

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Evolutionary medicine and bone loss in chronic inflammatory diseases—A theory of inflammation-related osteopenia[☆]

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ARTICLE INFO

Keywords:

bone loss
chronic inflammation
evolutionary medicine
osteopenia
osteoporosis
calcium physiology

ABSTRACT

Objective: Bone loss is typical in chronic inflammatory diseases such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases, pemphigus vulgaris, and others. It is also typical in transplantation-related inflammation and during the process of aging. While we recognized that bone loss is tightly linked to immune system activation or inflamm-aging in the form of acute, chronic active, or chronic smoldering inflammation, bone loss is typically discussed to be an “accident of inflammation.”

Methods: Extensive literature search in PubMed central.

Results: Using elements of evolutionary medicine, energy regulation, and neuroendocrine regulation of homeostasis and immune function, we work out that bone waste is an adaptive, evolutionarily positively selected program that is absolutely necessary during acute inflammation. However, when acute inflammation enters a chronic state due to the inability to terminate inflammation (e.g., in autoimmunity or in continuous immunity against microbes), the acute program of bone loss is a misguided adaptive program.

Conclusions: The article highlights the complexity of interwoven pathways of osteopenia.

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Introduction

In patients with chronic inflammatory diseases, there are three major pillars that helped to explain debilitating and disabling symptoms typical for these diseases such as sickness behavior, anorexia, and many others (Table 1) [1]. These pillars are (1) evolutionary medicine, (2) regulation of energy expenditure and energy storage, and (3) neuroendocrine regulation of homeostasis and immune function [1]. This manuscript presents an integrative theory how the three pillars explain bone loss in the context of acute and chronic inflammation.

The first pillar uses elements of evolutionary medicine that applies modern evolutionary theory to comprehend health and disease. Thus, evolutionary medicine is non-teleological in nature. It tries to understand why positively selected beneficial adaptive

programs can promote modern diseases in contemporary individuals [2]. For example, long-standing chronic inflammatory diseases over months and years with a high energy demand did not exist during most of our evolutionary time (including our primate and non-primate ancestors) [3,4]. Thus, genes and molecular networks have not been positively selected to serve long-standing, highly energy-consuming, chronic inflammation.

Secondly, high energy expenditure in consumer organs such as the immune system must happen in a transient manner during short-lived diseases such as infection [1]. Long-standing energy consumption as in chronic inflammatory diseases is incompatible with long life [1]. Thus, mechanism of strong energy expenditure were positively selected for short-lived highly energy-consuming immune activation but not for long-standing, highly energy-consuming chronic inflammatory diseases [1]. In contrast, energy storage of nutrients in storage organs (e.g., adipose tissue), immunoregulatory mechanisms, immune memory, and brain memory have been positively selected to save energy.

Thirdly, neuronal and hormonal pathways are instrumental in systemic regulation of energy expenditure and energy storage. In addition, systemic neuroendocrine regulation shapes the immune response and the immune response alters neuroendocrine

[☆]Rainer H. Straub has been supported by the Deutsche Forschungsgemeinschaft, Germany (DFG, e.g., For696). Maurizio Cutolo has been supported by the Italian Ministry of Health. Roberto Pacifici has been supported by grants from the National Institutes of Health, USA (AR54625, AR49659, and RR028009).

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Table 1
Sequelae of chronic inflammatory diseases in the light of altered energy regulation

| Disease sequelae | Pathophysiological elements in chronic inflammation leading to energy allocation to an activated immune system |
|---|--|
| Depressive symptoms/fatigue | Cytokine (e.g., IL-1 β)-driven sickness behavior and fatigue which increase time at rest (muscles and brain in an inactive state) |
| Anorexia | Consequence of sickness behavior |
| Malnutrition | Consequence of anorexia and sickness behavior |
| Muscle wasting cachexia | Protein break down in muscles as a consequence of anorexia, sickness behavior, IGF-1 resistance, and androgen deficit |
| Cachectic obesity | Protein break down in muscles as a consequence of anorexia and sickness behavior (protein break down greater than fat break down) |
| Insulin (IGF-1) resistance (with hyperinsulinemia) | Cytokine (e.g., TNF)-induced insulin signaling defects in liver, muscle, and fat tissue but not in immune cells. Immune cells need insulin so that high insulin levels support the activity of the immune system (similar for IGF-1). |
| Dyslipidemia ^a | Cytokine driven acute phase reaction of lipid metabolism leading to higher delivery of cholesterol and other lipids to macrophages |
| Increase of adipose tissue in the proximity of inflammatory lesions | Presence of adipose tissue surrounding lymph nodes and in the proximity of inflammatory lesions reflects a local store of energy-rich fuels (increased local estrogens might be important to drive local accumulation of adipose tissue). Adipokines play a proinflammatory role. |
| Alterations of steroid hormone axes | Cytokine/leptin-driven hypoandrogenemia supports muscle breakdown and protein delivery for gluconeogenesis and support of an activated immune system (alanine, glutamine). Cortisol-to-androgen preponderance in chronic inflammation is catabolic. |
| Elevated sympathetic tone and local sympathetic nerve fiber loss | Cytokine-driven increase of SNS activity increases gluconeogenesis and lipolysis. The parallel loss of sympathetic nerve fibers in inflamed tissue supports local inflammation. It also stimulates lipolysis in the surrounding adipose tissue because sympathetic nerve fibers are increased there. |
| Hypertension | Cytokine-driven activation of the water retention system due to systemic water loss during inflammation |
| Decreased parasympathetic tone | Cytokine-driven decrease of the PSNS activity supports allocation of energy-rich fuels to an activated immune system. |

References that demonstrate the respective disease sequelae and the pathophysiological explanation can be found in detail in Ref. [1].

HPA axis, hypothalamic–pituitary–adrenal axis; IGF, insulin-like growth factor; IL, interleukin; PSNS, parasympathetic nervous system; SNS, sympathetic nervous system; TNF, tumor necrosis factor.

^a Dyslipidemia in chronic inflammation reflects low levels of HDL cholesterol and/or apolipoprotein A-I and appearance of an “inflammatory HDL subfraction” with increased serum amyloid A and ceruloplasmin.

regulation in a tripartite way (neuronal system–endocrine system–immune system) [5]. The crosstalk between neuroendocrine networks and immune system has been positively selected to serve acute inflammatory illness like infections but not highly energy-consuming chronic inflammatory diseases of modern days.

During the last 2 decades, there was enormous progress in understanding inflammation-related bone loss [6–11], but the resulting osteopenia and osteoporosis seem to be discussed as an “accident of inflammation.” This objective of this article is to refine the existing theory [1,4] based on the above-mentioned pillars by discussing the role of bone in inflammatory diseases. It advances the hypothesis that a burst of bone loss is an adaptive program for short-lived inflammatory episodes, but long-term use in chronic inflammation is a misguided program that inevitably leads to osteopenia.

