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Retinoids and Bone

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1. Introduction

Vitamin A (retinol) can be produced in the body by hydrolysis of retinyl esters or reduction of retinal. Liver and eggs, which are good animal sources of vitamin A, contain retinyl esters. Plant sources such as carrots and spinach contain pro-vitamin A carotenoids, which can be cleaved to retinal. Retinal, also called retinaldehyde, is interconvertible with retinol (Fig. 1). Retinal also serves as an intermediate in the irreversible production of all-trans-retinoic acid (ATRA), which is considered the major biologically active derivative of vitamin A [Moise *et al.* 2007, Chambon 1996]. Another important derivative of vitamin A is the visual chromophore 11-cis-retinal [Wald 1968]. Binding of 11-cis-retinal to proteins called opsins is the chemical basis of vision. Vitamin A formed from retinyl esters or carotinoids in the normal diet, or ingested in fortified foods or dietary supplements, is stored in the liver and transported to tissues as a complex bound to retinol binding protein [Moise *et al.* 2007].

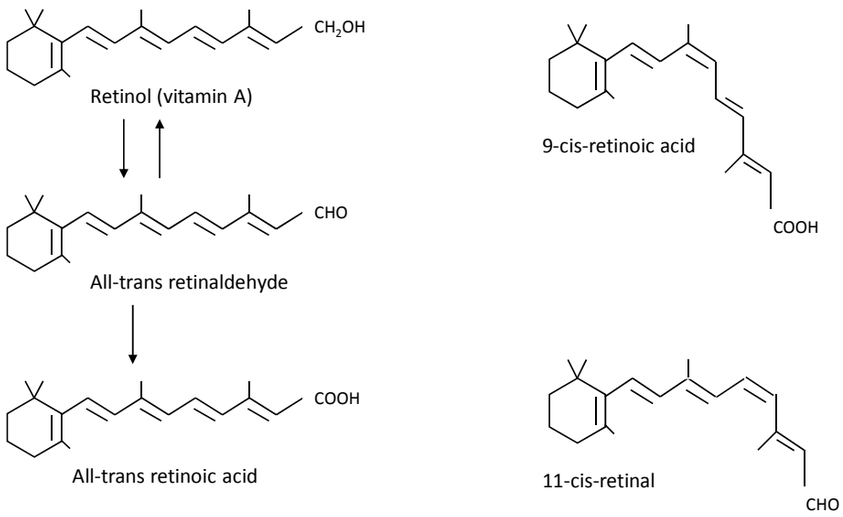


Fig. 1. Formation of all-trans retinoic acid from vitamin A and structures of 9-cis retinoic acid and 11-cis-retinal.

Effects of retinoids are mediated primarily by two families of nuclear hormone receptors, retinoic acid receptors (RARs) and the retinoid X receptors (RXRs) [Bastein *et al.* 2004]. Each receptor family is made up of three isoforms (α, β and γ), produced by separate genes. RARs can be activated by ATRA and the isomer 9-*cis* retinoic acid (9-cis RA), while RXRs are activated by 9-*cis* RA. RARs form heterodimers with RXRs and these heterodimers and RXR homodimers function as transcription factors, activating RAREs in the promoter regions of target genes. Most retinol signaling in cells is thought to be mediated by ATRA binding RAR in RAR/RXR heterodimers [Mic *et al.* 2003]. It is still not clear if 9-*cis* RA is formed physiologically in cells and what role this isomer may play as a specific ligand for RXR [Mic *et al.* 2003]. Activated retinoid receptors function as transcription factors, activating specific RA response elements (RAREs) for transcriptional regulation of target genes [Bastein *et al.* 2004, Mic *et al.* 2003].

Peroxisome proliferator-activated receptors (PPARs), α, β/δ, and γ, represent another group of nuclear hormone receptors that forms heterodimers with RXR. PPAR/RXR heterodimers also function as transcription factors, activating specific response elements of target genes [Mangelsdorf and Evans 1995, Bocher *et al.* 2002, Wilson *et al.* 2000]. Recent studies have indicated that ATRA not only can bind RARs, but can serve as a ligand for PPAR β/δ as well [Berry *et al.* 2007]. Channelling of ATRA to RARs or PPAR β/δ is suggested to depend on the intracellular binding proteins, RA binding protein II or keratinocyte fatty acid binding protein 5, which deliver ATRA to either RAR or PPAR β/δ, respectively [Schug *et al.* 2007].

