osteoblast activity causes bone loss, which leads to pain, deformity and fracture. Therefore, both osteoblasts and osteoclasts are crucial for normal bone function, but their activities must be controlled.

Skeletal homeostasis is maintained by the intricate mechanisms synchronizing osteoblast activation with osteoclast activation, thus coupling bone formation with bone resorption. For example, RANKL and osteoprotegerin, generated from osteoblasts, are important determinants of the rate of osteoclast differentiation. Enhanced understanding of bone cell differentiation and communication will undoubtedly have a major influence on the prevention and treatment of diseases associated with increased bone resorption and/or decreased bone formation, such as osteoporosis, arthritis and bone metastases of cancers.

**PPARγ activation suppresses osteoblastogenesis but promotes osteoclastogenesis**

Emerging evidence suggests that PPARγ plays important roles in skeletal homeostasis. It was first discovered that PPARγ activation suppresses osteoblast differentiation from mesenchymal stem cells by favoring adipogenesis (Figure 1) [17,18,32–34]. Homozygous PPARγ-deficient embryonic stem cells fail to differentiate into adipocytes, but spontaneously differentiate into osteoblasts; furthermore, PPARγ heterozygous mice display a high bone mass due to increased osteoblast number and bone formation [17]. Consistently, PPARγ suppression by canonical or noncanonical Wnt signaling enhances osteoblastogenesis by reducing adipogenesis [35,36]. Transient activation of the canonical Wnt/β-catenin signaling in bipotential ST2 cells rapidly suppresses PPARγ and CEBPα expression, followed by activation of osteoblastogenic transcription factors [35]. However, activation of the noncanonical Wnt signaling initiates a CaMKII–TAK1–TAB2–NLK

![Figure 1](image.png)
(Ca\textsuperscript{2+}/calmodulin-dependent kinase II–transforming growth factor β activated kinase 1–TAK1 binding protein2–serine/threonine-protein kinase) cascade, which in turn phosphorylates a histone methyltransferase SETDB1 (SET domain bifurcated 1), leading to the formation of a corepressor complex that represses PPARγ transactivation through histone H3K9 methylation of target genes [36]. Moreover, PPARγ activity and adipogenesis are inhibited by the tumor suppressor retinoblastoma (RB)1 gene, which potentiates Runx2 activity and osteoblastogenesis [37]. In addition, genetic deletion or pharmacologic inhibition of the type 1 cannabinoid (CB)1 receptor enhances adipocyte differentiation and reduces osteoblast differentiation by increasing the expression of PPARγ and CREB, suggesting that CB1 also represses PPARγ function [38]. By contrast, the circadian-regulated gene Nocturnin promotes adipogenesis but attenuates osteoblastogenesis by stimulating PPARγ nuclear translocation [39]. Collectively, these studies demonstrate that PPARγ suppression favors osteoblastogenesis over adipogenesis, whereas PPARγ activation favors adipogenesis over osteoblastogenesis (Figure 1).

Our recent study reveals that PPARγ also plays an independent role to promote osteoclast differentiation from hematopoietic stem cells (Figure 1) [19]. Genetically, loss of PPARγ function in mouse hematopoietic lineages causes osteoclast defects, which present as osteopetrosis and as extramedullary hematopoiesis in the spleen. Pharmacologically, gain of PPARγ function by rosiglitazone activation causes bone loss in mice by enhancing osteoclastogenesis and bone resorption in vivo. Mechanistically, PPARγ directly potentiates RANKL induction of c-fos, an essential mediator of osteoclastogenesis [19]. These findings uncovered a previously unrecognized pro-osteoclastogenic function of PPARγ, thus demonstrating that PPARγ activation acts as a double-edged sword to not only suppress bone formation but also to stimulate bone resorption (Figure 1).

PGC1β mediates PPARγ activation of osteoclastogenesis and rosiglitazone-induced bone loss

PPARγ modulates transcription through ligand-mediated recruitment of coactivators. Therefore, tissue-specific differences in coactivator expression can affect PPARγ function, adding another level of complexity to its gene and cell specific transcriptional regulation. PPARγ coactivator (PGC)1β (also known as Ppargc1b) is a transcriptional coactivator that regulates energy metabolism by stimulating mitochondrial biogenesis and cellular respiration [40–44]. Two recent studies identified PGC1β as a gene that is strongly upregulated by RANKL and rosiglitazone during osteoclast differentiation [20,45], revealing a function for PGC1β in RANKL and PPARγ signaling.