Sickness behavior, anorexia, and energy conservation lead to deficiency of essential nutrients

One of the hallmarks of acute inflammation is sickness behavior (recently reviewed in Ref. [12]). Sickness behavior is a uniform response with the following major features: malaise, fatigue/day-time sleepiness, loss of “energy,” numbness, feeling “cold,” muscle and joint aches, loss of appetite, anxiety, and depressive mood [12,13]. Sickness behavior can be induced in animals and humans by injection of proinflammatory cytokines or endotoxin into the brain or periphery [12,13]. Likewise, severe infection is accompanied by very similar symptoms, which restrains activity and confines the affected individual to a safe place (rest).

The enormous role of sickness behavior must be discussed in the context of bodily energy conservation, because many features of this adaptive program save energy-rich fuels that can be provided to an activated immune system [1,4]. Usually, we need approximately 10,000 kJ/d in our sedentary way of life [14]. Energy expenditure of a mildly to moderately activated immune system reaches 2100 kJ per day (without inflammation it is \approx 1600 kJ/d), which is similar to the amount of energy needed by the brain

(2200 kJ/d) and resting muscles (2500 kJ/d) [1]. Anorexia in the context of acute infections has been recognized as an acute phase reaction or better, an adaptive behavioral program to support survival [15,16]. For example, injection of lipopolysaccharide into otherwise healthy mice reduces food intake by nearly 80% [17].

In order to get a better picture of the energy-saving value of anorexia, it can be important to study energy expenditure and intake in otherwise healthy people under natural conditions in the wild. In traditional Pygmy hunter-gatherers in Cameroon (they need less energy than tall Caucasians!), the energy balance on 3 typical days was negative between total energy intake per day (men, 7200 kJ/d; women, 6700 kJ/d) and total energy expenditure per day (men, 8100 kJ/d; women, 7300 kJ/d) [18]. In this observational study, under natural conditions in non-inflamed subjects, individuals spent more energy than they brought in. It tells that normal life in the wild with typical foraging behavior is pretty energy-demanding (and one expects that there are also better days). The question arises as to what would happen when a hunter-gatherer needs extra energy during acute inflammation.

With an activated immune system during systemic mild to moderate inflammation, a human needs approximately 400–500 kJ more per day as compared to a situation without inflammation [1]. Indeed, 400–500 kJ of extra energy consumption is a strong stimulus to induce an energy redistribution program, in which sickness behavior is a major component. Particularly, increased sleep and anorexia would save energy. Alone during sleep (resting brain and resting muscles), humans need 25% less energy compared to the wake state [19,20]. During the wake state, it was measured that humans need 6430 kJ in 16 h of wakefulness [19]. If one assumes that a similar amount would be needed during the remaining 8 h of sleep, consumption is computed to be 0.5×6430 kJ (3215 kJ). However, the actual number is lower because only 2000 kJ are needed during 8 h of sleep [19]. This indicates that we can save a lot of energy during sleep because brain and muscles are in a dormant state.

From the perspective of acute inflammation, sickness behavior with an increased time spent at rest and sleeping, and with

anorexia to avoid energy-consuming foraging, enough energy is conserved to nourish the activated immune system for a while. However, the consequence of this adaptive program during acute infection/inflammation would be deficiency of energy-rich fuels (carbohydrates, free fatty acids, and proteins), loss of essential ions such as calcium, phosphorus, magnesium, iron, and lower levels of essential vitamins like vitamin D and others. This can lead to malnutrition, which is a typical finding in many inflammatory diseases [21]. Intake of energy-rich fuels and other essential nutrients is reduced in rheumatoid arthritis [22,23], systemic sclerosis [24], multiple sclerosis [25], juvenile idiopathic arthritis [26], and other chronic inflammatory systemic diseases. Under anorexia conditions, the body is absolutely dependent on stored reserves. The question appears how long self-subsistence can happen during acute inflammation.

It was recently calculated that a modern human male subject with mild to moderate inflammation can survive for approximately 41 days, if anorexia is strong and uptake of major energy-rich nutrients is zero (carbohydrates, free fatty acids, and proteins) [4]. In a smaller and lighter *Homo habilis* this consumption time amounts to 22 days. This calculation does not account for the lack of essential nutrients other than free fatty acids and proteins and,

thus, may be shorter than 22–41 days because of life-threatening deficiencies in ions, vitamins, or other factors.

In summary, acute inflammation induces sickness behavior and anorexia to conserve energy-rich fuels (redistribution program). Sickness behavior and anorexia are adaptive programs for transient inflammatory episodes. During acute inflammation, the body mainly depends on stored energy-rich fuels, essential ions, and vitamins. An important redistribution program is needed to break down stored nutrients and deviate them to activated immune cells. Some aspects of this energy redistribution program are demonstrated in Table 1. The bone-related aspects are given in the following text.

Calcium balance under normal and inflamed conditions

The normal calcium balance is depicted in Figure 1A. The average adult human body contains approximately 1 kg of calcium, which corresponds to 25 mol calcium [27]. A total of 99% is stored in bone and teeth. Most of the calcium is inaccessible to most physiological processes [27]. Approximately 1% of the stored calcium (10 g or 0.25 mol) is immediately accessible [27]. This

