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BONE MARROW AND ADIPOSE TISSUE (B LECKA-CZERNIK AND G DUQUE, SECTION EDITORS)

Update on the Role of Glucocorticoid Signaling in Osteoblasts and Bone Marrow Adipocytes During Aging

Husam Bensreti[1] · Dima W. Alhamad[1] · Alejandro Marrero Gonzalez[1] · Manuel Pizarro-Mondesir[1] · Wendy B. Bollag[2,3] · Carlos M. Isales[4,5,6] · Meghan E. McGee-Lawrence[1,5]

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Abstract

Purpose of Review Bone marrow adipose tissue (BMAT) in the skeleton likely plays a variety of physiological and pathophysiological roles that are not yet fully understood. In elucidating the complex relationship between bone and BMAT, glucocorticoids (GCs) are positioned to play a key role, as they have been implicated in the differentiation of bone marrow mesenchymal stem cells (BMSCs) between osteogenic and adipogenic lineages. The purpose of this review is to illuminate aspects of both endogenous and exogenous GC signaling, including the influence of GC receptors, in mechanisms of bone aging including relationships to BMAT.

Recent Findings Harmful effects of GCs on bone mass involve several cellular pathways and events that can include BMSC differentiation bias toward adipogenesis and the influence of mature BMAT on bone remodeling through crosstalk. Interestingly, BMAT involvement remains poorly explored in GC-induced osteoporosis and warrants further investigation.

Summary This review provides an update on the current understanding of the role of glucocorticoids in the biology of osteoblasts and bone marrow adipocytes (BMAds).

Keywords Glucocorticoid · BMAT · BMAd · Dexamethasone · Osteoporosis · BMSC

Introduction

Aging is typically characterized by the deterioration of the structural and functional characteristics of an organism over time [1]. One of the hallmarks of aging is an accumulation of senescent cells, leading to a decline in regenerative capabilities and the creation of a pro-inflammatory environment [2] that favors the development of disease states [3]. Osteoporosis is a metabolic bone disease associated with aging in both men and women, although women are typically more deleteriously affected due to hormonal changes that occur during menopause [4, 5]. Aberrant bone metabolism is a key feature in the pathophysiology of osteoporosis, in which an imbalance between bone formation and resorption activity occurs [6, 7]. On the cellular level, this imbalance can be caused by decreased activity or abundance of bone-forming cells (osteoblasts) and/or over-activation or increased abundance of bone resorptive cells (osteoclasts), resulting in a lower bone mineral density (BMD), destruction of bone microstructure, and subsequent bone fracture [4, 5].

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✉ Meghan E. McGee-Lawrence
mmcgeelawrence@augusta.edu

[1] Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta University, Augusta, GA, USA

[2] Department of Physiology, Medical College of Georgia, Augusta University, Augusta, GA, USA

[3] Charlie Norwood VA Medical Center, Augusta, GA, USA

[4] Department of Neuroscience and Regenerative Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA

[5] Department of Orthopaedic Surgery, Medical College of Georgia, Augusta University, Augusta, GA, USA

[6] Department of Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA

Bone marrow mesenchymal stem cells (BMSCs) are multipotent cells that can differentiate into various cell lineages including osteoblasts and adipocytes [8]. Accordingly, BMSCs are positioned to have a profound influence on bone metabolism and play a key role in metabolic bone diseases including osteoporosis [8–10]. BMSC differentiation pathways can be guided via signaling cascades like Wnt/β catenin and Notch [11]. Certain transcription factors also play an important role in BMSC differentiation, such that runt-related transcription factor 2 (Runx2) and osterix (Osx) are critical for osteoblastogenesis, and peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (C/EBPα) enhance adipogenesis [9, 11, 12]. It has been reported that the cellular composition of bone marrow changes with age [13, 14]. Bone marrow adipocytes (BMAds) are sparse in the bone marrow at early stages of life, but gradually accumulate in long bones beginning around puberty [13]. With older age, bone marrow adiposity increases significantly resulting in the development of a fatty marrow [13]. On a molecular level, expression levels of adipogenic transcription factors such as PPARγ2 are elevated with advancing age [13]. Furthermore, older osteoblasts have been found to accumulate more intracellular lipids than younger osteoblasts, which could contribute to their diminished function and, in turn, to greater marrow adiposity with age [15, 16]. This accumulation may in part be facilitated by epigenetic changes. For example, we showed that expression of the epigenetic enzyme Hdac3 was reduced in aged wild-type osteoblasts [16], and BMSCs from Hdac3-insufficient mice cultured in an osteogenic medium accumulated more lipid droplets compared to cells from control mice [16]. At the organ level, conditional deletion of Hdac3 in Osterix-expressing cells of young mice resulted in a phenotype of low bone mass and elevated abundance of bone marrow adipose tissue (BMAT) [17], which may have been related to these cellular-level changes.