Vitamin A plays an essential role in numerous biological processes, including vision, cellular proliferation, differentiation, and apoptosis, organ development and function, and immunity [Moise *et al.* 2007, Mark *et al.* 2006, Mark *et al.* 2009]. Numerous malformations and impaired vision, growth, organ function, and reproduction have been noted with vitamin A deficiency. Vitamin A is used in developing countries to help correct vitamin A deficiency [Moise *et al.* 2007]. Supplementation with vitamin A has had an enormous worldwide impact, saving countless lives, at minimal costs per patient. There is also widespread use of vitamin A derivatives (retinoids) for treatment of various skin conditions, such as acne [Peck *et al.* 1979], and for different cancers, including acute promyelocytic leukemia (APL), Kaposi's sarcoma, head and neck squamous cell carcinoma, ovarian carcinoma, and neuroblastoma [Siddikuzzaman *et al.* 2010]. Use of retinoids has proved particularly useful for treatment of APL [Siddikuzzaman *et al.* 2010]. Pharmacological concentrations (10^{-7} - 10^{-6}M) of ATRA block repression by a PML- RARα fusion protein that interferes with normal RARα transcriptional regulation in APL.

Besides serving as an intermediate in retinoic acid formation, recent studies have shown that retinal (retinaldehyde) is present at biologically active concentrations in fat tissue, where it antagonizes PPAR-γ activity, inhibits adipogenesis, and improves insulin sensitivity [Ziouzenkova *et al.* 2007]. These observations suggest that retinal may be an additional vitamin A derivative that plays an important role as a mediator of biological processes.

Hypervitaminosis A in experimental animals has been linked to increased bone resorption, decreased bone mass, and increased fractures [Frankel *et al.* 1986, Hough *et al.* 1988, Johansson *et al.* 2002]. There are also case studies in humans showing that significantly increased intake of vitamin A increases bone resorption, causes hypercalcemia, and induces skeletal pain [Frame *et al.* 1974]. Supplementation of the diet with vitamins is a common occurrence in developed countries and there is presently debate over whether more modest

increases in vitamin A might promote skeletal abnormalities. Some studies have shown that increased vitamin A intake or elevated serum retinol levels [Michaelsson *et al.* 2003] are associated with an increased incidence of hip fracture or decreased bone mass [Melhaus *et al.* 1998, Feskanich *et al.* 2002, Promislow *et al.* 2002]; however, other studies have shown no deleterious effect on bone mass or fracture risk, and, in some instances, protection from bone loss because of increased vitamin A has been reported [Ribaya-Mercado and Blumberg 2007, Caire-Juvera *et al.* 2009]. In studies where vitamin A analogues have been evaluated, decreases in bone mass have been reported following isotretinoin and acitretin usage in some instances, but a recent, large scale, case-control study has found no increased risk of fracture with these agents [Vestergaard *et al.* 2010].

2. Bone tissue

Skeletal tissue is comprised primarily of either cortical (compact) or trabecular (cancellous) bone. In the adult, approximately 80% of skeletal mass is cortical bone and 20% trabecular bone. Cortical bone is found in the shafts of long bones and the outer surfaces of all other bones in the body. It is organized around blood vessels into cylinders of consolidated bone called osteons, or Haversian systems. Unlike trabecular bone, cortical bone does not contain bone marrow. Trabecular bone is characterized as a network of thin spicules of bone ("spongy bone"), which is found in the interior of vertebrae, flat bones in the skull, the pelvis and sacrum, and the distal and proximal parts of long bones. Both cortical and trabecular bone are important for bone strength. In the adult skeleton, both types of bone are remodelled and modelled [Martin and Seeman 2008]. Modelling of bone is a process that changes the size and shape of bone either by bone resorption without subsequent bone formation, or bone formation without prior bone resorption. Remodelling of bone is the process by which old bone is replaced by new bone. It is initiated by bone resorption to remove damaged bone, followed by new bone formation in the area resorbed. Remodelling does not change the size or shape of the bones. Remodelling is more frequent in trabecular bone than in cortical bone, one of the reasons why a metabolic bone disease like postmenopausal osteoporosis affects primarily bones with proportionally increased amounts of trabecular bone, e.g. vertebrae, distal radius, and proximal femur. Remodelling is believed to be initiated by microcracks in the mineralized bone extracellular matrix and subsequent osteocytic apoptosis, which triggers osteoclast formation and resorption of the micro-damaged area [Martin and Seeman 2008]. The process causes release of "coupling factors" which attract and activate osteoblasts to form new bone under a canopy of bone lining cells [Martin and Sims 2005, Boyce *et al.* 2009, Martin *et al.* 2009]. When osteoblasts fill the resorption lacunae made by osteoclasts with new bone in the bone multicellular unit (BMU), remodelling is in balance and bone mass remains constant. This equilibrium involves bidirectional interactions between osteoclasts and osteoblasts to fine tune the balance between bone formation and bone resorption.