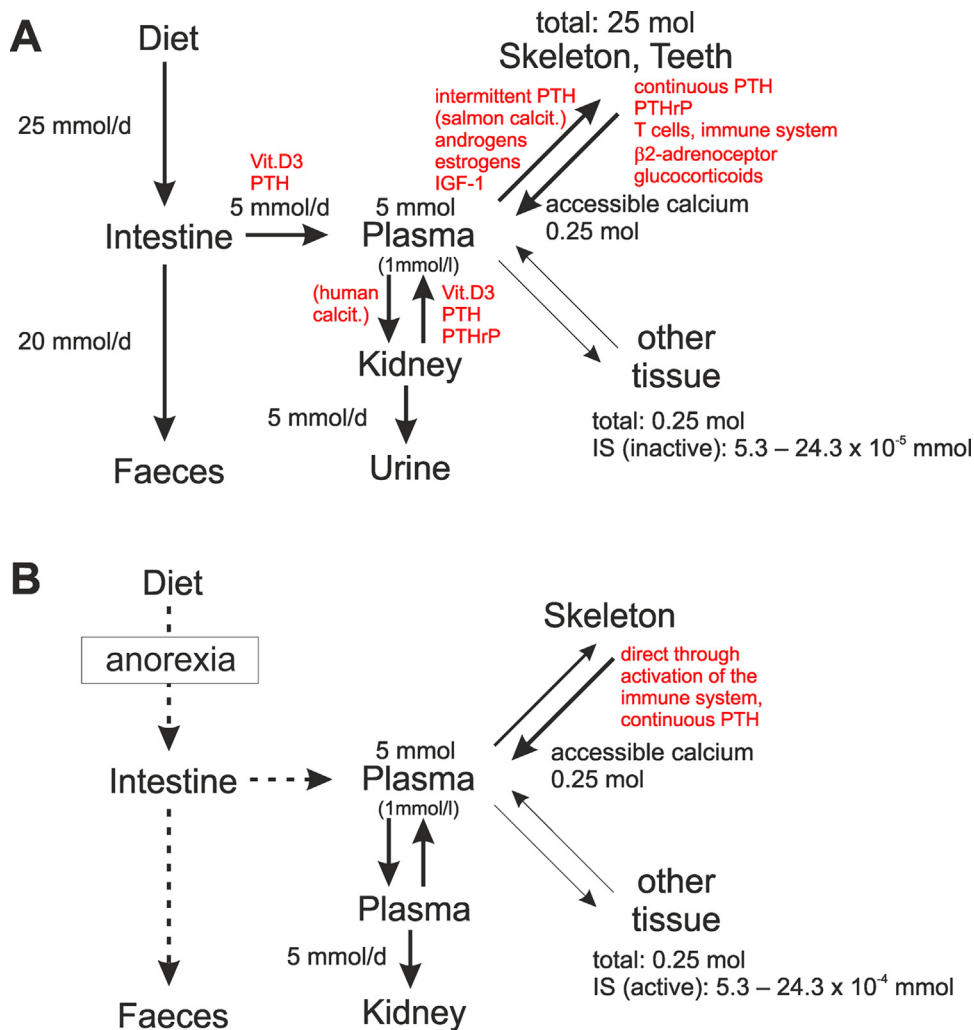


Fig. 1. Calcium homeostasis in physiology (A) and inflammation (B). The major hormonal regulators are given in red. Dotted arrows indicate strong reduction of calcium shifts due to anorexia. The numbers for the immune system (IS) demonstrate the total amount of calcium within all immune cells. Note that the activated immune system contains 10 times more calcium compared to the inactive immune system when all cells would be involved (which is not the case in reality). Numbers are derived from information of Refs. [1,27,28,30,31]. Calcit., calcitonin; IGF-1, insulin-like growth factor 1; IS, immune system; PTH, parathyroid hormone; PTHrP, PTH-related peptide; Vit. D3, vitamin D3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fraction serves many different roles, which range from intracellular signaling and maintenance of membrane integrity to muscle contraction, neuronal transmission, and immune cell function. Immune cells depend on calcium as indicated by *calcium release activated calcium channel* (CRAC) channelopathies that lead to severe immunodeficiency in affected individuals [28]. Others demonstrated that extracellular calcium is important to stimulate the NLRP3 inflammasome through G protein-coupled calcium-sensing receptors [29]. This stimulation leads to increased intracellular calcium, inflammasome assembly, and caspase-1 activation. At this point, the question appears whether immune cells really need most of the accessible calcium for proper function in acute inflammation.

Since immune cells have a diameter of 12–20 μm and $\approx 5.8 \times 10^{11}$ immune cells exist in the body (total volume of all cells together in liter = 0.53–2.43 l) [1], the total amount of calcium in all immune cells together is $5.3\text{--}24.3 \times 10^{-5}$ mmol, which is miniscule in relation to the accessible calcium store of 250 mmol (Fig. 1A). With activation of immune cells as in acute inflammation, intracellular calcium concentration increases from 10^{-7} mol/L to 10^{-6} mol/L [28]. This factor of 10 increases the amount of calcium in all immune cells in a minimal way (from $5.3\text{--}24.3 \times 10^{-5}$ mmol to $5.3\text{--}24.3 \times 10^{-4}$ mmol, if all immune cells would be activated, which is not the case).

From these considerations, it is clear that quantitative calcium redistribution from bone to activated immune cells is unlikely. In the presence of inflammation-induced anorexia, bone loss is directly stimulated by inflammatory factors from activated immune cells (Table 2). This uniform response of the immune system is surprisingly strong given the fact that immune cells do not need so much calcium. Thus, it seems that immune-mediated bone loss is a program to supply calcium to the rest of the non-skeleton tissue. This is particularly true when renal calcium loss or glomerular filtration rate remain normal or even increase during acute and chronic inflammation when there is no structural kidney injury [30–33] (Fig. 1B). The non-skeleton tissue are all organs and muscles.

Indeed a simple calculation from numbers in Figure 1A, shows that in the absence of dietary calcium intake but remaining renal loss of 5 mmol/d, the non-skeleton tissue store of 0.25 mol would be emptied within 50 days (250 mmol divided by 5 mmol/d). This number is surprisingly similar to the total consumption time of a modern human as if accessible amount of stored calcium was evolutionarily positively selected to serve calcium provision during this critical time of acute inflammation with sickness behavior and anorexia. Although the activated immune system only needs miniscule amounts of accessible calcium, it is the driving system that starts in the first place bone resorption. During sickness behavior and anorexia, immune system-activated bone resorption and calcium provision can be seen as an offered service to the rest of the non-skeleton body. Figure 1B summarizes the situation in inflammation.

Table 2
Typical inflammation-related factors of bone loss (recently reviewed in Refs. [6–11])

| Inflammation-related factor |
|---|
| CD4+ T cells ^a via TNF, RANKL, IFN- γ , LIGHT, IL-15, and IL-17 |
| CD8+ T cells ^a via TNF and RANKL |
| Macrophages via TNF, IL-1 β , and IL-6 |
| Neutrophils via reactive oxygen species |
| Immunologically stimulated bone stromal cells via RANKL and M-CSF |

^a In contrast, T regulatory cells and B cells suppress bone resorption in ovariectomy-induced bone loss and in models of rheumatoid arthritis by secreting anti-osteoclastogenic factors like osteoprotegerin.

Phosphate balance under normal and inflamed conditions

Similar as with calcium, plasma concentration of inorganic phosphorus (Pi) depends on dietary intake, passive intestinal absorption, release from bone and non-skeleton tissue, and renal excretion (the picture would look like Figure 1A). Usually, 30 mmol are excreted with the urine, and dietary intake equals renal and fecal Pi excretion.

However, the situation is pretty different with Pi compared to calcium because Pi reabsorption in the kidneys can be almost 100% [34]. This adaptation happens very fast in conditions of low phosphate intake, and this adaptation is relatively independent of hormonal regulation [35]. In the case of acute inflammation, sickness behavior, and anorexia, the kidneys prevent phosphate loss. Given the above-mentioned 0.25 mol accessible calcium from skeleton tissue, approximately 0.14 mol of phosphate are also accessible, because the molar ratio of calcium to Pi in bone is $\approx 1.7:1$ [36]. In summary, during acute inflammation with anorexia, there will never exist Pi deficiency due to the nearly complete reabsorption of Pi in the kidneys and the huge amount of accessible Pi from bone.