Both osteoblasts and bone marrow adipocytes (BMAds) are derived from the same pool of multipotent mesenchymal stem cell progenitors, and bone marrow space is a unique location where skeletal and adipose tissues directly interface [18], although emerging data from large-scale single-cell RNA-sequencing (scRNA-seq) studies has shown that preadipocyte-like cells represent a distinct state from osteoblasts and their precursors among BMSCs [19–22]. These studies identified unique clusters of adipocyte precursor cells (preadipocyte-like cells) that express the leptin receptor (Lepr), in addition to cell clusters that might correspond to skeletal stem and progenitor cells, preosteoblasts, and other stromal cells [23]. BMAT can be further characterized into two distinct subpopulations: regulated BMAT (rBMAT) located in regions such as the proximal tibia and distal femur, and constitutive BMAT (cBMAT) which can be found in locations like the distal tibia and caudal vertebra [24, 25]. By definition, rBMAT is more responsive to stimuli than cBMAT [25]. While the functions of BMAT are still being elucidated, key studies have shown that BMAT is an important endocrine organ in that it produces physiologically relevant levels of adiponectin during caloric restriction [26], aids in regulation of glucose homeostasis [27], and serves as an important energy source for the skeleton during metabolic challenges such as injury repair, cold exposure, and caloric restriction [28]. An inverse relationship between bone and BMAT abundance has been reported in a variety of disease states and natural phenomena, including aging, estrogen deficiency, anorexia, calorie restriction, diabetes, and physical disuse [24, 29–34]. BMAT also expands in cases of spinal cord injury, high-fat diet, and exogenous glucocorticoid treatment [12, 35–37], and an increase in BMAT is negatively correlated with outcomes in multiple hematopoietic disorders [38]. Historically speaking, this often-observed inverse relationship between BMAT and bone density was interpreted to indicate that BMAT is a negative regulator of bone mass [25, 30, 31, 39], either due to preferential differentiation of BMSC into the BMAd lineage at the expense of osteoblastogenesis, or due to crosstalk between osteoblast and BMAds. For example, when osteoblasts are cocultured with adipocytes or adipocyte-conditioned media, osteoblastic differentiation is inhibited [40, 41]. Interestingly, however, several prior investigations have shown that BMAT is not necessarily a causal factor for osteoporosis, as elimination of BMAds did not improve bone mass [42–44], and bone loss can occur independently of BMAT expansion [45]. As a result, and considered in light of the emerging roles for BMAT that have been uncovered in recent studies [26–28], a more accurate interpretation is that BMAT likely plays a variety of physiological and pathophysiological roles which are yet to be fully understood.

In elucidating the complex relationship between bone and BMAT, glucocorticoids (GCs) are positioned to play a key role, as they have been implicated in the decision of BMSCs to differentiate into osteogenic or adipogenic lineages [9]. GCs are essential steroid hormones that orchestrate the stress response of the body and circadian rhythm [9]. They are functionally involved in many physiological processes including growth, immune responses, and bone metabolism [9]. Although great attention has been paid to the deleterious skeletal effects of exogenous GC in causing glucocorticoid-induced osteoporosis (GIO), endogenous physiological GC have been much less extensively studied [46]. Notably, it has been proposed that increases in circulating endogenous glucocorticoids drive BMAT expansion during the metabolic challenge of caloric restriction [45]. The purpose of this review is to illuminate aspects of both endogenous and exogenous GC signaling, including the influence of GC receptors, in bone aging and the relationship of this signaling to marrow adiposity. In particular, this review will attempt to provide an update on the current understanding of the role of glucocorticoids in the biology of osteoblasts and BMAds.