The skeleton is a support structure that serves as a reservoir for calcium, phosphate, and numerous other minerals, protects vital organs such as brain, heart, lung, and bone marrow, and recently has been implicated in glucose- and energy metabolism [Confavreux *et al.* 2009]. Three systemic hormones that play primary roles in calcium homeostasis and bone formation and resorption are parathyroid hormone (PTH), 1,25$(OH)_2$-vitamin D_3, and calcitonin. PTH and 1,25$(OH)_2$-vitamin D_3 stimulate bone resorption when serum calcium decreases, whereas calcitonin inhibits bone resorption when serum calcium is increased. Sex

hormones also play important roles, with increased bone resorption and decreased bone formation occurring when levels of either estrogen or testosterone are decreased. Other agents known to play significant roles in bone turnover are the thyroid hormones, glucocorticoids, follicle stimulating hormone, and the retinoids. Interestingly, there is also a great deal of cross talk between bone cells and the immune system. This occurs during both normal physiological remodelling and in pathological inflammatory conditions involving bone, like rheumatoid arthritis and peridontitis [Takayanagi 2009].

3. Osteoclast differentiation

Osteoclasts are multinucleated giant cells found on bone surfaces that stain for tartrate resistant acid phosphatise (TRAP). They are formed by fusion of mononucleated progenitor cells derived from hematopoetic myeloid stem cells, which also give rise to macrophages and dendritic cells. For fusion of osteoclast precursors to occur, they must be differentiated specifically along the osteoclastic lineage [Lorenzo and Horowitz 2008, Edwards and Mundy 2011]. Formation of osteoclasts is controlled by osteoblasts at the bone surface. Thus, osteoblasts are responsible for not only bone formation, but regulate bone resorption as well. In addition to hematopoetic cells, bone marrow also contains pluripotent mesenchymal cells which are able to support differentiation of osteoclasts [Askmyr *et al.* 2009]; however, mature osteoclasts do not form within bone marrow, but enter the circulation as mononucleated osteoclast progenitors and home to periosteal and endosteal tissues. The details of this attraction are not known at present, but stomal cell-derived factor-1 (SDF-1 or CXCL12) produced by osteoblasts and CXCR4 expressed by osteoclast progenitors may play important roles [Kollet *et al.* 2006]. To what extent the circulating osteoclast progenitor cells are primed in the bone marrow, or to what extent priming occurs in the periosteum and endosteum is also not known at present. Nor is it known if osteoclast formation in trabecular bone in the close vicinity of bone marrow is different from osteoclast formation in periosteal tissues, which are always some distance from bone marrow. Recently, one group has presented evidence for the existence of a unique periosteal macrophage – osteomac which not only can form osteoclasts, but is also able to control bone formation [Chang *et al.* 2008]. Increasing evidence indicates that osteoclast formation does not follow a common pathway and that osteoclasts are different in different parts of the skeleton [Everts *et al.* 2009, Henriksen *et al.* 2011].

