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HIV: Inflammation and Bone

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Abstract

HIV infection and antiretroviral therapy (ART) are now established independent risk factors for osteoporosis. With a spate of recent studies reporting significant elevations in fracture prevalence in HIV patients, and a rapidly aging demographic, defining the mechanisms underlying HIV/ART-induced skeletal decline has become imperative. The recent emergence of the field of "osteoimmunology" has provided a conceptual framework to explain how the immune and skeletal systems interact. Furthermore, it is becoming clear that inflammatory states leading to perturbations in the immuno-skeletal interface, a convergence of common cells and cytokine mediators that regulate both immune and skeletal systems, conspire to imbalance bone turnover and induce osteoporosis. In this review we examine the role of inflammation in the bone loss associated with diverse inflammatory conditions and new concepts into how the underlying mechanisms by which inflammation and immune dysregulation impact bone turnover may be pertinent to the mechanisms involved in HIV/ART-induced bone loss.

Keywords

HIV; AIDS; osteoporosis; inflammation; immune-skeletal interface

Introduction

Evidence continues to emerge for the existence of an inexplicable convergence within the immune and skeletal systems, the result of a centralization of common cell types and cytokine mediators that may be described as the "immuno-skeletal interface" [1]. The clinical implications of the immuno-skeletal interface are underscored by the changes in bone turnover and loss of bone mineral density (BMD) commonly associated with conditions such as rheumatoid arthritis [2], periodontal infection [3], inflammatory bowel disease [4], type I and II diabetes [5–7], systemic lupus erythematosus [5], and sickle cell disease [8]. All of these pathologic conditions are intimately associated with immune dysregulation and chronic inflammation. Interestingly, animal models, backed up by limited clinical data, now support the contention that postmenopausal osteoporosis, the archetypal bone disease of women, is itself the result of immune dysregulation associated with a

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persistent low-grade inflammatory state [9, 10]. Given the well-documented correlation between inflammation and bone disease and the importance of the immuno-skeletal interface in the regulation of basal and pathological bone turnover, we recently proposed that disruption of the immune system may in part underlie the skeletal abnormalities ubiquitously documented in the setting of HIV infection [11••], a condition associated with severe immune deficiency and a persistent state of immune activation and chronic inflammation [12, 13]. This review examines the depth of the integration between the immune and the skeletal systems and emerging concepts pertinent to immune and inflammatory changes that may underlie skeletal deterioration in the setting of HIV-1 infection and antiretroviral therapy (ART).

The Skeletal Profile in the Setting of HIV Infection and ART

The Direct Effects of HIV Infection on the Skeleton

As a result of a series of observational cohort studies conducted over the past decade we have come to appreciate the extent of skeletal abnormalities associated with HIV infection [14–16]. In fact, it is now clearly established that HIV infection is an independent risk factor for osteopenia and osteoporosis [17, 18]. Current data suggest that two of every three HIV-seropositive individuals naïve to ART exhibit osteopenia and have a 3.7 higher odds of developing osteoporosis [14]. Teasing out the relative contribution of direct viral effects on the skeleton vis-à-vis the contribution of other traditional osteoporosis risk factors such as drug abuse, smoking and alcohol consumption, associated with patient lifestyle, and AIDS-related pathologies such as muscle wasting, kidney disease, vitamin D deficiency, and hypogonadism that abound in this patient population, has been challenging. As a consequence, many believe that the etiology of bone decline in the setting of HIV infection is likely multifactorial.

Indirect Effects of Antiretroviral Therapy on the Skeleton

Another perplexing paradox is that unlike its effect on many other HIV-related pathologies, ART exacerbates, rather than ameliorates bone loss [19, 20]. Interestingly, the skeletal effects of ART, though varied in magnitude, appear universal regardless of regimen [21•] and are typically documented within the first 1–2 years of therapy [20, 22–24]. Clinical studies routinely find an average loss in BMD of 2%–6% at the femur, lumbar spine, or hip [20, 25, 26], all common fracture prone anatomical sites in the body. Contextually, bone loss of this magnitude is not inconsequential, and approaches that sustained in women during the first 2–5 years following menopause, a time when rapid bone deterioration is in effect [20, 27]. This loss of BMD further compounds the bone loss already sustained in the majority of patients as a result of chronic HIV infection.