Exogenous Glucocorticoids in Osteoblasts and BMAds

Exogenous GC are chemically synthesized molecules used therapeutically to treat inflammatory diseases such as rheumatoid arthritis [47]. Commonly used GC therapies include dexamethasone, prednisone, methylprednisolone, and hydrocortisone, which vary in their relative potencies and activity (Table 1) [48–51]. In vitro and in vivo studies have established that high levels of pharmacological GCs exert detrimental effects on all stages of osteoblastogenesis [12, 52, 53] (Fig. 1). The underlying molecular mechanism involves suppression of key signaling pathways that are essential for differentiation of BMSCs to osteoblasts, such as the WNT pathway. In fact, exogenous GC can induce osteoblast apoptosis, which decreases bone density and elevates the risk of fracture in animal models and in humans [54]. In addition, previous studies have shown that humans and rodents that are exposed to exogenous GCs have fewer osteoblast progenitor cells and increased BMAT [12, 55]. Mechanistically, GCs inhibit osteoblast progenitor cells through upregulating cell cycle inhibitors such as p21, p27, and p53, and downregulating cell cycle activators including cyclin D3, cyclin-dependent kinase (CDK) 4 and CDK6 [56–58]. Moreover, it has been shown that exposure to supra-physiological levels of GCs leads to significant suppression of bone formation. Accordingly, serum markers of osteocalcin, procollagen type I N-terminal propeptide (P1NP), and bone-specific alkaline phosphatase (ALP) are reduced upon GC treatment [59]. The secretion of collagen and osteocalcin is also reduced upon exposure to exogenous GCs, which indicates that bone mineralization was negatively influenced. Furthermore, GCs increase bone matrix degradation by upregulating the synthesis of metalloproteinases [59].

The use of exogenous GCs also affects osteocytes, which are terminally differentiated osteoblasts fully embedded in mineralized matrix. Several in vivo and in vitro studies have demonstrated that exogenous GCs increase apoptosis and reduce the lifespan of osteocytes [60–63]. However, other studies failed to correlate reduced bone mass upon GC exposure with higher osteocyte apoptosis [64]. One of the possible explanations for this discrepancy is that exogenous GCs exert their effects on bone cells in a dose and time-dependent manner [54, 63]. Dose-dependent effects can be due to the modulation of autophagy and antioxidant gene expression which eventually leads to apoptosis [54, 63, 65]. Exogenous GCs influence osteocytes in several ways, including up-regulating the production and secretion of sclerostin and dickkopf-related protein-1 (Dkk-1) [66]. These two proteins inhibit bone formation by blocking the osteoblastic Wnt/β-catenin signaling pathway [67]. Importantly, sclerostin has been shown to increase adipogenesis in a variety of experimental models, which could contribute to the mechanisms by which GC influence BMAds [68–70]. GCs also compromise bone strength via effects on the osteocyte lacunocanalicular system; GCs increase the lacunar size and change the bone matrix [26]. In vitro studies have found that exogenous GCs have detrimental effects on connectivity between osteocytes by disrupting gap junctions between cells [71].

It has been well established that GC treatment reduces bone mass and elevates BMAT [12] (Fig. 1). Both osteoblasts and adipocytes are derived from progenitor populations within the broader BMSC pool, and previous studies have suggested that when BMSCs commit to one lineage, they may begin to lose the ability to differentiate along another lineage [72]. To understand the molecular mechanism underlying dexamethasone-induced osteoporosis and fat accumulation, Li et al. treated mice with dexamethasone to create an osteoporotic model [12]. They found that upon dexamethasone treatment, BMSC differentiation shift towards adipocytes rather than osteoblasts. They also demonstrated that dexamethasone inhibits the methylation of the C/EBPα promoter (a key transcription factor for adipocyte differentiation) through the Wnt/beta-catenin pathway. As a result, C/EBPα expression is significantly higher in dexamethasone-treated mice, consistent with their increased bone marrow adiposity [12]. Other studies have shown that adipocytes secrete substances that negatively influence osteoblast differentiation and function [73–75]. For example, Wang

Table 1 Pharmacological characteristics of exogenous GCs

Name	Equivalent glucocorticoid dose (mg)	Duration of action in humans (hrs)	Potency relative to hydrocortisone (cortisol)
Cortisone	25	Short (8–12)	0.8
Hydrocortisone (cortisol)	20	Short (8–12)	1
Prednisone	5	Intermediate (12–36)	4
Prednisolone	5	Intermediate (12–36)	4
Triamcinolone	4	Intermediate (12–36)	5
Methylprednisolone	4	Intermediate (12–36)	5
Dexamethasone	0.75	Long (36–72)	25
Betamethasone	0.75	Long (36–72)	25