However, states of low phosphate serum levels can exist, which typically appear as refeeding hypophosphatemia after states of anorexia. This form of phosphate deficiency is not an absolute loss of Pi but rather a rapid transmembrane shift of Pi from extracellular to intracellular space, which is well known in the context of alkalosis or hyperglycemia/hyperinsulinemia [37]. This may lead to deficits in intracellular ATP in certain organs, which can lead to cardiac arrhythmias and heart failure, muscular fatigue (respiratory problems), even rhabdomyolysis, neurologic manifestations (confusion, seizure, weakness, and fatigue), and hemolytic anemia [37]. Such a situation might appear after refeeding after prolonged anorexia, and it can even be a critical factor in patients with anorexia nervosa [38]. Thus, there might exist a relative Pi deficiency after inflammation-induced anorexia due to refeeding. Nevertheless, it is expected that inflammation-induced bone resorption would counterbalance severe hypophosphatemia after refeeding since 0.14 mol Pi is immediately accessible. Another form of hypophosphatemia happens in rickets. These patients can demonstrate low Pi levels after vitamin D substitution and accelerated bone formation (hungry bone syndrome). Such a rapid bone formation is not expected after inflammation-induced anorexia and later refeeding.

Similarly as discussed for calcium, after sickness behavior, anorexia, and subsequent refeeding, immune system-activated bone resorption and Pi provision can be seen as an offered service to the rest of the non-skeleton body.

Other pathways of inflammation-stimulated bone loss

Due to energy requirements of the activated immune system in the presence of anorexia, fatigue, muscle breakdown (leading to a relative increase of fat over muscular tissue called cachectic obesity), and inflammation-related anemia are ways to support immobility. While immobility reduces energy requirements of activated brain and muscles (redistribution to the activated immune system), immobility also stimulates bone loss [39]. Bone loss happens already during the first 4–6 weeks of immobilization [40,41]. In addition, immobilization leads to hypercalcemia and subsequent hypercalciuria that strongly increased from week 1 to week 4 [42]. The fact that immobilization-related bone loss happens within 4–6 weeks is another good indication of an adaptive program because it well fits into the time window of 6 weeks given by the total consumption time (see above).

Another important aspect of acute inflammation is hypogonadism. This phenomenon has been described in rats after cytokine or endotoxin injection [43] and in humans with infectious diseases [44–47]. Subcutaneous injection of IL-6 into human volunteers rapidly decreased serum free testosterone within 24 h [48]. Since gonadal hormones play an instrumental role in bone generation, inflammation-related acute loss of gonadal hormones support bone resorption.

Two other important systems change bone homeostasis during acute inflammation. Both, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, are activated during acute inflammation [5]. The major hormones of the two systems are cortisol and adrenaline/noradrenaline, whose role on bone resorption are well known. While negative effects of cortisol or glucocorticoids on bone are known since long, recent studies clearly demonstrated that the sympathetic nervous system via β 2-adrenoceptors has strong bone-resorbing effects, too [49,50]. Along with sympathetic activation, a decrease of parasympathetic function is observed in inflammation [51]. This can lead to changes in gastrointestinal function leading to malabsorption.

In addition, anorexia-induced hypovitaminosis D (and K) is a well-known factor in acute inflammation and critical illness [52,53], but similarly in chronic inflammation (summarized in

Ref. [54]). Such a situation would aggravate bone resorption during inflammatory episodes with anorexia.

Importantly, parathyroid hormone (PTH) is often elevated in acute inflammation such as septic shock [55], sepsis [56], or after endotoxin injection [57], but levels are normal, high, or low in chronic inflammation [58–62]. Catabolic effects of PTH on bone might be largely determined by parallel inflammation [6] or by an increase in parallel glucocorticoids [63]. The starvation associated with inflammation causes PTH to be secreted in a continuous fashion. Continuous PTH production causes cortical bone loss and often trabecular bone loss. Thus, under inflammatory conditions, hyperparathyroidism is common and the net effect of PTH is stimulation of bone resorption and bone loss. In addition, inflamed tissue and activated immune cells can produce parathyroid hormone-related peptide (PTHrP), which can be elevated in acute and chronic inflammation [64–66]. Endotoxin can directly induce PTHrP secretion [67], and blockade of PTHrP reduces bone loss in experimental arthritis [68]. Thus, both PTH and PTHrP, do not protect bone in acute and chronic inflammation, which most probably depends on the circumstances of high inflammation and appearance of other bone-resorbing factors.

Figure 2 summarizes the different factors leading to inflammation-related osteopenia. It is hypothesized that all these elements serve an adaptive program for acute inflammatory illness.