The Health Hazards of Combined HIV/ART-Related Skeletal Deterioration

Because fragility fractures are typically a rare event in younger populations, especially in men, evidence for higher fracture incidence in the comparatively young HIV/AIDS population has until very recently been mostly anecdotal and contentious. However, a series of recent clinical studies have now unambiguously demonstrated a dramatic rise in fracture prevalence with HIV infection. Fracture rates twofold to fourfold higher than the general population have consistently been documented over a wide age range. In the landmark study by Triant et al. [28••] involving 8525 HIV-infected and 2,208,792 non–HIV-infected control patients, an increase in fracture prevalence among HIV-infected patients of up to fourfold was observed in both men and women over a wide age range. Importantly, while fracture rates in HIV-seronegative men have been historically low until advanced age because of intrinsically higher BMD and increased bone size, HIV-infected men in this cohort demonstrated a dramatic rise in fracture prevalence at relatively young ages. Similarly,

fracture rates for the HIV/AIDS population were twofold to fourfold higher in the HIV Outpatient Study (HOPS) cohort, a study involving 5826 HIV-infected patients [29••]. In the Veteran Administration (VA) cohort comprising 39,375 HIV-infected patients, fracture rates were 24%–32% higher [30]. A smaller Canadian study with 138 HIV-infected women and 402 controls reported a close to twofold higher fracture rate with HIV infection [31]. These important epidemiological data underscore the clinical and public health implication of fragility bone disease in the HIV/AIDS population and highlight the urgency of uncovering the underlying mechanisms of HIV-induced and ART-induced bone loss.

Bone Modeling and the Homeostatic Bone Remodeling Processes

Full appreciation of the depth of the immuno-skeletal interface and its impact on bone health requires an understanding of the structure and regulation of the skeleton and the roles of the key cells involved in skeletal remodeling. Eighty-five percent of adult bone mass is achieved by 18 years of age in girls and by 20 years of age in boys [32]. By early adulthood (25–35 years of age), skeletal formation is essentially complete. At this time “bone remodeling,” a process of bone renewal, begins and involves the clearance of damaged bone and bone with diminished load-bearing properties by osteoclasts, and the resynthesis of new bone by osteoblasts. In early adulthood, this process of bone breakdown and reformation ultimately leads to a period of relative stability in BMD because the amount of old bone removed is balanced by the amount of new bone formed with no net gain or loss of BMD, a state of “homeostatic” balance. However, this state of skeletal stability is relatively transient, and by the forth decade of life, the rate of bone resorption typically exceeds that of formation, resulting in a gradual but persistent decline in BMD. While in men this process of age-related skeletal decline is relatively linear, in women bone loss is markedly accentuated for approximately 5–10 years following menopause [33]. This accelerated bone loss associated with menopause is compounded by the fact that the bones in women are typically smaller and less dense than those in men, resulting in bone fracture incidence that is in excess of twofold higher in women than men [33]. Nonetheless, both sexes are at risk and 50% of women and 20% of men over the age of 50 will sustain a fracture in their remaining lifetimes as a consequence of osteoporosis [32].

The Depth of the Immuno-Skeletal Interface

The process of homeostatic bone remodeling is complex and susceptible to changes in many physiologic processes and biochemical systems in the body, and as such, can be impacted by diverse pathologic conditions. Over the last decade we have begun to appreciate the degree of the influence of immune cells on bone metabolism [5, 34, 35].

Although our understanding of the interactions between the immune system and the bone building machinery is still rudimentary, it is well recognized that mesenchymal stem cells (MSCs) give rise to bone marrow stromal cells, a population containing the precursor of bone-forming osteoblasts. MSCs are known to exert an important regulatory influence on immune cell function [36] while osteoblasts themselves regulate the hematopoietic stem cell niche from whence all other immune and blood cells are derived [37]. In addition, cytokine mediators of immune origin such as tumor necrosis factor alpha (TNFα) are potent inhibitors of bone formation [38, 39] and may drive down bone formation under inflammatory states, widening the gap between formation and resorption and exacerbating bone loss. By contrast, activated T cells also secrete factors with the capacity to stimulate the differentiation of bone marrow stromal cells into the osteoblast phenotype [40]. Recently we identified a novel T-cell–secreted cytokine termed secreted osteoclastogenic factor of activated T cells (SOFAT) that not only promotes osteoclast formation but is capable of eliciting production of interlukin-6 (IL-6) from osteoblasts [41•]. Finally, osteoblasts may feedback on T cells by

secretion of interlukin-7 (IL-7) [42], a master regulator of T-cell development and function [43].