Crude bone marrow cultures, or co-cultures of periosteal osteoblasts and purified osteoclast progenitors from either bone marrow or spleens, have shown that osteoclast formation requires close physical contact of progenitor cells with either stromal cells in the bone marrow or osteoblasts. Molecularly, it has been found that macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor κB ligand (RANKL) are two products of stromal cells/osteoblasts that play key roles in regulating osteoclast formation. M-CSF supports progenitor cell proliferation and survival, and RANKL is responsible for progenitor differentiation to osteoclasts, rather than to macrophages or dendritic cells [Takayanagi 2009, Lorenzo and Horowitz 2008, Nakashima and Takayanagi 2009]. RANKL, which is a member of the TNF superfamily, functions by binding to RANK on osteoclast progenitor cells. Osteoprotegerin (OPG), a soluble protein released from stromal cells/osteoblasts, is another key factor regulating osteoclastogenesis. OPG functions as a decoy receptor for RANKL, blocking interaction between RANKL and RANK. The expression of RANKL is thought to be restricted to a relatively small number of cells: bone marrow stromal cells, osteoblasts,

periodontal ligament cells, synovial fibroblasts, T-, B- and NK-cells, while OPG appears to be ubiquitously expressed. It is the relative expression of RANKL and OPG which determines whether osteoclast formation will take place. Enhancement of the RANKL/OPG ratio in stromal cells or osteoblasts by hormones and cytokines causes stimulation of bone resorption.
Following RANKL binding to trimeric RANK, association of the cytoplasmic tail of RANK with TNF receptor-associated factor 6 (TRAF 6) leads to activation of several kinases, including IKKβ, MAPKs such as p38 and JNK, and PI3K (Fig. 2). Subsequently, transcription factors such as NF-κB, AP-1, MITF, NFATc1 and Akt are activated. Within the NF-κB family of transcription factors, p50 and p52 seem to be the most important subunits [Boyce *et al.* 2010]. RANK signaling leads to induction and activation of c-fos, which functions as a component of the transcription factor, activator protein-1 (AP-1). Mice with double knockouts of p50/p52 or with deletion of the c-Fos gene lack osteoclasts and exhibit osteopetrosis. The induction of the master transcription factor for osteoclastogenesis, NFATc1, is dependent on NF-κB and c-fos signaling by RANK [Negishi-Koga and Takayanagi 2009]. In cooperation with RANK, immunoglobulin-like receptors associated with adaptor proteins harboring the immunoreceptor tyrosine-based activation motif (ITAM) activate phospholipase Cγ, calcium signaling, and the formation of calcineurin required for activation of NFATc1 [Nemeth *et al.* 2011]. The activation of specific genes necessary for osteoclastogenesis and osteoclast function is regulated by NFATc1 cooperating with other transcription factors, such as AP-1, CREB, PU.1, and MITF. Important osteoclast genes include those encoding calcitonin receptor and TRAP, which serve as osteoclast markers, cathepsin K, which is involved in breakdown of bone matrix collagen, Atp6i and chloride chanel-7, involved in acidification and dissolution of bone mineral crystals, and the integrins α_v and β_3, which are important for attachments of osteoclasts to bone surfaces.