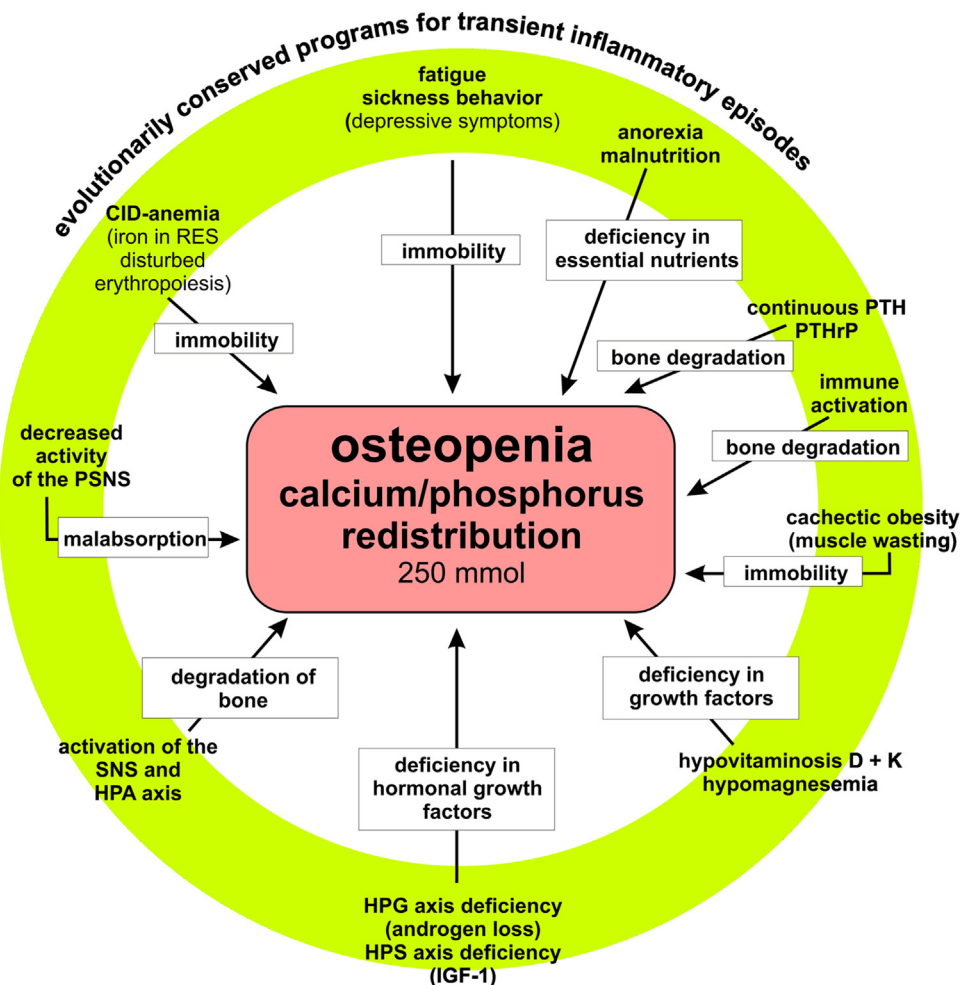


Fig. 2. Disease sequelae of inflammation leading to osteopenia. The number in the pink middle area of 250 mmol represents the accessible amount of calcium provided from the bone [27]. CID-anemia; inflammation-related anemia of chronic inflammatory diseases; HPG axis, hypothalamic–pituitary–gonadal axis; HPA axis; hypothalamic–pituitary–adrenal axis; HPS axis, hypothalamic–pituitary–somatic axis (growth hormone, IGF-1); IGF-1, insulin-like growth factor 1; PSNS, parasympathetic nervous system; PTH, parathyroid hormone; PTHrP, PTH-related peptide; RES, reticuloendothelial system; SNS, sympathetic nervous system.

Evolutionary medicine

Infectious and non-infectious inflammation was present throughout human evolution and evolution of our non-human and non-mammalian ancestors. With rats and mice, we share many similar inflammatory mechanisms, although the last common ancestor of humans and rodents lived 80 million years ago [69]. Humans and chicken had their last common ancestor 310 million years ago, but both species use immunoglobulin gene rearrangement and somatic hypermutation to shape the antibody response towards infectious agents [69]. Thus, when we talk about activation of the immune system in the context of the most prevalent danger of infection, human share many similarities with non-human ancestors way back in evolutionary time. For example, rodents show immune responses but also sickness behavior and anorexia similar as compared to humans [17].

We recognize that acute inflammation must have been a common and old problem during evolution. However, a highly activated immune/repair system cannot be switched on for a long time because this would impose an excessive energy demand [4]. A highly activated immune system is accompanied by sickness behavior and anorexia, which prevents adequate food intake and necessitates life on stored reserves (inflammation-induced anorexia). Under systemic inflammatory conditions, breaking down all reserves in humans and their immediate ancestors takes 19–43 days [4]. Most acute disease states are terminated within this time frame such as infectious diseases, wound healing, and repair (e.g., bone fractures).

When we observe homeostatic regulation in chronic inflammation, we expect that they have not been evolutionarily conserved in the context of chronic energy-consuming inflammation but for acute inflammation. In acute inflammation, observed programs of Figure 2 are adaptive programs. They have been positively selected and maintained for eons to serve a short-lived energy-consuming inflammatory process.

In contrast, if programs were helpful to protect energy reserves, they were positively selected during evolution and maintained in modern species. It is hypothesized that this is true for energy storage of nutrients in storage organs (e.g., adipose tissue), for immunoregulatory mechanisms (T regulatory cells), immune memory (T and B lymphocytes), and brain memory (hippocampal neurogenesis), because memory saves energy. Another organ that stores important expedients for cellular energy reactions is bone. Bone stores calcium and phosphorus, and a small part of it can be used as accessible pool (250 mol of the total 25 mol) (Fig. 1).

We hypothesize that bone resorption stimulated by immune-mediated pathways (Table 2) is an adaptive program to provide calcium and phosphorus (and magnesium) to the non-skeleton tissue essential for survival over 19–43 days. At this point, the question appears as to why the immune system serves calcium to the rest of the non-skeleton body although it only needs miniscule amounts of calcium as demonstrated above.

Why does the immune system serves calcium to the rest of the non-skeleton body

In an environment without any calcium and phosphate stores, in the absence of an exoskeleton (in crustaceans or mussels) or endoskeleton (in bony fish or tetrapods) bone degradation does not exist. For example, this is true for the tunicate sea squirt (*Ciona intestinalis*), a sessile animal permanently attached to a rock under seawater (Protochordates). In need, *C. intestinalis* receives calcium from the surrounding seawater (seawater has a calcium concentration of 10 mmol/L; serum calcium in humans is approximately 2.4 mmol/L).

However, sea squirts already have a primitive immune system with eukaryotic orthologs of such important bone-degrading factors such as TNF, IL-17, and receptor activator of nuclear factor- κ B (RANK) [70]. In addition, they possess the critical bone-degrading enzyme of osteoclasts, the tartrate-resistant acid phosphatase [70]. It was observed that sea squirts produce a TNF-like cytokine upon stimulation with lipopolysaccharide [71]. Thus, it is highly likely that *C. intestinalis* used TNF to overcome infectious disease. *C. intestinalis* also possess granulocytes and primitive ancestors of modern antigen receptors [72].

The role of an orthologous protein to RANK in *C. intestinalis* is presently not known. Such a Ciona RANK molecule might have something to do with insulin signaling because insulin has been found in *C. intestinalis* [73], and the RANK/RANKL system has been critically linked to insulin resistance in mammals [74]. It was discussed that insulin resistance is an adaptive program to deviate energy-rich fuels from stores to the activated immune system [1]. A similar mechanism might exist in *C. intestinalis* but this is hypothetical at the moment.

Nevertheless, it tells us that Ciona orthologs of bone-degrading cytokines already existed many million years before the development of an endoskeleton in an animal without bone or calcium stores. When the endoskeleton appeared during the process of evolution, the already existing bone-degrading cytokines were not counterproductive, but most probably necessary for an inflammation-dependent short-lived burst release of calcium from the endoskeleton, particularly, in terrestrial animals.

Low bone mass is a typical disease sequelae of many chronic inflammatory diseases

While we learned that episodic bone resorption is an adaptive program for acute inflammatory illness, long-term application of this program might induce low bone mass. Indeed, bone loss is absolutely typical in rheumatoid arthritis, psoriasis, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases, pemphigus vulgaris, and others (recently reviewed in Refs. [75–81]). It is also typical in transplantation-related inflammation [6].

In addition, bone loss is a normal phenomenon of the aging process [82]. The aging process is associated with an increase in the levels of pro-osteoclastogenic inflammatory cytokines such as TNF and IL-6, and a decrease in bone-anabolic factors like gonadal hormones and adrenal androgens (reviewed in Ref. [83]). Increased C-reactive protein was linked to an increased fracture rate due to osteoporosis [84,85], and circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults [86]. Aging was compared to a process of chronic smoldering inflammation, called inflamm-aging [87].

At this point, one needs to recall that ageing on a population level, in men and women, beyond postmenopausal age is a new phenomenon of the last 200 years. The inflammatory process that appears during aging is new to the evolution of humans. Since we know that acute inflammation can stimulate an adaptive bone loss program (Fig. 2), it is not surprising that a chronic inflammatory process induces ever increasing osteopenia. This is also true for osteopenia in the chronic smoldering variant of inflamm-aging.