In contrast to the cross-talk between osteoblasts and immune cells, our understanding of the immuno-skeletal interface in the regulation of osteoclastic bone resorption is relatively well developed. First, it has long been recognized that osteoclasts, the bone resorbing cells, are of myeloid origin and derived from precursors that circulate within the macrophage and monocyte lineage. More recently, was the recognition that these precursors may be distinguished from other monocytic cells by the expression on their membrane surface of receptor activator of NF-κB (RANK). The ligand for RANK (RANK ligand [RANKL]) is recognized to have important immunological functions including the integration and regulation of T-cell growth and dendritic cell functions [44]. However, in the context of bone biology RANKL is now generally considered to be the key final effector of osteoclast differentiation and activity [45]. The association of RANKL with RANK on osteoclast precursors induces their differentiation into pre-osteoclasts which ultimately fuse together into the mature multinucleated giant cells, osteoclasts, responsible for bone resorption.

A delicate control network involving osteoprotegerin (OPG), a TNF receptor superfamily member and RANKL decoy receptor, prevents RANKL from binding to RANK, moderating RANKL-induced osteoclast formation and activity [45–47].

B Cells: A Major Source of OPG in response to T-Cell Costimulation

B cells are an essential component of the adaptive immune system and of humoral immunity. Although B cells also present antigens to T cells, a principal function of B cells is to make antibodies against soluble antigens. B cells, however, are also central to basal skeletal regulation. Although it was initially thought that basal osteoclastogenesis is controlled primarily by RANKL and OPG production by cells of the osteoblast lineage [48], studies in the human system identified B cells as a prominent additional source of OPG, and responsive to T-cell costimulatory ligands in vitro [49]. More recently, in vivo data from our group have validated B-lineage OPG production as critical to the regulation of basal osteoclastogenesis and the maintenance of basal bone mass in the murine system [50]. Interestingly, as originally suggested by in vitro studies using human B cells [49], association of CD40L on activated T cells with its cognate receptor CD40 on B cells potently enhances B-cell OPG secretion in mice in vivo. The importance of this interaction was further reflected by the documentation of diminished OPG production and severe osteoclastic bone loss in murine models of B-cell, T-cell, CD40, and CD40L deficiency [50]. The importance of CD40L in the regulation of basal bone mass is further underscored by evidence of a high rate of osteopenia and fractures in humans with the inherited immune deficiency disorder X-linked hyper-IgM syndrome, a genetic disease caused by mutations in the CD40L gene [51].

T Cells and B Cells: A Significant Source of RANKL Under Inflammatory Conditions

Besides the influence of T cells and B cells on the basal production of bone-sparing OPG, under inflammatory conditions activated T cells [9, 52–54] and B cells [11••, 54] become a significant additional source of RANKL. In fact, activated lymphocytes have been implicated as key protagonists of the bone loss associated with pathologies as diverse as postmenopausal osteoporosis [10, 55, 56], rheumatoid arthritis [2], and in alveolar bone loss associated with periodontal infection [3, 54]. We have also recently reported the identification of SOFAT, a novel cytokine secreted by activated T cells that has the capacity to promote osteoclast formation in a RANKL-independent fashion that may further directly drive up osteoclastic bone resorption during inflammation, as well as indirectly promote

osteoclastogenesis by stimulating RANKL production from osteoblasts through induction of IL-6 [41•].

In the presence of permissive concentrations of the survival factor macrophage colony-stimulating factor (M-CSF), RANKL (and SOFAT) are final unique effectors of osteoclast formation. However, it is recognized that many other inflammatory cytokines play a significant role in driving bone loss. Prominent among these are IL-1, IL-6, IL-7, TNFα, IFNγ, M-CSF, VEGF, IGF-1, and IL-17 [9, 57]. These inflammatory cytokines are able to upregulate osteoclastogenesis through one or more distinct mechanisms including stimulating RANKL production by lymphocytes and/or osteoblast-lineage cells, upregulating the RANKL receptor RANK on osteoclast precursors, or in the case of TNFα by amplifying the activity of RANKL at the level of signal transduction [9, 56]. By contrast, cytokines such as IL-4 and IFN-γ may mediate inhibitory actions on osteoclastogenesis. While IFNγ potently upregulates antigen presentation and drives up T-cell activation and TNFα and RANKL production [58, 59], it paradoxically has direct inhibitory effects on osteoclast differentiation by impeding RANK signal transduction [60]. Interestingly, in the context of HIV infection, high levels of suppressor of cytokine signaling-1 (SOCS-1) may modify IFNγ responses by impeding its signal transduction [61]. The actions of common inflammatory cytokines on osteoclastogenesis are summarized in Table 1.