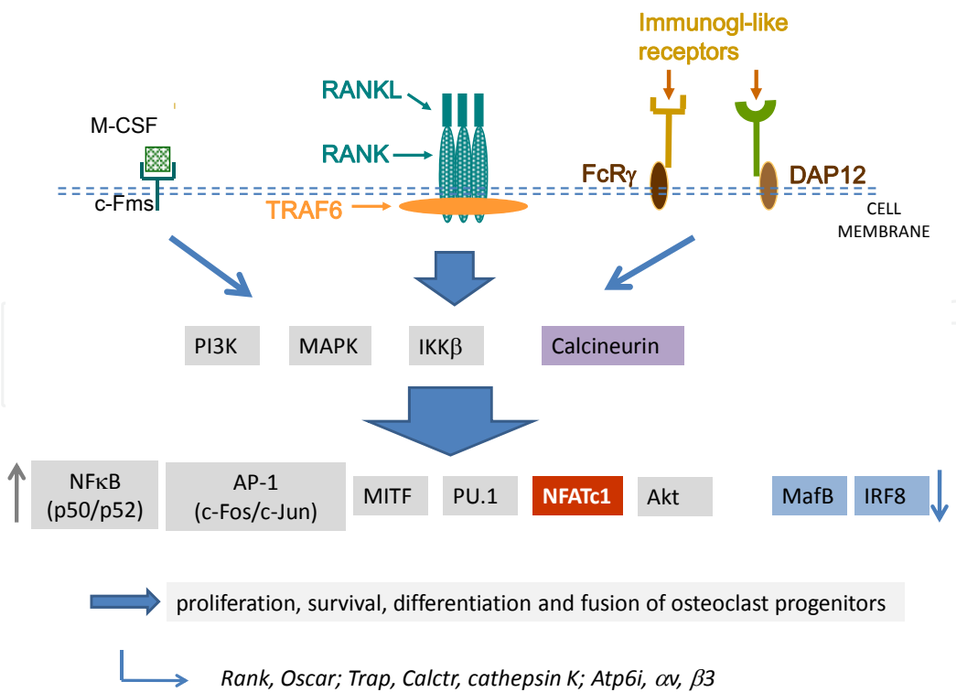


Fig. 2. Osteoclastogenic pathways, transcription factors, and genes stimulated by M-CSF and RANKL.

4. Retinoids and bone resorption in vitro

The effect of vitamin A on bone resorption has been studied the most thoroughly in rodent models. It has been known since the 1920´s that excess vitamin A has effects on the skeleton. In classical experiments in 1952 employing cultured fetal mouse limb bones, Dame Honor Fell showed that hypervitaminosis A stimulated osteoclast formation and bone resorption [Fell and Mellanby 1952]. Thirteen years later, Larry Raisz showed that vitamin A could stimulate bone resorption in organ cultures of fetal rat long bones [Raisz 1965]. Since those early experimental reports, there have been additional studies in organ cultures of fetal rat long bones [Scheven and Hamilton 1990], fetal rat calvariae [Delaissé *et al.* 1988] and calvarial bones from both fetal [Delaissé *et al.* 1988] and newborn [Raisz *et al.* 1977, Togari *et al.* 1991, Kindmark *et al.* 95, Conaway *et al.* 1997] mice confirming the osteoclastogenic effects of vitamin A and derivatives. An investigation indicating that ATRA increases mRNA expression of *RANKL* in primary human osteoblast-like cultures and decreases mRNA expression and protein formation of OPG in human MG-63 osteosarcoma cells [Jacobson *et al.* 2004] led to the suggestion that bone resorption stimulated by the retinoid is due to an increased RANKL/OPG ratio; however, until recently, there had been no data from bone or bone culture systems showing how vitamin A or derivatives stimulated bone resorption. In a recent investigation, we have reported that stimulation of osteoclastogenesis and bone resorption by retinoids in neonatal mouse calvarial bone is due to increased RANKL mRNA and protein expression. Supporting evidence for the role of RANKL was the observation that exogenous OPG administration blocked retinoid induced calvarial bone resorption [Henning *et al.* 2011].

Resorption in the bone organ culture systems depends on increased osteoclast formation and/or enhanced osteoclast activity. Attempts to elucidate effects of vitamin A on mature osteoclasts have generated conflicting results. It has been reported that bone resorbing activity of rabbit osteoclasts incubated on dentine slices is enhanced by ATRA [Saneshige *et al.* 1995]. Additionally, the vitamin A derivative isotretinonin has been observed to increase activity of rat osteoclasts incubated on cortical bone slices [Lakkakorpi and Väänänen 1991]. In contrast, bone resorbing activity of embryonic chicken osteoclasts on either bovine cortical bone or sperm whale dentine has been reported to be decreased by ATRA [O´Neill *et al.* 1992]. Furthermore, degradation of bone particles incubated with chicken osteoclasts is said to be enhanced by retinol and ATRA [Oreffo *et al.* 1988], which differs from experiments using osteoclast-like cell lines from human giant cell bone tumors, where Colucci *et al.* have found that ATRA inhibits degradation of bone matrix in rat bone particles [Colucci *et al.* 1996].