When does an acute inflammatory disease become chronic inflammation?

In this review, we repeatedly touched on a time span that lasts from 21 to 60 days, because either energy or calcium are lost from stores in the context of sickness behavior/anorexia. This time span

Table 3
Time frame of typical acute inflammation-related phenomena

| Acute inflammation-related phenomena | Time span in days |
|---|-------------------|
| Total consumption time (time to death under complete anorexia) ^a | 21–41 |
| Calcium consumption time ^b | 50 |
| Germinal center reaction of B lymphocytes (antibody maturation & termination) ^a | 21–28 |
| Maximum of immobilization-induced bone loss ^a | Until 42 |
| Healing time of uncomplicated, non-infected, unilateral fracture in rural Africa ^a | 60 |
| Definition criterion of RA ^a | Longer than 42 |
| Definition criterion of juvenile idiopathic arthritis ^a | Longer than 42 |

^a According to Refs. [4,42,89–91].

^b A theoretical time to depletion of all calcium from non-skeleton tissues in the presence of normal renal calcium excretion and without supply from the bone.

is also visible when looking on germinal center reaction of B cells, maximum of calcium loss during immobilization, healing time of uncomplicated fractures, and empirical definition criteria of chronic inflammatory diseases such as rheumatoid arthritis and juvenile idiopathic arthritis (Table 3).

As discussed above, phenomena leading to osteopenia during acute inflammation belong to an adaptive program (Fig. 2). This adaptive program cannot last forever. It needs to be terminated because, otherwise, it would be incompatible with life in the wild. From examples given in Table 3, it seems that acute inflammation should be terminated within 21–60 days, which includes complete restoration of normal tissue and function.

For this time span of 21–60 days, many coordinated and regulated mechanisms of starting and terminating acute inflammation have been positively selected because the affected individual survived acute inflammation. Necessarily, after termination of acute inflammation, survival of the individual supported his reproduction. Now, beneficial mutations that supported survival in a formerly affected subject can be transferred to the progeny. During evolution, this is the way how adaptedness can become an *a posteriori* result [88]. However, if an affected individual had chronic inflammation, reproductive capacity is lower (negative selection pressure).

From these considerations, it is expected that there exist a formal time limit between acute and chronic inflammation ranging between 21 and 60 days. Beyond this time limit, coordination of starting and terminating an inflammatory event does not exist anymore, because it is outside the time limit of adaptedness. Coordination of immune system, endocrine system, and neuronal system, etc. to fight an inflammatory trigger (e.g., microbe) was positively selected for acute inflammation. Beyond the time limit, an adaptive program can become a misguided program.

Conclusions

The three pillars of evolutionary medicine, energy regulation, and neuroendocrine regulation of homeostasis and immune function explain that adaptive programs for acute inflammation are wrongly used in chronic inflammation. One of these adaptive programs in acute inflammation is provision of calcium and phosphorus from bone to the non-skeleton tissues. Thus, an acute burst of bone loss is not an accident but an important program.

In order to steer calcium/phosphorus provision, many specific immune-mediated pathways are switched on (Table 2). Importantly, several specific immune-mediated pathways can induce bone resorption independent of classical hormonal pathways. This is indicative of adaptation to acute inflammation. While these

considerations might explain the deeper meaning of bone resorption in inflammation, we are critically dependent on finding the major molecular pathways to better treat these disease sequelae. This review should also stimulate the idea that sometimes the critical pathways leading to osteopenia can be outside usual main stream thinking. It also demonstrates that osteopenia must be a multifactorial affair.

Contributions

Rainer H. Straub—development of the concept, drafting the paper, generating figures, and final approval.

Maurizio Cutolo—discussing the contents, revising the paper, and final approval.

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References

- [1] Straub RH, Cutolo M, Buttgerit F, Pongratz G. Energy regulation and neuroendocrine-immune control in chronic inflammatory diseases. *J Intern Med* 2010;267:543–60.
- [2] Williams GC, Nesse RM. The dawn of Darwinian medicine. *Q Rev Biol* 1991;66:1–22.
- [3] Straub RH, Besedovsky HO. Integrated evolutionary, immunological, and neuroendocrine framework for the pathogenesis of chronic disabling inflammatory diseases. *FASEB J* 2003;17:2176–83.
- [4] Straub RH. Evolutionary medicine and chronic inflammatory state—known and new concepts in pathophysiology. *J Mol Med* 2012;90:523–34.
- [5] Besedovsky HO, del Rey A. Immune-neuro-endocrine interactions. *Endocr Rev* 1996;17:64–102.
- [6] Pacifici R. Osteoimmunology and its implications for transplantation. *Am J Transplant* 2013;13:2245–54.
- [7] Braun T, Schett G. Pathways for bone loss in inflammatory disease. *Curr Osteoporosis Rep* 2012;10:101–8.
- [8] Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discov* 2012;11:234–50.
- [9] Geusens P, Lems WF. Osteoimmunology and osteoporosis. *Arthritis Res Ther* 2011;13:242.
- [10] Mundy GR. Osteoporosis and inflammation. *Nutr Rev* 2007;65:S147–51.
- [11] Schett G, Hayer S, Zwerina J, Redlich K, Smolen JS. Mechanisms of disease: the link between RANKL and arthritic bone disease. *Nat Clin Pract Rheumatol* 2005;1:47–54.
- [12] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9:46–56.
- [13] Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001;58:445–52.
- [14] Blaxter K. Energy metabolism in animals and man. Cambridge, New York, New Rochelle, Melbourne, Sydney: Cambridge University Press; 1989.
- [15] Exton MS. Infection-induced anorexia: active host defence strategy. *Appetite* 1997;29:369–83.
- [16] Murray MJ, Murray AB. Anorexia of infection as a mechanism of host defense. *Am J Clin Nutr* 1979;32:593–6.
- [17] Carter ME, Soden ME, Zweifel LS, Palmiter RD. Genetic identification of a neural circuit that suppresses appetite. *Nature* 2013;503:111–4.
- [18] Yamauchi T, Sato H. Nutritional status, activity pattern, and dietary intake among the Baka hunter-gatherers in the village camps in Cameroon. *Afr Study Monogr* 2000;21:67–82.
- [19] Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. *J Clin Invest* 1986;78:1568–78.
- [20] Fraser G, Trinder J, Colrain IM, Montgomery I. Effect of sleep and circadian cycle on sleep period energy expenditure. *J Appl Physiol* (1985) 1989;66:830–836.
- [21] Montalcini T, Romeo S, Ferro Y, Migliaccio V, Gazzaruso C, Pujia A. Osteoporosis in chronic inflammatory disease: the role of malnutrition. *Endocrine* 2013;43:59–64.
- [22] van de Laar MA, Nieuwenhuis JM, Former-Boon M, Hulsing J, van der Korst JK. Nutritional habits of patients suffering from seropositive rheumatoid arthritis: a screening of 93 Dutch patients. *Clin Rheumatol* 1990;9:483–8.
- [23] Hansen GV, Nielsen L, Kluger E, Thysen M, Emmertsen H, Stengaard-Pedersen K, et al. Nutritional status of Danish rheumatoid arthritis patients and effects of a diet adjusted in energy intake, fish-meal, and antioxidants. *Scand J Rheumatol* 1996;25:325–30.
- [24] Lundberg AC, Akesson A, Akesson B. Dietary intake and nutritional status in patients with systemic sclerosis. *Ann Rheum Dis* 1992;51:1143–8.