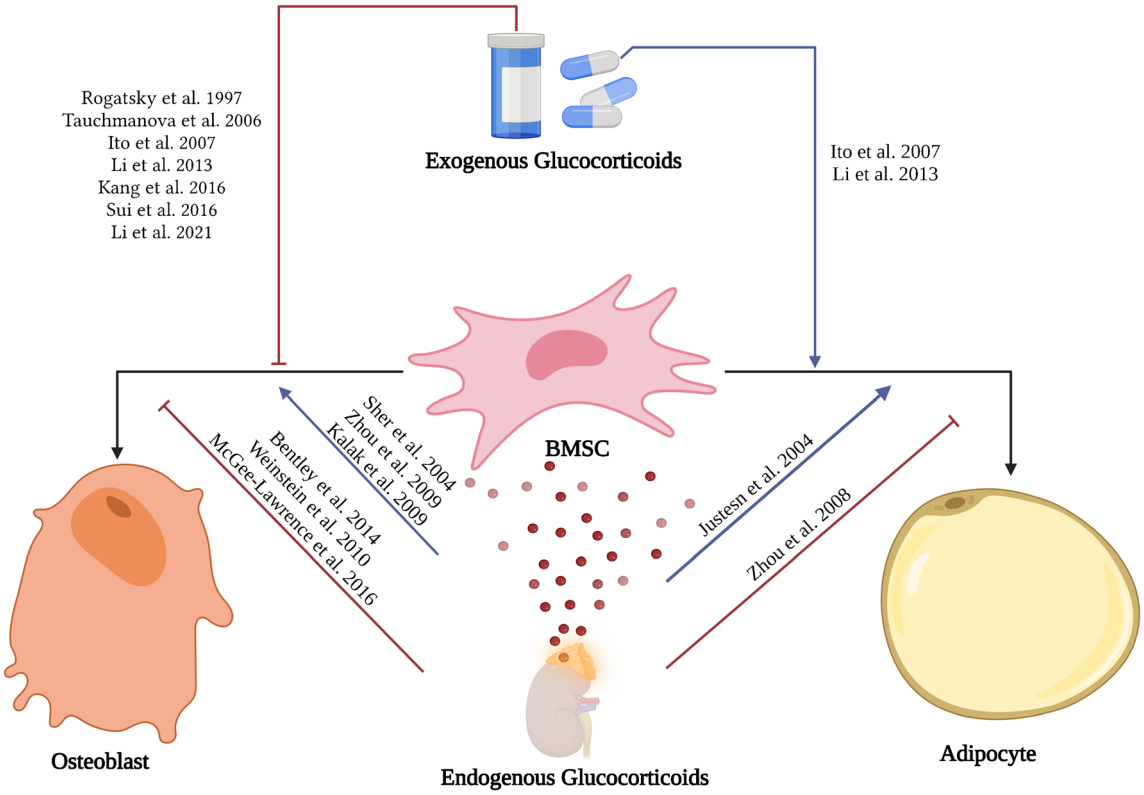

Fig. 1 Reported effects of exogenous and endogenous GC on bone marrow stem cells differentiation into osteoblast and adipocyte lineages. Figure created with BioRender.com

et al. co-cultured adipocytes and osteoblasts obtained from a human mesenchymal stem cell line with dexamethasone, finding that six days of co-culture in the presence of dexamethasone reduces alkaline phosphatase activity, bone mineralization and expression of osteogenic markers like Runx2 and osteocalcin [74]. The conditioned media of dexamethasone-treated co-cultures contains higher fatty acid levels compared to the control co-cultures [74]. Further investigation revealed that fatty acids are produced by adipocytes, leading to increased reactive oxygen species levels, which eventually results in osteoblast apoptosis [74]. A recent clinical study also indicated that patients with glucocorticoid-induced osteoporosis present with altered BMAT lipid profiles as compared to patients with non-GC-related osteoporosis [76].