Together these observations have led to the emergence of the field of “osteoimmunology” and have given rise to the notion that overexpression of inflammatory cytokines by cells of the immune system underlies the high rate of skeletal abnormalities associated with inflammatory and autoimmune disorders [5] and in postmenopausal osteoporosis, a condition that exhibits significant characteristics of an inflammatory state [9].

HIV-1 Infection and Inflammation

HIV infection is another disease that has now been shown to be associated with high rates of osteopenia and osteoporosis [1, 18]. A hallmark of HIV infection is a continuous stimulation of the immune system contributing to loss of CD4+ T cells as a consequence of activation-induced cell death. This process is further exacerbated by poor T-cell restoration due to reduced thymic function associated with HIV infection [12]. Although near total depletion of $CD4^+$ T cells is a hallmark of HIV infection, there is extensive damage to the entire immune system affecting cellular, humoral, and innate immune response. This leads to severe B-cell and T-cell (both $CD4^+$ and $CD8^+$) exhaustion [62, 63] resulting in a dysfunctional memory B-cell compartment, and predisposing patients to AIDS-related secondary diseases and opportunistic infections [64, 65••]. Loss of $CD4^+$ T cells is accompanied by increased immune activation affecting all major cell populations of the immune system [65••].

As previously stated, T cells are critical for B-cell function, and consequently HIV infection causes numerous direct and indirect (via T cells) perturbations in the B-cell population. B-cell numbers are significantly diminished along with a concomitant increase in the frequency of immature/transitional B cells that are associated with $CD4^+$ T-cell lymphopenia [65••]. Lymph nodes (LNs) represent the principal site where antigen-specific memory T-cell and B-cell responses are primed and differentiated into memory and effector cells. During chronic HIV infection substantial structural changes to LNs occur, leading to fibrotic LNs. These changes are only partly reversed by ART [66] in part due to diminished space for B-cell engraftment. Furthermore, while memory B cells ($CD27^+$) in the peripheral blood of healthy individuals comprise both $B220^+$ and $B220^-$ subsets, HIV-infected individuals show a significant reduction in $CD27^+$ $B220^-$ populations [65••, 67]. The cause of these changes in B-cell number and in memory subpopulations is poorly understood but

cytokine imbalance, decreased T-cell function, and direct exposure to virus and viral antigens all play significant roles [67].

In addition to the direct disruption of the immune cells described above, chronic immune activation is a recognized feature of HIV infection and a strong predictor of disease progression [68•]. This is thought to result in part from HIV-induced gastrointestinal mucosal damage leading to systemic translocation of bioactive microbial cell wall products including lipopolysaccharide (LPS) that are capable of activating both the innate and adaptive immune systems [69]. LPS is well established to stimulate osteoclast production by promoting osteoblast production of RANKL, IL-1, and TNFα [70].

Taken together, these data indicate that the pathophysiologic changes associated with HIV infection could affect bone metabolism at multiple levels including the direct disruption of B-cell and T-cell functions, and induction of chronic activation of the innate and adaptive immune response via translocation of gut microbial cell wall products.

Evidence of HIV Disruption of the Immuno-Skeletal Interface

In an attempt to better understand the pathophysiology of HIV-induced bone loss, our group recently evaluated the impact of HIV infection on the immuno-skeletal interface using the HIV-1 transgenic rat model. In this murine model, there is constitutive expression of HIV-1 viral proteins as a consequence of a replication defective HIV-1 viral genome integrated into the rat DNA [71]. This animal has been demonstrated to recapitulate many of the immunologic and clinical abnormalities seen with human HIV/AIDS [71]. Similar to the skeletal changes observed in human HIV infection, HIV-1 transgenic rats underwent severe loss of BMD and extensive disruption of bone architecture and structure. Histologic and serum biochemical markers were consistent with markedly increased osteoclast number and in vivo bone resorption. Mechanistically, osteoclastogenesis was associated with altered B-cell function leading to a significant decline in production of bone-sparing OPG, an increased expression of the osteoclastogenic cytokine RANKL, and compounded by a dramatic increase in the number of osteoclast precursors [11••]. These intriguing observations provided some of the first evidence of a direct disruptive impact of HIV on the immuno-skeletal interface. This model of HIV-induced bone loss is outlined diagrammatically in Figure 1. Studies to ratify these findings in human HIV infection are currently underway and if validated will broaden our understanding of the mechanisms of HIV-induced skeletal damage.