- [25] Payne A. Nutrition and diet in the clinical management of multiple sclerosis. *J Hum Nutr Diet* 2001;14:349–57.
- [26] Bacon MC, White PH, Raiten DJ, Craft N, Margolis S, Levander OA, et al. Nutritional status and growth in juvenile rheumatoid arthritis. *Semin Arthritis Rheum* 1990;20:97–106.
- [27] Kopic S, Geibel JP. Gastric acid, calcium absorption, and their impact on bone health. *Physiol Rev* 2013;93:189–268.
- [28] Feske S. Calcium signalling in lymphocyte activation and disease. *Nat Rev Immunol* 2007;7:690–702.
- [29] Rossol M, Pierer M, Raulien N, Quandt D, Meusch U, Rothe K, et al. Extracellular Ca^{2+} is a danger signal activating the NLRP3 inflammasome through G protein-coupled calcium sensing receptors. *Nat Commun* 2012;3:1329. <http://dx.doi.org/10.1038/ncomms2339>:1329.
- [30] Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. *Rheumatol Int* 2012;32:2279–83.
- [31] Stapleton FB, Hanissian AS, Miller LA. Hypercalciuria in children with juvenile rheumatoid arthritis: association with hematuria. *J Pediatr* 1985;107:235–9.
- [32] Udy AA, Putt MT, Shanmugathasan S, Roberts JA, Lipman J. Augmented renal clearance in the Intensive Care Unit: an illustrative case series. *Int J Antimicrob Agents* 2010;35:606–8.
- [33] Fabrizi F, Martin P, Dixit V, Messa P. Hepatitis C virus infection and kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2012;7:549–57.
- [34] Biber J, Hernandez N, Forster I, Murer H. Regulation of phosphate transport in proximal tubules. *Pflugers Arch* 2009;458:39–52.
- [35] Murer H, Lotscher M, Kaissling B, Levi M, Kempson SA, Biber J. Renal brush border membrane Na/Pi-cotransport: molecular aspects in PTH-dependent and dietary regulation. *Kidney Int* 1996;49:1769–73.
- [36] Geigy Pharmazeutika. Wissenschaftliche Tabellen. Wehr: Ciba-Geigy; 1973.
- [37] Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care* 2010;14:R147.
- [38] Marinella MA. Refeeding syndrome and hypophosphatemia. *J Intensive Care Med* 2005;20:155–9.
- [39] Sievanen H. Immobilization and bone structure in humans. *Arch Biochem Biophys* 2010;503:146–52.
- [40] Uthoff HK, Jaworski ZF. Bone loss in response to long-term immobilisation. *J Bone Joint Surg Br* 1978;60-B:420–9.
- [41] Tsakalakos N, Magiatis B, Tsekoura M, Lyritis G. The effect of short-term calcitonin administration on biochemical bone markers in patients with acute immobilization following hip fracture. *Osteoporos Int* 1993;3:337–40.
- [42] Yusuf MB, Ikem IC, Oginni LM, Akinyoola AL, Badmus TA, Idowu AA, et al. Comparison of serum and urinary calcium profile of immobilized and ambulant trauma patients. *Bone* 2013;57:361–6.
- [43] Rivier C. Neuroendocrine effects of cytokines in the rat. *Rev Neurosci* 1993;4:223–37.
- [44] Petzke F, Heppner C, Mbulamberi D, Winkelmann W, Chrousos GP, Allolio B, et al. Hypogonadism in Rhodesian sleeping sickness: evidence for acute and chronic dysfunction of the hypothalamic-pituitary-gonadal axis. *Fertil Steril* 1996;65:68–75.
- [45] Reincke M, Arlt W, Heppner C, Petzke F, Chrousos GP, Allolio B. Neuroendocrine dysfunction in African trypanosomiasis. The role of cytokines. *Ann N Y Acad Sci* 1998;840:809–21.
- [46] Oktenli C, Doganci L, Ozgurtas T, Araz RE, Tanyuksel M, Musabak U, et al. Transient hypogonadotropic hypogonadism in males with acute toxoplasmosis: suppressive effect of interleukin-1 beta on the secretion of GnRH. *Hum Reprod* 2004;19:859–66.
- [47] Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. *Endocrinol Metab Clin North Am* 2007;36:333–48.
- [48] Tsigos C, Papanicolaou DA, Kyrou I, Raptis SA, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on the pituitary-testicular axis. *J Interferon Cytokine Res* 1999;19:1271–6.
- [49] Amling M, Takeda S, Karsenty G. A neuro (endo)crine regulation of bone remodeling. *Bioessays* 2000;22:970–5.
- [50] Takeda S, Karsenty G. Molecular bases of the sympathetic regulation of bone mass. *Bone* 2008;42:837–40.
- [51] Sloan RP, McCreath H, Tracey KJ, Sidney S, Liu K, Seeman T. RR interval variability is inversely related to inflammatory markers: the CARDIA study. *Mol Med* 2007;13:178–84.
- [52] Schnedl C, Pieber TR, Amrein K. Vitamin D intervention trials in critical illness. *Inflamm Allergy Drug Targets* 2013;12:282–7.
- [53] Sauneuf B, Brunet J, Lucidarme O, du CD. Prevalence and risk factors of vitamin D deficiency in critically ill patients. *Inflamm Allergy Drug Targets* 2013;12:223–9.
- [54] Cutolo M, Pizzorni C, Sulli A. Vitamin D endocrine system involvement in autoimmune rheumatic diseases. *Autoimmun Rev* 2011;11:84–7.
- [55] Pinheiro da SF, Zampieri FG, Barbeiro HV, Filho FT, Goulart AC, Jorgetti V, et al. Decreased parathyroid hormone levels despite persistent hypocalcemia in patients with kidney failure recovering from septic shock. *Endocr Metab Immune Disord Drug Targets* 2013;13:135–42.
- [56] Lind L, Carlstedt F, Rastad J, Stiernstrom H, Stridsberg M, Ljunggren O, et al. Hypocalcemia and parathyroid hormone secretion in critically ill patients. *Crit Care Med* 2000;28:93–9.
- [57] Toribio RE, Kohn CW, Hardy J, Rosol TJ. Alterations in serum parathyroid hormone and electrolyte concentrations and urinary excretion of electrolytes in horses with induced endotoxemia. *J Vet Intern Med* 2005;19:223–31.
- [58] Prosnitz AR, Leonard MB, Shults J, Zemel BS, Hollis BW, Denson LA, et al. Changes in vitamin D and parathyroid hormone metabolism in incident pediatric Crohn's disease. *Inflamm Bowel Dis* 2013;19:45–53.
- [59] Sainaghi PP, Bellan M, Antonini G, Bellomo G, Pirisi M. Unsuppressed parathyroid hormone in patients with autoimmune/inflammatory rheumatic diseases: implications for vitamin D supplementation. *Rheumatology (Oxford)* 2011;50:2290–6.