As acid and proteinase secreting polykaryons, osteoclasts are in a state of high energy demand and possess abundant mitochondria [45,46]. PGC1β coordinates with iron uptake to orchestrate mitochondrial biogenesis during osteoclast development [45], and is induced during osteoclast differentiation by reactive oxygen species (ROS) via a cAMP response element-binding protein (CREB)-dependent mechanism. Knockdown of PGC1β in vitro inhibits osteoclast differentiation and mitochondria biogenesis, and global PGC1β deletion in mice results in increased bone mass due to defects in both osteoclasts and osteoblasts [45]. Thus, this study identified PGC1β as a novel regulator of bone homeostasis, and suggests a potential link between PGC1β and PPARγ during osteoclastogenesis.

Owing to the heightened iron demand in osteoclast development, transferrin receptor (TfR)1 expression is induced post-transcriptionally via iron regulatory protein 2. TfR1-mediated iron uptake promotes osteoclast differentiation and bone-resorbing activity, and is associated with the induction of mitochondrial respiration, production of ROS and accelerated transcription of PGC1β. These findings establish mitochondrial biogenesis orchestrated by PGC1β, iron uptake through TfR1 and iron supply coupled to mitochondrial respiratory proteins as crucial events linked to osteoclast activation and bone metabolism [45]. Future studies are required to determine whether PPARγ activation also promotes TfR1-mediated iron uptake during osteoclastogenesis.

Our recent study further examined the specific role of osteoclastic PGC1β in PPARγ activation of osteoclastogenesis and rosiglitazone-induced bone loss [20]. Using both genetic and pharmacologic approaches, this investigation provided compelling evidence that PGC1β is an essential mediator of the pro-osteoclastogenic and bone resorption-enhancing effects of PPARγ and rosiglitazone. Strikingly, targeted deletion of PGC1β in the osteoclast lineage resulted in complete resistance to rosiglitazone-induced bone loss in vivo and severe attenuation of rosiglitazone-stimulated osteoclastogenesis ex vivo [20]. Mechanistic studies revealed that PPARγ promotes osteoclastogenesis by activating PGC1β and estrogen-related receptor (ERRα). PPARγ activation indirectly induces PGC1β expression by downregulating β-catenin, thus derepressing c-jun, which directly activates the PGC1β promoter; in turn, PGC1β functions as a PPARγ coactivator to stimulate the transcription of its target genes such as c-fos, thus promoting osteoclast differentiation. PGC1β also coordinates with ERRα to induce genes required for mitochondrial biogenesis and fatty acid oxidation, thereby activating osteoclast function (Figure 2) [20]. Therefore, this study deepens our understanding of the roles of PGC1β in osteoclastogenesis by identifying crucial upstream stimuli and downstream targets.

ERRα has been reported to inhibit osteoblastogenesis and enhance adipogenesis [47]. Our study revealed a previously unrecognized role for ERRα in promoting osteoclastogenesis by inducing the expression of mitochondrial genes via a PGC1β-dependent mechanism [20]. Interestingly, a polymorphic autoregulatory hormone response element in the human ERRα promoter [48] has been found to be associated with bone mineral density [49]. Together, these findings not only identify ERRα as a novel regulator of skeletal and mineral homeostasis, but also highlight a functional link between PPARγ and ERRα pathways, which converge at the transcriptional coactivator PGC1β.

The signaling pathways controlling osteoclast differentiation and mitochondrial activation crosstalk with each other and synergistically enhance osteoclastogenesis (Figure 2). For example, ROS generated by mitochondria can stimulate osteoclast differentiation by inducing Ca\textsuperscript{2+} oscillations and NFATc1 activation [50]; conversely, transcription factors
activated during osteoclast differentiation can induce target gene expression to promote osteoclast function and mitochondrial biogenesis [31,45]. Hence, during osteoclastogenesis, the direct ERRα targets are mitochondrial genes; however, ERRα also indirectly promotes osteoclast differentiation [20]. Consequently, ERRα deletion in mice causes decreased osteoclast number, bone resorption and increased bone mass [20]. Because of the crucial role of estrogen deficiency in post-menopausal osteoporosis, it will be interesting in future studies to determine whether and how the PPARγ–PGC1β–ERRα pathway interacts with the ER signaling in bone remodeling.

The fact that PPARγ deletion impairs osteoclast differentiation indicates that basal PPARγ activity, potentially induced by endogenous PPARγ ligands, is required for efficient osteoclastogenesis [19]. Therefore, both PGC1β and ERRα deletions compromise basal PPARγ activity, resulting in fewer osteoclasts induced by RANKL ex vivo and lower bone resorption in vivo [20]. Taken together, these findings demonstrate that PGC1β mediates the pro-osteoclastogenic function of PPARγ as a coactivator of both PPARγ itself and ERRα, thus activating two distinct transcriptional programs and linking osteoclast differentiation with osteoclast activation (Figure 2).