Evidence of ART Disruption of the Immuno-Skeletal Interface

It is also now clear that ART affects bone turnover independently of the bone loss associated with HIV infection itself [72]. Like HIV infection, studies to isolate and define the underlying mechanisms of ART-induced bone loss have been confounded by independent osteoporosis risk factors associated with traditional osteoporosis risk factors, body mass, and lifestyle factors [22, 23, 73]. Further hindrance by the wide range of classes and individual drugs combined into the ART formulations employed in modern clinical practice has added to the confusion as to the direct effects of ART on bone turnover. While answers from clinical studies have been contradictory and slow in coming, an inability to effectively replicate effects of ART in vitro or in animal models in vivo in the absence of viral infection has further confounded our understanding of this issue. In one study the protease inhibitor (PI) ritonavir, but not the related PI indinavir, was actually found to be bone sparing in mice in vivo and was found to inhibit osteoclast differentiation and abrogated bone resorption by disrupting the osteoclast cytoskeleton in vitro [74]. In another study nucleoside reverse transcriptase inhibitors (NRTIs) were found to have no effect on osteoclastogenesis but suppressed the activity of osteoblasts [75]. While there is presently no agreement on the

direct effects of ART on bone cells in vivo, recently a consensus has begun to emerge that all classes of ART may be detrimental to the skeleton [21•, 76]. The evidence also suggests that the preponderance of BMD decline occurs relatively early in the course of ART initiation (typically within the first 48 weeks) [19, 20, 26] and at a time of heightened immune restoration [77], lending support to the notion that bone loss might be driven by a mechanism aligned with HIV-disease reversal, in particular immune-regeneration. Furthermore, viral suppression by ART leads to a partial recovery of depleted T cells through poorly understood mechanisms involving both peripheral expansion of existing T-cell pools, as well as IL-7–mediated thymic reactivation pathways [77, 78]. In fact, IL-7–driven thymic-dependent differentiation of bone marrow–derived progenitors and thymic-independent, peripheral expansion of mature T cells has previously been demonstrated to play a critical role in the etiology of ovariectomy-induced bone loss, a model of postmenopausal osteoporosis [79].

Based on these principles we speculate that regeneration of the immune system following ART initiation may once again promote renewed disruption of the delicate immuno-skeletal interface initiating a new wave of bone resorption and loss of BMD. A unifying mechanism for ART-induced bone loss centered on excessive osteoclastogenic cytokine production following T-cell restoration will support the current epidemiologic observation that bone loss occurs early during ART and is a common feature of almost all ART types regardless of the component drugs in the regimen. Studies to address such a mechanism are currently underway.

Conclusions

While ART has radically improved patient quality of life and longevity, some of these gains are beginning to be offset by troublesome metabolic complications including osteoporosis and elevated fracture prevalence. While skeletal deterioration has been associated with HIV and ART for more than a decade, the consequences are only now becoming apparent as the HIV population begins to shift to an older demographic, and is likely to become more acute as persistent bone loss associated with natural aging in both men and women compounds the bone loss caused by HIV infection and ART. An increase in bone fractures at an uncharacteristically young age, especially for men, is already becoming evident and is likely to increase exponentially in the future as these patients continue to age. While the mechanisms responsible for the skeletal aberrations in HIV patients appear to be extremely complex and multifactorial, recent studies have opened a window into how persistent inflammatory responses associated with HIV infection and ART may underlie disruptions to the immuno-skeletal interface that may explain in large measure the bone loss associated with both HIV infection and the exacerbation of this bone loss by ART. A better understanding of the underlying pathology and the molecular mechanisms responsible for skeletal deterioration will be essential to devise effective therapeutic interventions to safeguard the significant gains made in the long-term health of AIDS patients over the last decade.