MicroRNAs are single-stranded non-coding RNAs that regulate a plethora of biological functions [77]. Many microRNAs have been associated with bone health including miR-106b [77], and miR-188 [78]. Kang et al. found that the synthetic GC dexamethasone regulates microRNA-34a-5p, which is crucial to the dexamethasone-mediated inhibition of BMSC proliferation and osteogenic differentiation [79]. This effect is established through targeting of CDK4, CDK6, and Cyclin D1, and activation of Notch signaling with the ultimate outcome of inhibiting osteogenic differentiation [79]. Wang et al. showed that dexamethasone induces high miR-133a expression, and a miR-133a antagomir significantly enhances osteoblast differentiation and inhibits adipocyte differentiation, highlighting the role of synthetic GC's effects on microRNAs in the process [80]. Dexamethasone was also found to inhibit let-7f-5p expression, and Shen et al. showed that let-7f-5p reverses dexamethasone-induced bone loss in mice [81]. MicroRNAs transported in exosomes (extracellular vesicles containing cargoes of proteins, lipids, and nucleic acids) [82], may play a role in cellular crosstalk between adipocytes and osteoblasts [83, 84], and there is growing evidence showing that certain exosome cargoes can counter deleterious effects of GC in bone [52, 85, 86]. However, it remains unknown whether GCs regulate exosome secretion and function in various bone cells and bone marrow adipocytes and if this plays a role in GC-induced osteoporosis.

Endogenous Glucocorticoids in Osteoblasts and BMAds

Endogenous GCs are steroid hormones synthesized and released by the adrenal glands in response to biological, physiological, and environmental cues. The hypothalamic-pituitary-adrenal axis regulates GC secretion [46, 87]. Physiological and biological triggers like changes in metabolism, cardiac output, or inflammation trigger the release of corticotropin-releasing hormone (CRH) from the

hypothalamus [87]. This hormone stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), which in turn acts on the zona fasciculata of the adrenal cortex to synthesize GC from its precursor cholesterol [9, 87]. Cells of zona fasciculata produce and release active GCs (corticosterone in rodents and mainly cortisol in humans) within 5 min of an ACTH pulse [88, 89]. However, more than 90% of GCs are bound by corticosteroid-binding globulins, which renders them biologically inactive [90]. When released from protein binding, free GCs can exert their effects in target tissues [90]. Local activity of GCs is regulated through the enzymes 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and -HSD2. 11β-HSD2 inactivates cortisol and corticosterone through an oxidation reaction which converts them to cortisone and 11-dehydrocorticosterone (11DHC), respectively [91]. This is especially important in mineralocorticoid (aldosterone) target tissues, to prevent GCs from occupying mineralocorticoid receptors (MRs) [92]. As a result, 11β-HSD2 protects organs such kidney [93], placenta [94], and colon [95] from overactivation by GCs. In contrast, 11β-HSD1 is present throughout most tissues in the body [9, 96]; it reactivates cortisone and 11DHC through a reduction reaction to yield functional (active) cortisol and corticosterone [96, 97]. In fact, 11β-HSD1's action in a given cell was proven to be predominantly GC recycling, acting as a local signaling amplifier [98, 99] to render local levels of both active and inactive GCs equally potent in activating target receptors, as described below [99].

Once inside cells, active GCs can exert their function through genomic or non-genomic pathways. In the genomic pathway, GCs bind to a target receptor such as the glucocorticoid receptor (GR) [9]. Subsequently, the receptor-GC complex is translocated to the nucleus, where it binds directly to a glucocorticoid response element (GRE) sequence in the DNA of target genes and acts as a transcription factor to elicit altered gene expression and protein synthesis [9]. Non-genomic GC-signaling, in contrast, occurs rapidly and does not necessarily involve protein synthesis [100]. Instead, once GC are bound to their target receptor, chaperone proteins are released from the complex and play a role in secondary signaling cascades utilizing the activity of various kinases like mitogen-activated protein kinases (MAPKs) and AKT [100].