Evaluations of the effects of vitamin A on osteoclast formation have also generated conflicting data. In human bone marrow cultures, ATRA has been reported to stimulate formation of osteoclast-like multinucleated cells that are incapable of resorbing bone [Thavarajah *et al.* 1991]. Formation of multinucleated osteoclasts unable to resorb bone has also been reported following ATRA treatment of bone marrow cultures from egg laying hens [Chiba *et al.* 1996]. Scheven and Hamilton [1990] found no effect of ATRA on osteoclast formation in rat bone marrow cultures; however, when Hata *et al.* [1992] stimulated osteoclast formation in rat bone marrow cultures with 1,25$(OH)_2$-vitamin D_3, they found inhibition with ATRA. Using an acyclic retinoid, geranylgeranoic acid, Wang *et al.* [2002] also found that osteoclast formation in mouse bone marrow cultures stimulated by 1,25$(OH)_2$-vitamin D_3 was inhibited. Inhibition by the retinoid was most likely due to

inhibition of osteoclast progenitor cells, since inhibition of osteoclast formation by geranylgeranoic acid was also observed in mouse bone marrow macrophage (BMM) cultures stimulated by RANKL. In agreement with these latter observations, we have recently shown that ATRA, as well as 9-cis retinoic acid, inhibit osteoclast formation in mouse bone marrow cell cultures stimulated with either $1,25(OH)_2$-vitamin D_3 or PTH [Conaway *et al.* 2009], an effect associated with decreased expression of the osteoclast genes *Calcr*, *Acp5,* and *Catsk*, which code for the calcitonin receptor, TRAP, and cathepsin K, respectively. ATRA did not affect 1, $25(OH)_2$-vitamin D_3 stimulated mRNA expression of *Rankl*, nor did the retinoid affect the decrease of *Opg* expression induced by $1,25(OH)_2$-vitamin D_3, suggesting that the inhibitory effect was at the level of osteoclast progenitors rather than stromal cells. Osteoclast formation in both crude bone marrow cultures and spleen cell cultures stimulated by RANKL was also inhibited by ATRA and 9-cis retinoic acid. Moreover, osteoclast formation stimulated by RANKL in highly purified mouse BMM cultures was inhibited by ATRA and 9-cis retinoic acid, providing good evidence that the retinoids inhibited osteoclastogenesis by directly affecting osteoclast progenitor cells.

Inhibition of osteoclast progenitor cell differentiation by ATRA was due to inhibition of AP-1 and Nfatc1 pathways, but did not involve the NF-κB pathway [Conaway *et al.* 2009]. ATRA inhibited mRNA and protein expression of the transcription factors c-Fos and Nfatc1 induced by RANKL. RANKL also enhanced the mRNA expression of *Fra-1*, *Fra-2* and *JunB* in mouse BMM, but ATRA inhibited only *Fra-2*. The decrease of the macrophage transcription factor MafB caused by RANKL during osteoclastogenesis was blunted by ATRA, suggesting that ATRA arrested precursor cells at the macrophage stage. In agreement with these observations, it has been observed that ATRA inhibits Nfatc1 expression, translocation, and DNA-binding in RAW264.7 cells and mouse BMM [Balkan *et al.* 2011].

Mouse BMM express RARα and RARβ, but little RARγ. By use of different agonists and antagonists, it was demonstrated that ATRA induced inhibition of RANKL stimulated osteoclast formation in BMM was mediated by RARα [Conaway *et al.* 2009]. As discussed above, ATRA can also serve as a ligand for PPARβ/δ. However, ligands specific for this receptor did not mimic the inhibitory effect of ATRA.

Effects of retinoids on osteoclast formation have also been studied using osteoclast progenitor cells isolated from peripheral blood. Woods *et al.* [1995] found that monocytes from chicken peripheral blood spontaneously formed giant cells with osteoclast like features and that this process was inhibited by ATRA. Recently, it was shown that ATRA inhibited osteoclast formation in RANKL stimulated cultures of human $CD14^+$ monocytes from peripheral blood [Hu *et al.* 2010]. In agreement with observations in RANKL stimulated mouse BMM, inhibition of osteoclast formation in human $CD14^+$ cells was associated with decreased mRNA expression of osteoclastic genes such as *ACP5* and *CATSK,* and the transcription factor *NFATc1,* indicating that retinoids inhibit osteoclast formation by inhibiting osteoclast differentiation rather than fusion of differentiated progenitor cells. The authors attributed the inhibition to decreased expression of RANK mRNA and protein; however, it remains to be shown if this is the primary event.