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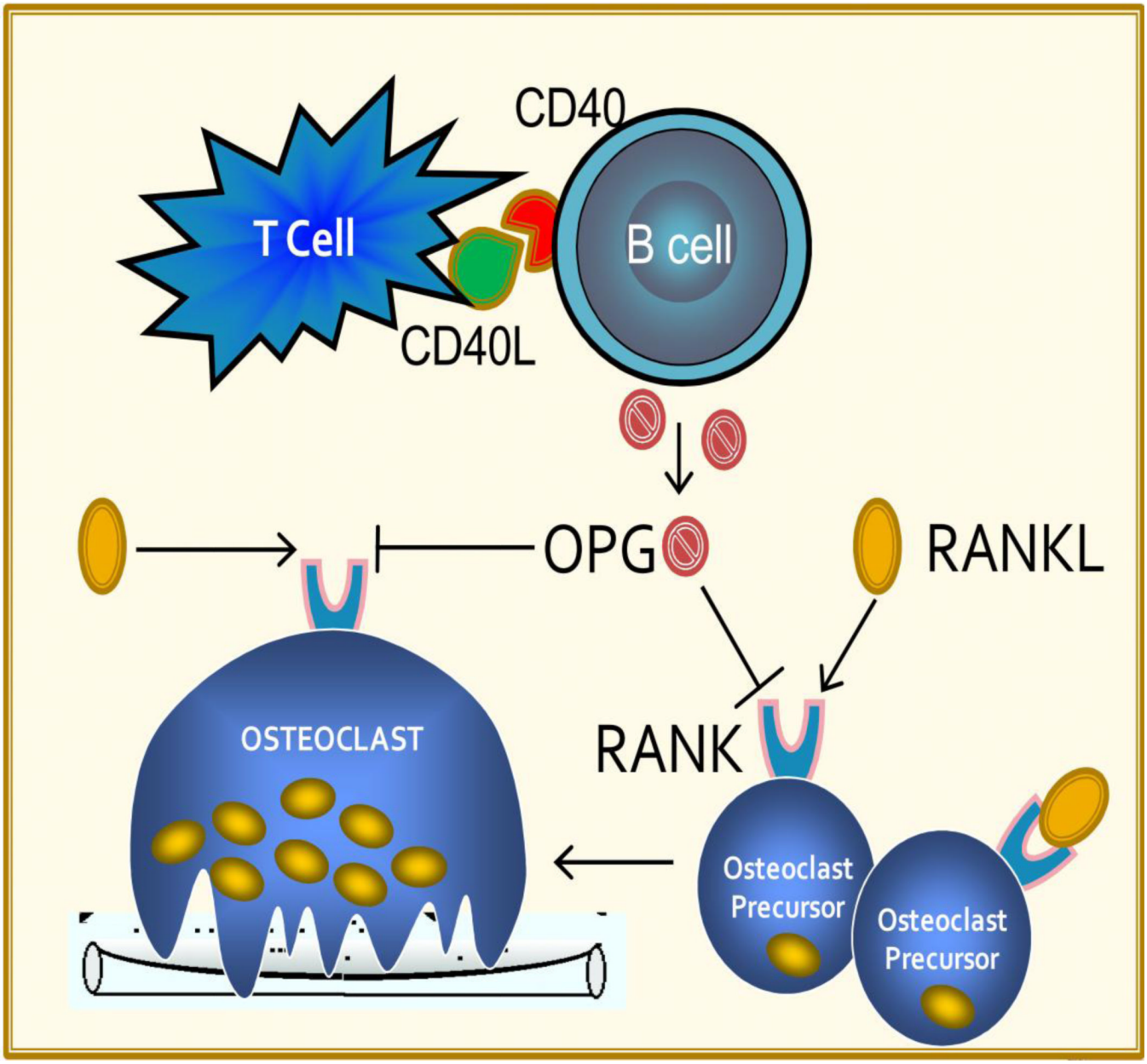

Figure 1.
Model of HIV-induced disruption of the immune-skeletal interface: B-cell production of OPG, regulated in part through CD40 to CD40 ligand co-stimulation by T cells, counteracts the key osteoclastogenic cytokine RANKL, moderating osteoclast formation and activity. HIV infection leads to a disruption of the immuno-skeletal interface disrupting T-cell to B-cell communication and leading to elevated RANKL and diminished OPG production by B cells. The elevated RANKL/OPG ratio is biased in favor of increased osteoclast formation. (*Adapted with permission from* Ofotokun et al. [18].)