**PPARγ effects on bone are context-dependent**

Genetic evidence for a role of PPARγ in bone homeostasis is supported by pharmacologic studies, which demonstrate that TZD treatment causes bone loss in both mice and rats [19,20,51–54]. Collectively, these studies reveal that TZD-induced bone loss is attributable to decreased bone formation and increased bone resorption, both of which are required for the uncoupling of bone remodeling. However, the relative magnitude of these two effects varies between different studies, possibly because of the differences in the age and sex of the experimental animals, the specific TZD compound used, and the dosage and duration of TZD treatment. This suggests that regulation of skeletal homeostasis by PPARγ and TZDs is context-dependent. For example, age influences the effects of TZDs, with rosiglitazone preferentially increasing resorption in old mice (24 months) but mainly decreasing formation in young mice (1 and 6 months) [52]. This indicates that in old mice, rosiglitazone increases bone resorption while sustaining (rather than increasing) bone formation; by contrast, in young mice, rosiglitazone decreases bone formation while sustaining (rather than decreasing) bone resorption [52]. This is further demonstrated by our study in which an 8-week course of rosiglitazone significantly increased

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**Figure 2.** Rosiglitazone stimulates osteoclastogenesis via a transcriptional network of PPARγ, PGC1β and ERRα. Rosiglitazone-activated PPARγ, in concert with RANKL signaling, indirectly induces PGC1β expression by downregulating β-catenin, stimulating both basal and c-jun-induced PGC1β transcription. PGC1β in turn forms a positive feedback loop by functioning as a PPARγ coactivator to induce PPARγ target genes such as c-fos, thereby stimulating osteoclast differentiation. Likewise, rosiglitazone-activated PPARγ also induces ERRα expression during osteoclast differentiation. PGC1β acts as an ERRα coactivator (or protein ligand) to induce mitochondrial genes involved in fatty acid β-oxidation and oxidative phosphorylation, thereby promoting mitochondrial biogenesis and activation [20]. Furthermore, TIR1-mediated iron uptake promotes osteoclast differentiation, whereas RANKL-activated ROS and CREB induce PGC1β expression and mitochondria biogenesis [45]. Importantly, the signaling pathways controlling osteoclast differentiation and mitochondrial biogenesis crosstalk and synergistically promote osteoclastogenesis [45,50]. Therefore, rosiglitazone activates a transcriptional network comprised of PPARγ, PGC1β and ERRα to orchestrate the induction of both osteoclast differentiation and mitochondrial biogenesis, which ultimately enhances osteoclast function and bone resorption.
osteoclast number and bone resorption in 8–10-month-old mice [20]. If the coupling of bone remodeling was intact, there should have been an increase in osteoblast number and bone formation also, yet we observed a reduction in the osteocalcin bone formation marker (Figure 2) and unaltered osteoblast numbers [20]. Thus, rosiglitazone indeed suppresses osteoblast number and bone formation in these older mice, and the resorption-enhancing effect must act in concert with the formation-suppressing effect to induce uncoupling and a net loss of bone.

This age-dependent regulation suggests that the metabolic state might also influence the effects of rosiglitazone on bone. An important question for future study is whether and how different metabolic states such as obesity, diabetes and insulin resistance modulate the relative effect of TZDs on bone resorption versus formation. Towards this end, groundbreaking studies by the Karsenty and Ducy group reveal that skeletal remodeling is intimately connected to energy metabolism via crosstalk between bone and brain, fat, gut and pancreas. For example, leptin and serotonin regulate bone mass; conversely, decarboxylated osteocalcin secreted from bone regulates glucose homeostasis [55–57]. Provocatively, two recent studies demonstrate that insulin signaling in osteoblasts not only regulates bone acquisition, but is also required for whole body glucose homeostasis [58,59]. In particular, insulin signaling in osteoblasts stimulates osteoclast differentiation, and the associated acidification of bone matrix enhances the decarboxylation, activation and release of the hormonal form of osteocalcin, which promotes glucose metabolism [58]. This begs the intriguing questions of (i) whether the resorption-enhancing effect of PPARγ activation is required or at least contributes to its glucose lowering and insulin sensitizing effect and (ii) whether hyperinsulinemia in patients with T2DM leads to increased bone resorption and skeletal fragility.