Although less extensively studied than exogenous GCs, several previous articles make the case that endogenous GCs play a key role in the differentiation of BMSC-lineage cells (Fig. 1). Sher et al. created a transgenic mouse model that overexpressed 11β-HSD2 in osteoblasts and demonstrated that GCs are needed for proper skeletal development, as local inactivation of GC led to vertebral osteopenia and decreased cortical bone area and thickness [101]. Interestingly, overexpression of 11β-HSD2 in this manner displayed a sexually dimorphic effect, with female mice more adversely affected than males [101]. In another report, a similar mouse model displayed delayed cranial bone formation and could not properly resorb parietal cartilage postnatally [102]. These effects were attributed to reduced expression of Wnt9a and Wnt10b [102]. In addition, β-catenin levels were reduced in BMSCs, chondrocytes and osteoblasts, which disrupted the activity of matrix metalloproteinase 14 and reduced cranial cartilage removal [102]. Therefore, the authors concluded that endogenous GCs are important regulators of bone formation, acting in a paracrine mechanism not only to direct BMSC commitment towards the osteoblastic lineage but also to control cartilage dissolution postnatally [102]. Similarly, Kalak et al. studied a Col2.3-11β-HSD2 transgenic mouse model and showed that young (3- and 7-week-old) mice with 11β-HSD2 overexpression in osteoblasts had reduced mechanical bone strength compared to wild-type mice, highlighting the important role of GCs in bone development and the maintenance of a healthy bone phenotype [103]. Several other studies showed comparable findings, in which the overexpression of 11β-HSD2 reduced bone mass, trabecular number, and bone strength [104, 105]. *Ex vivo* studies demonstrated lower alkaline phosphatase staining, reduced levels of bone sialoprotein, and decreased osteocalcin mRNA expression in cultures derived from transgenic mice with 11β-HSD2 overexpression [104]. Examining another aspect of GC activation, Justensen et al. showed that mice with germline (whole body) deletion of 11β-HSD1 presented with little to no BMAT compared to wild-type mice, but their bone formation rate and bone mass were comparable [96]. Consistent with this role for 11β-HSD1, we showed that the loss of Hdac3 in Osterix-expressing osteoprogenitors increased expression of 11β-HSD1 and lipid storage genes like Plin1 and Fsp27/Cidec [16], as well as increasing bone marrow adiposity. These results suggest that high endogenous GC activity contributes to increased marrow adiposity [16]. In contrast, Zhou et al. noted that osteogenic cultures from mice that overexpress 11β-HSD2 in osteoblasts had a higher number of adipocytes compared to cultures from wild-type mice [106]. They also indicated that Wnt signaling was reduced in transgenic mice with 11β-HSD2 overexpression, explaining the shift from osteogenic to adipogenic lineage commitment [106]. Taken together, these studies demonstrate that tight regulation of endogenous GCs is important in the balance of osteogenesis and adipogenesis.

Despite the evidence showing that endogenous GCs are needed for osteoblastogenesis, when GC levels increase substantially in diseases such as Cushing's syndrome, they negatively influence bone [107]. A mouse model for Cushing's syndrome exhibits low bone mineral density, osteoblast numbers, and bone formation rates along with higher numbers of BMAds in the bone marrow [107]. Similarly, Belaya et al. revealed that hypercortisolism suppresses osteoblast function and maturation through downregulating genes like BMP2 and RUNX2, while upregulating the expression of Wnt-signaling

antagonists such as Dkk1 and SOST [108]. Levels of certain miRNAs known to suppress osteoblastogenesis including miR-125b-5p, miR-218-5p, miR-34a-5p are also altered [108]. Tauchmanova et al. designed a cross-sectional case control study to evaluate the effect of excess endogenous GCs on vertebral fractures and bone mass in human subjects [53]. Their results showed that the prevalence of vertebral fractures is significantly higher in patients with GC excess as compared to healthy controls [53]. Among the different etiologies studied, cortisol levels are highest in patients with ectopic ACTH secretion, which is accompanied by low lumbar bone mineral density, and high fracture frequency [53]. The results also indicated that women are more adversely affected by excess cortisol secretion than men and that androgens exhibit protective effect in both genders [53]. Another retrospective study on 104 patients with Cushing's syndrome reported that the increased fracture risk is higher before diagnosis and therapy, but it is minimized after therapy [109]. This suggested that bone loss is reversible upon correcting the abnormality, and that reducing GC levels by adrenal or pituitary surgery might reduce the risk of bone fractures [109]. Relating more specifically to BMAT, a recent clinical study of young individuals revealed that daily adrenal GC secretion levels are inversely related to bone marrow density, i.e., directly correlated with BMAT abundance [36]. Collectively, these studies described above suggest that the impact of GC on bone and BMAT depends on the concentrations, with low amounts favoring bone formation, but excessive levels adversely affecting bone and increasing BMAT.