Table 1

Effect of inflammatory cytokines on bone cells

Inflammatory cytokine	Abbreviation	Bone effect
Interferon-gamma	IFNγ	A major product of activated T cells, IFNγ has been found to promote inflammatory bone loss during estrogen deficiency by upregulating the activity of antigen-presenting cells (especially macrophages) and leading to further T-cell activation and enhanced osteoclastogenic cytokine production [59]. Conversely, IFNγ has been reported to mediate direct inhibitory activity on osteoclast differentiation by inducing degradation of the RANK adapter protein, TRAF6, which is required for RANKL signal transduction [60].
Interleukin	IL-1	IL-1 is a potent inflammatory cytokine long associated with bone loss in postmenopausal osteoporosis [80] and animal models of estrogen deprivation [81]. IL-1 promotes RANKL production by osteoblasts [82] and is a potent amplifier of TNF-induced RANKL production by bone marrow stromal cells [83].
Interleukin	IL-6	IL-6, a potent inflammatory cytokine, has long been associated with estrogen deprivation [84] and inflammatory states leading to bone loss. IL-6 is a major product of osteoblasts and their progenitors [85] and appears to be potently osteoclastogenic; however, the exact role of IL-6 and its mechanism of action in bone turnover remains unclear. IL-6 is reported to stimulate the proliferation of osteoclast progenitors [86] and RANKL expression by synovial cells [87], but not osteoblasts [82]. Osteoclastogenic effects of IL-6 in models of rheumatoid arthritis may also stem from indirect generalized proinflammatory effects on the immune system [88].
Interleukin-7	IL-7	IL-7 is a master regulator of T-cell production and function [43] and a potent upstream osteoclastogenic cytokine as it promotes RANKL production by T cells and is a central player in the bone loss associated with estrogen deprivation in mice by stimulating bone resorption and suppressing bone formation [9, 42, 79, 89, 90].
Macrophage colony-stimulating factor	M-CSF	M-CSF is a key survival factor for cells of the monocyte/macrophage lineage including osteoclasts and their precursors and although required for osteoclast formation, M-CSF alone is incapable of stimulating osteoclast differentiation in the absence of RANKL [91, 92]. M-CSF may further aid osteoclastogenesis by upregulating expression of the RANKL receptor RANK on osteoclast precursors, expanding the osteoclast precursor pool [11••, 93].
Osteoprotegerin	OPG	OPG is a decoy receptor for RANKL and moderates RANKL activity by binding to it and preventing RANKL from binding to, and initiating signal transduction from, its receptor RANK. The ratio of RANKL to OPG is a key determinant of osteoclast formation and activity [45–47, 91, 92].
Receptor activator of NF-κB ligand	RANKL	RANKL, also known as osteoprotegerin ligand (OPGL), tumor necrosis factor–related activation-induced cytokine (TRANCE), and osteoclast differentiation factor (ODF), is a TNF receptor superfamily member that enhances T-cell growth and dendritic cell function [44]. RANKL is also considered to be the key osteoclastogenic cytokine and the final effector of osteoclast formation and activity [45, 91, 92, 94].
Secreted osteoclastogenic factor of activated T cells	SOFAT	A recently identified novel cytokine secreted by activated T cells that directly promotes osteoclastogenesis in a RANKL-independent manner, and indirectly by inducing IL-6 production by osteoblasts [41•].
Transforming growth factor-β	TGF-β	TGF-β is an important multifaceted regulator of bone metabolism. TGF-β possesses anti-inflammatory properties that suppress T-cell activation, thus reducing production of osteoclastogenic cytokines, and may limit bone loss associated with estrogen deficiency [95]. TGF-β also directly suppresses osteoclastogenesis by initiating apoptosis of osteoclasts [96, 97] and may further antagonize osteoclast formation by inducing OPG production by osteoblasts [98, 99]. Paradoxically, in vitro TGF-β can promote RANKL-induced osteoclastogenesis [100]. TGF-β is also an early osteoblast differentiation commitment factor [101] and promotes migration of osteoblast progenitors to sites of bone resorption [102].
Tumor necrosis factor-alpha	TNFα	TNFα is a unique osteoclastogenic cytokine by virtue of its capacity to synergize with RANKL to amplify its osteoclastogenic and resorptive activity [56, 103–106]. TNFα can also promote RANKL production by osteoblasts [82, 83]. Furthermore, TNFα is a potent inhibitor of osteoblast differentiation and activity

Inflammatory cytokine	Abbreviation	Bone effect
		[39] and in vivo bone formation leading to reduced peak BMD in mice [38]. TNFα is a key protagonist of bone loss associated with estrogen deficiency [9].