- [60] Lange U, Teichmann J, Strunk J, Muller-Ladner U, Schmidt KL. Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. *Osteoporos Int* 2005;16:1999–2004.
- [61] Jensen T, Hansen M, Madsen JC, Kollerup G, Stoltenberg M, Florescu A, et al. Serum levels of parathyroid hormone and markers of bone metabolism in patients with rheumatoid arthritis. Relationship to disease activity and glucocorticoid treatment. *Scand J Clin Lab Invest* 2001;61:491–501.
- [62] af Ekenstam E, Benson L, Hallgren R, Wide L, Ljunghall S. Impaired secretion of parathyroid hormone in patients with rheumatoid arthritis: relationship to inflammatory activity. *Clin Endocrinol (Oxf)* 1990;32:323–8.
- [63] Oxlund H, Ortoft G, Thomsen JS, Danielsen CC, Ejerstedt C, Andreassen TT. The anabolic effect of PTH on bone is attenuated by simultaneous glucocorticoid treatment. *Bone* 2006;39:244–52.
- [64] Deans C, Wigmore S, Paterson-Brown S, Black J, Ross J, Fearon KC. Serum parathyroid hormone-related peptide is associated with systemic inflammation and adverse prognosis in gastroesophageal carcinoma. *Cancer* 2005;103:1810–8.
- [65] Walsh NC, Crotti TN, Goldring SR, Gravalles EM. Rheumatic diseases: the effects of inflammation on bone. *Immunol Rev* 2005;208:228–51.
- [66] Fierer J, Burton DW, Haghighi P, Deftos LJ. Hypercalcemia in disseminated coccidioidomycosis: expression of parathyroid hormone-related peptide is characteristic of granulomatous inflammation. *Clin Infect Dis* 2012;55:e61–e66.
- [67] Funk JL, Moser AH, Grunfeld C, Feingold KR. Parathyroid hormone-related protein is induced in the adult liver during endotoxemia and stimulates the hepatic acute phase response. *Endocrinology* 1997;138:2665–73.
- [68] Funk JL, Chen J, Downey KJ, Davee SM, Stafford G. Blockade of parathyroid hormone-related protein prevents joint destruction and granuloma formation in streptococcal cell wall-induced arthritis. *Arthritis Rheum* 2003;48:1721–31.
- [69] Cortez D, Marin R, Toledo-Flores D, Froidevaux L, Liechti A, Waters PD, et al. Origins and functional evolution of Y chromosomes across mammals. *Nature* 2014;508:488–93.
- [70] Zdobnov E, et al. OrthoDB: Database of Orthologous Groups. <http://www.orthodb.org/orthodb7>.
- [71] Parrinello N, Vizzini A, Arizza V, Salerno G, Parrinello D, Cammarata M, et al. Enhanced expression of a cloned and sequenced *Ciona intestinalis* TNFalpha-like (CTNF alpha) gene during the LPS-induced inflammatory response. *Cell Tissue Res* 2008;334:305–17.
- [72] Kasahara M, Suzuki T, Pasquier LD. On the origins of the adaptive immune system: novel insights from invertebrates and cold-blooded vertebrates. *Trends Immunol* 2004;25:105–11.
- [73] Sherwood NM, Tello JA, Roch GJ. Neuroendocrinology of protochordates: insights from *Ciona* genomics. *Comp Biochem Physiol A Mol Integr Physiol* 2006;144:254–71.
- [74] Kiechl S, Wittmann J, Giaccari A, Knoflach M, Willeit P, Bozec A, et al. Blockade of receptor activator of nuclear factor-kappaB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. *Nat Med* 2013;19:358–63.
- [75] Keller JJ, Kang JH, Lin HC. Association between osteoporosis and psoriasis: results from the Longitudinal Health Insurance Database in Taiwan. *Osteoporos Int* 2013;24:1835–41.
- [76] Sambrook PN, Geusens P. The epidemiology of osteoporosis and fractures in ankylosing spondylitis. *Ther Adv Musculoskelet Dis* 2012;4:287–92.
- [77] Bultink IE, Vis M, van der Horst-Bruinsma IE, Lems WF. Inflammatory rheumatic disorders and bone. *Curr Rheumatol Rep* 2012;14:224–30.
- [78] Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2012;64:2–8.
- [79] Kampman MT, Eriksen EF, Holmoy T. Multiple sclerosis, a cause of secondary osteoporosis? What is the evidence and what are the clinical implications? *Acta Neurol Scand Suppl* 2011:44–9.
- [80] Wohl Y, Dreier J, Cohen AD. Pemphigus and osteoporosis: a case-control study. *Arch Dermatol* 2010;146:1126–31.
- [81] Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. *Am J Med* 2009;122:599–604.
- [82] Faienza M.F., Ventura A., Marzano F., Cavallo L. Postmenopausal osteoporosis: the role of immune system cells. *Clin Dev Immunol* 2013;575936. [10.1155/2013/575936](https://doi.org/10.1155/2013/575936). [Epub@2013 May 23.:575936].
- [83] Straub RH, Cutolo M, Zietz B, Schölermerich J. The process of aging changes the interplay of the immune, endocrine and nervous systems. *Mech Ageing Dev* 2001;122:1591–611.
- [84] Schett G, Kiechl S, Weger S, Pederiva A, Mayr A, Petrangeli M, et al. High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. *Arch Intern Med* 2006;166:2495–501.
- [85] Eriksson AL, Moverare-Skrktic S, Ljunggren O, Karlsson M, Mellstrom D, Ohlsson C. High-sensitivity CRP is an independent risk factor for all fractures and vertebral fractures in elderly men: the MrOS Sweden study. *J Bone Miner Res* 2014;29:418–23.

- [86] Ding C, Parameswaran V, Udayan R, Burgess J, Jones G. Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. *J Clin Endocrinol Metab* 2008;93:1952–1958.
- [87] Franceschi C, Bonafe M, Valensin S, Olivieri F, De LM, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000;908:244–54.
- [88] Mayr E. The idea of teleology. *J Hist Ideas* 1992;53:117–35.
- [89] Meyer-Hermann M. A mathematical model for the germinal center morphology and affinity maturation. *J Theor Biol* 2002;216:273–300.
- [90] de Souza LJ. Healing time of tibial fractures in Ugandan Africans. *J Bone Joint Surg Br* 1987;69:56.
- [91] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham COCO III, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.