The effects of TZDs on osteoclastogenesis are also influenced by the immunologic state of the subject. PPARγ and TZDs possess anti-inflammatory properties [13–15]. Recent studies show that TNFα-induced osteoclastogenesis and inflammatory periodontal bone loss are inhibited by TZDs [60–62]. Although more in vivo studies are required, these findings suggest that the anti-inflammatory effect of TZDs might be dominant over their pro-osteoclastogenic effect when the osteoclast stimulii originate from immune cell types activated by inflammatory cytokines. Thus, the physiologic and pathologic environment must be considered as a whole to understand the systemic effect of TZDs on skeletal integrity.

**Rosiglitazone causes bone loss in humans by inhibiting formation and enhancing resorption**

Epidemiologic studies suggest that skeletal fragility is increased in patients with T2DM [63,64]. A further understanding of the fracture risk linked to diabetes and diabetic drugs is clinically important, given the worldwide diabetes epidemic. Recent clinical trials report that long-term use of rosiglitazone increases fracture rates among patients with diabetes [65,66]. Thus, rosiglitazone administration exacerbates skeletal fragility in a population already at increased fracture risk. Considering the millions of patients with diabetes currently using rosiglitazone or pioglitazone therapy, it is of paramount importance to understand the cellular and molecular mechanisms underlying the regulation of bone metabolism by PPARγ and TZDs.

An earlier clinical study in 2007 showed that short-term rosiglitazone therapy exerts detrimental skeletal effects by inhibiting bone formation without affecting bone resorption [67]. However, a more recent clinical study in 2010, which examined circulating bone biomarkers in participants randomized to rosiglitazone in the A Diabetes Outcome Progression Trial (ADOPT) [68] demonstrated that rosiglitazone treatment not only inhibits bone formation, but also elevates bone resorption. The results showed that C-terminal telopeptide (for type 1 collagen), a marker for bone resorption and osteoclast activity, was significantly increased in women, but not men, taking rosiglitazone, compared with patients taking metformin or glyburide [68]. Procollagen type 1 N-propeptide (P1NP) and bone alkaline phosphatase, two markers for bone formation and osteoblast activity, were reduced in women and men in almost all treatment groups [68]. Thus, the authors concluded that elevated bone resorption might be partly responsible for the increased fracture risk in women taking TZDs. The discrepancy between these two clinical studies regarding the effects on bone resorption might originate from the differences in study design. In the 2007 study, healthy postmenopausal women were treated with rosiglitazone for 14 weeks (8 mg/day, n=25). In the 2010 study, patients with T2DM were treated with rosiglitazone for 12 months (4–8 mg/day, n=250 women, n=299 men). It is conceivable that a longer-term rosiglitazone treatment in patients with diabetes, who often have more fragile bones than do healthy individuals, might have magnified the resorption-enhancing effect of PPARγ activation. To address this hypothesis, future studies need to compare groups divided by disease status and treatment duration.

In summary, the genetic and pharmacologic evidence in humans and mice suggests that TZDs mediate bone loss by activating PPARγ in both mesenchymal and hematopoietic progenitor cells to inhibit osteoblastogenesis and activate osteoclastogenesis, respectively. Therefore, TZDs increase skeletal fragility by suppressing bone formation while sustaining or increasing bone resorption, leading to the uncoupling of bone remodeling and a net loss of bone. The anti-osteoblastogenic effect of PPARγ is mainly achieved by inhibiting signaling pathways such as Wnt and RB1. The pro-osteoclastogenic effect of PPARγ is mainly achieved by activating a transcriptional network comprised of c-fos, PGC1β and ERRα (Figure 1). Provocatively, although PPARγ activation of osteoclastogenesis is mediated by the coactivator PGC1β [20], PPARγ activation of adipogenesis and suppression of osteoblastogenesis is partially mediated by the coactivator SRC-2 [69]. Therefore, PPARγ recruits distinct transcriptional coactivators in hematopoietic and mesenchymal lineages to confer differential regulation of osteoclast and adipocyte development.

The future of rosiglitazone as a diabetic drug is currently tenuous because of its cardiovascular side effects. Three independent meta-analyses have shown that rosiglitazone is associated with an increased risk of myocardial ischemia.
These cardiovascular and skeletal side effects of rosiglitazone indicate a need for alternative therapeutic strategies. To this end, mechanistic understanding of cell type-specific gene regulation by PPARγ will facilitate the design of improved diabetic drugs, such as selective PPARγ modulators, which retain the insulin-sensitizing benefits but dampen the detrimental side effects. What is equally significant and promising, in light of the dual roles of PPARγ in regulating bone formation and bone resorption, is that bone-specific PPARγ antagonists might represent a potential therapeutic strategy for the simultaneous ana-
tabolism and adipocytokine production. The authors declare that they have no financial conflict of interest.

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Conflict of interest

The authors declare that they have no financial conflict of interest.

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