5. Retinoids and bone resorption in vivo

In short term *in vivo* studies where rodents were treated with increased concentrations of retinoids (ATRA or Ro 13-6298), it has been reported that thinning of cortical bone due to significant stimulation of periosteal resorption occurs at the same time that cancellous bone

resorption is inhibited [Kneissel *et al.* 2005]. Furthermore, in a recent one week study where rats were fed increased vitamin A, increased cortical osteoclasts and cortical bone thinning were also observed; however, in these animals, endosteal osteoclasts disappeared because of impaired endosteal/marrow blood flow, which resulted in hypoxia and pathological endosteal mineralization [Lind *et al.* 2011]. This resulted in thinner, more brittle bones with little apparent affect on bone mass. Vitamin A and retinoids stimulate resorption in cultured fetal mouse and rat limb bones [Fell and Mellanby 1952, Raisz 1965, Scheven *et al.* 1990], but these studies are normally based on calcium release to medium and do not distinguish between cortical and cancellous bone breakdown. On the other hand, calvarial bone is considered to be a good model for periosteal resorption of cortical bone and it is established that vitamin A and ATRA are effective stimulators of osteoclastogenesis and bone resorption in calvarial bone [Raisz *et al.* 1977, Togari *et al.* 1991, Kindmark *et al.* 1995, Conaway *et al.* 1997]. As stated previously, retinoids are also good inhibitors of osteoclastogenesis in mouse bone marrow cell and BMM cultures. Thus, when comparing results of *in vitro* and *in vivo* experimental studies attempting to access the effects of increased vitamin A, it appears there may be good agreement regarding cortical osteoclast formation and function stimulated by vitamin A. In contrast, it seems a continuum of effects may occur in the endosteum, with increased vitamin A inhibiting endosteal osteoclast formation and function, and impaired blood flow and hypoxia promoting osteoclast death.

6. Conclusion

In developed countries, the diet is often supplemented with vitamin A and there is presently controversy over whether increased intake of vitamin A might promote skeletal fragility [Michaelsson *et al.* 2003, Melhaus *et al.* 1998, Feskanich *et al.* 2002, Promislow *et al.* 2002, Ribaya-Mercado and Blumberg 2007, Caire-Juvera *et al.* 2009]. If cortical bone thinning and suppression of osteoclastogenesis in cancellous bone play prominent roles in fracture incidence in humans following increased intake of vitamin A, this would be substantially different from conditions such as postmenopausal osteoporosis and glucocorticoid excess, where the increased incidence of fracture is due primarily to cancellous bone loss. These different paradigms for bone fragility may help explain some of the differing outcomes in studies evaluating vitamin A intake and fracture risk. It also seems possible that a duality of retinoid action on osteoclast precursors in cortical and cancellous bone might be manifest as different degrees of cortical resorption and cancellous inhibition, depending on other systemic and environmental factors. This would also affect bone mass and fracture risk, as would the development of hypoxia and death of endosteal osteoclasts. Our improving understanding of vitamin A action in bone cells is not only promising to be extremely valuable for future experimentation, but appears to warrant new evaluations of bone mass and fracture risk in patients with increased intake of vitamin A as well.

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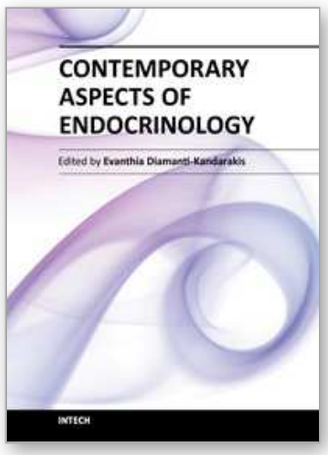
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This book aims to provide readers with a general as well as an advanced overview of the key trends in endocrine disorders. While covering a variety of topics ranging from thyroid carcinogenesis and pituitary adenomas to adrenal tumors and metabolic bone disease, this book also focuses on more specific issues not yet fully elucidated (e.g. the molecular pathways involved in thyrotropin beta gene regulation or monogenic phosphate balance disorders). Readers of different fields and background will have the opportunity to update their knowledge and more importantly to clarify areas of uncertainty and controversies in several topics of endocrine disorders.

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