During aging, the beneficial impact of endogenous glucocorticoids on bone may be blunted and instead contribute to bone loss in the aged skeleton [46]. Dysregulated glucocorticoid signaling may contribute to age-related bone loss through effects on osteoblastic senescence and osteoprogenitor lineage selection bias (i.e., affecting the ratio of osteoblastic versus adipogenic differentiation of progenitor cells) even in young individuals [36, 37, 110]. In aging individuals, local activation of endogenous GCs by 11β-HSD1 is substantially enhanced; this phenomenon contributes to increased cortisol levels and altered circadian cortisol variation, both of which may be associated with bone frailty [111–113]. Weinstein et al. demonstrated that the production of GCs from the adrenal gland increases in aged mice, and that the effect of GCs is potentiated due to higher local expression of 11β-HSD1 [114]. The resulting high level of active GCs adversely influences bone since it reduces the lifespan of osteoblasts and osteocytes, decreases bone vasculature, and impairs the transport of solutes from peripheral circulation to the lacunar-canalicular system [114]. The authors concluded that GCs are causative in the observed bone phenotype because transgenic mice with overexpression of 11β-HSD2 are protected against the deleterious effects of GCs in bone and show higher bone mass with age [114]. This finding contrasts with results in younger animals, in which bone density, strength and histomorphometry are not different between 11β-HSD2 and wild-type mice [54]. A more recent study demonstrated that skeletal GC signaling is involved in bone's role as an endocrine organ, as Col2.3-11β-HSD2-overexpressing mice are protected against the development of age-related obesity and insulin resistance, but intriguingly found a contrasting phenotype to that of Weinstein et al, in that 11β-HSD2-overexpressing mice have a mild phenotype of decreased trabecular bone mass in the spine [115]. Thus, the role of endogenous GCs in skeletal aging, at least at the level of the active GCs ligand, remains somewhat unclear.

GC Receptors in Osteoblasts and BMAds

GCs can exert downstream effects via activating the glucocorticoid receptor (GR), a transcription factor encoded by the NR3C1 gene [116, 117]. GR is a member of the nuclear receptor (NR) superfamily of intracellular receptors belonging to subclass 3C of the steroid/thyroid hormone receptor superfamily [118]. Nuclear receptors, including mineralocorticoid receptor (MR), progesterone receptor (PR), estrogen receptor (ER), and androgen receptor (AR), contain a variable N-terminal domain (NTD), a DNA binding domain (DBD), a hinge region, a conserved ligand-binding domain (LBD), and a variable C-terminal domain [119]. Phylogenetic analysis by Vlachakis et al. revealed a novel evolutionary relationship between the LBD of NRs, indicating a potential functional overlap in LBD between members of the NR superfamily [120]. Indeed, GCs can bind to both GR and MR as target receptors, with MR having much higher affinity for GC than GR [121]. Consequently, GR tends to be bound by GCs during stress and at the circadian peak of GC secretion, while MR is occupied at basal hormone levels [121, 122]. Nonetheless, in MR-rich tissues, the effect of GCs is often limited through 11β-HSD2, which unidirectionally converts active GCs to an inactive form [9, 96, 121].

The role of GR-mediated signaling of endogenous GCs in bone health has been investigated by us and others through the use of osteoblast-targeted disruption of GR signaling in rodent models. Rapp et al. showed that global deletion of GR interferes with fracture healing by disrupting post-fracture endochondral ossification [123]. Furthermore, Rauch et al. disrupted GC-GR signaling axis in the osteoblasts by utilizing a $GR^{Runx2Cre}$ transgenic mouse line, revealing a significant decrease of trabecular bone density in the GR knockout animals compared to their WT littermates [64]. Similarly, our laboratory demonstrated that conditional deletion of GR in Osterix (Osx1) expressing cells ($GR^{osx1Cre}$) leads to a significant decrease in cortical and trabecular bone mass and a significant increase in BMAT in young, adult, and aged female mice [39, 124]. Moreover, BMSC-derived osteoblasts from

Table 2 List of pharmacological GR antagonists

Name	Nuclear receptor specificity	References
Mifepristone (RU486)	PR antagonist	[128]
	GR antagonist	[129]
	AR agonist/antagonist	[137, 155]
PT150 (ORG-34517)	GR antagonist	[133]
	AR antagonist	[135]
ORIC-101	GR antagonist	[137]
CORT125281	GR antagonist	[136]
CORT118335 (Miricorilant)	GR antagonist	[156]
	MR antagonist	
CORT108297	GR antagonist	[139]
CORT125134 (Relacorilant)	GR antagonist	[140]
Dicyclohexyl phthalate (DCHP)	GR antagonist	[141]
FX5	GR antagonist	[142]

GR glucocorticoid receptor, *PR* progesterone receptor, *MR* mineralocorticoid receptor, *AR* androgen receptor

these GR-deficient animals surprisingly still demonstrate excessive lipid storage in the presence of GCs, a phenomenon that can be reversed by treating the cells with MR antagonists [39]. Interestingly, Fumoto et al. showed that the deleterious effects of prednisolone are negated either by pharmacological inhibition or knocking down MR in osteocytes [125].

The GC effects that are mediated through GR can be disrupted using GR antagonists [126] (Table 2). Mifepristone, also known as RU486, was first reported in 1981 as a GR antagonist but later recognized as also antagonizing the PR [126–128]. Mifepristone was approved by the US Food and Drug Administration (FDA) based on its PR antagonist effects for medical termination of pregnancy through 70 days gestation [129], and later granted approval for the treatment of Cushing's syndrome due to its GR-targeting effects [130]. Despite showing efficacy as a GR antagonist, mifepristone treatment has notable limitations; overtreatment may lead to adrenal insufficiency, increased cortisol levels, endometrial hyperplasia in females, and interference with negative feedback mechanisms of GCs [131, 132]. Other GR antagonists and selective GR modulators designed to have no effect on PR activity have been investigated and are in various stages of development including PT150 (formerly known as ORG-34517) [133–135]. CORT125281 [136], ORIC-101 [137], CORT118335 (miricorilant) [138], CORT108297 [139], CORT125134 (relacorilant) [140], dicyclohexyl phthalate (DCHP) and FX5 [141, 142]. Among the selective GR modulators, CORT118335 has been found to antagonize MR as well as GR [139]. Interestingly, although the deleterious effects of exogenous corticosteroids on bone have been widely reported, comparatively less is known about the skeletal effects of the above listed pharmacological GR antagonists. Mifepristone's skeletal effects were mainly reported in vitro as counteracting/reversing the effects of exogenous GC (dexamethasone, prednisolone) [39, 143], rather than describing its effects independently of GC co-treatment. Mifepristone's lack of selectivity for the GR, and the relative lack of available FDA approved GR antagonists other than mifepristone have likely contributed to the knowledge gap surrounding the skeletal effects of GR antagonists [128, 130].

Conclusions

Although physiological concentrations of GCs are important for healthy bone development and homeostasis, prolonged exposure to elevated GC levels (both endogenous and exogenous) can be harmful to the skeleton through promotion of altered bone remodeling activity, including reduced bone formation. It is important to remember that endogenous GC are counter-regulatory hormones, released during times of stress to help mobilize nutrients including glucose, amino acids, and fatty acids from less immediately critical body systems (e.g., peripheral fat, muscle, bone) to maintain energy homeostasis in systems essential for survival (e.g., brain, heart) [144]. To this end, BMAT may represent an important fuel source for hematopoietic and immune cell populations within the bone marrow, as supported by recent publications [28, 145]. In addition, recent work has shown that BMAds may act as a critical fuel source for bone remodeling cells during times of stress; for instance, lipolysis by BMAds was important for the maintenance of trabecular bone mass under conditions of caloric restriction in male (but not female) mice, as well as for proper bone cell function in the face of cold stress and during energetically-expensive processes of bone repair/regeneration [28, 146]. These findings are consistent with the idea that fatty acids are an important fuel source for both osteoblasts [147, 148] and osteoclasts [149]. However, targeted deletion of BMAds provided a net benefit, rather than detriment, to the skeleton, enhancing cortical and trabecular bone formation in

cBMAT-rich regions of the skeleton, and protecting against cortical bone loss induced by caloric restriction [145]. These studies highlight the important role of BMAds not only as a nearby fuel source for osteoblasts, but also the potential impact of their role as a paracrine source of adipokines and cytokines in times of stress. The specific role of GCs in mediating these dynamics of crosstalk between BMAds and bone remodeling cells in the presence and absence of stress is not yet clear, and represents an exciting area for future research. Deleterious effects of GCs in the skeleton involve several cellular pathways and events and include a complex interplay of both local and systemic factors that bias BMSC differentiation toward adipogenesis [7, 8, 11, 31, 44, 150, 151], affecting cellular crosstalk between mature BMAds and osteoblasts [152]. Several published studies highlight the positive influence of GCs on BMAT development; however, a clear connection between GC effects on BMAT and bone health has yet to be defined [9, 12, 36, 39, 40, 153, 154]. Future studies focused on the effects of GCs on crosstalk between bone and BMAT, including the role of various GC-binding nuclear receptors in these mechanisms, are needed to fully elucidate these relationships and their impact on skeletal aging and frailty.

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Declarations

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Conflict of interest The contents of this publication do not represent the views of the Department of Veterans Affairs or the US Government. The authors state that they do not have existing conflicts of interest.

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