Bone 103 (2017) 102–115

Contents lists available at ScienceDirect

Bone

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

Review Article

Postmenopausal osteoporosis in rheumatoid arthritis: The estrogen deficiency-immune mechanisms link

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ARTICLE INFO

Article history:
Received 26 March 2017
Revised 13 June 2017
Accepted 26 June 2017
Available online 27 June 2017

Keywords:
Postmenopausal osteoporosis
Postmenopausal rheumatoid arthritis
Inflammatory cytokines
CD + T-cells
RANKL
ACPA

ABSTRACT

Rheumatoid arthritis (RA) is characterized, among other factors, by systemic bone loss, reaching ~50% prevalence of osteoporosis in postmenopausal women. This is roughly a doubled prevalence in comparison with age-matched non-RA women. Postmenopausal RA women are more likely to be sero-positive for the anti-citrullinated peptide antibody (ACPA). Our extensive review of recent scientific literature enabled us to propose several mechanisms as responsible for the accelerated bone loss in ACPA(+) RA postmenopausal women. Menopause-associated estrogen deficiency plays a major role in these pathological mechanisms, as follows:

1) Estrogen withdrawal causes immune dysregulation manifested in a skewed distribution of T helper-cell subsets, and enhanced reactivity of T helper-17 (Th17) cells. This results in a shift toward elevated levels of inflammatory cytokines, especially TNFα, IL-17, and RANKL, as well as accelerated net bone loss.
2) The proposed interaction between estrogen deficiency and RA-genetic risk alleles promotes enhanced Th17-cell autoreactivity, manifested by ACPA(+) RA. Such interactions exacerbate the inflammatory conditions and cause massive bone destruction.
3) TNFα and IL-17 play a dual role in RA because they stimulate bone resorption and inhibit bone formation.
4) An RA-unique factor, the pathogenic appearance of ACPA, promotes an inflammation independent-mechanism, resulting in direct osteoclastogenesis and bone resorption.

Contents

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http://dx.doi.org/10.1016/j.bone.2017.06.020
8756-3282/

1. Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unclear complex etiology. RA is the most common inflammatory arthritis, with an estimated global prevalence in 2010 (from 5 to 100 years of age) of 0.24%; it was about two times higher in females than males [1]. RA global prevalence remained stable from 1990 to 2010, with the major peak of RA prevalence occurring in older ages. The previous estimates for RA were based on a small number of studies that primarily collected data from Western Europe and North America, reporting a prevalence of between 0.3% and 1% [1]. RA is a chronic and progressive symmetrical polyarthritis disorder in which arthritis, particularly the small joints of the hands and feet, cause significant functional impairment. The characteristic features of the disease are synovial inflammation and proliferation, accompanied by cartilage erosion and bone loss. It causes significant morbidity, a reduced life span, and loss of work productivity [2–4]. The two known antibodies, produced against autoantigens, which are widely expressed inside and outside the joints, are the rheumatoid factor (RF) and the anti-citrullinated peptide antibody (ACPA) [5]. The citrullinated peptides are found in many matrix proteins such as fibrinogen, filaggrin, keratin, alpha-enolase, and vimentin. This implies that post-translational citrullination might expose some cryptic epitopes, which eventually results in loss of tolerance in RA pathogenesis [6].

2. Estrogen deficiency and RA

RA peak incidence in women coincides with a perimenopausal period, suggesting a relationship between estrogen deficiency and the development of RA [7]. Indeed, early menopause is a risk factor for developing RA: those women who reached menopause before 45 years of age had a higher risk for RA than did women who reached menopause in a later age [8–10]. Postmenopausal women with an earlier age of menopause are more likely to be seropositive (for RF or ACPA) and have worse patient-reported pain and global assessment scores than those with the usual age of menopause [8]. Thus, earlier menopause, together with the fact that women with RA have been reported to experience a later menarche [11], represents a shorter duration up to menopause for the bone tissue to be exposed to estrogenic protection against a negative balance between bone formation and resorption, which results in bone loss.

Data gathered from both animal and human-epidemiologic studies support this notion of the distinct beneficial effects of estrogens on arthritis. Female mice subjected to ovariectomy (OVX), and therefore having reduced levels of estrogens, display a higher frequency and an increased severity of collagen-induced arthritis (CIA), as compared with OVX mice treated with estrogen or sham-operated mice with intact levels of estrogen [12]. Epidemiologic studies revealed that other estrogen-related factors, such as longer durations of breast feeding have appeared protective, whereas parity and oral contraceptive use have been neutral [10,13,14]. Although the use of hormonal replacement therapy (HRT) does not appear to influence the risk of developing RA [15], HRT has been shown to improve both the symptoms and the progression of the disease, with decreased joint destruction, reduced inflammation, increased bone density, and better patient health assessment [16–19]. Importantly, women who had used HRT were less likely to have ACPA, and the longer duration of HRT conferred greater odds of being seronegative [18]. HRT also reduced the risk for ACPA positivity conferred by having RA-high risk HLA alleles [17]. Thus, female sex hormone exposure can modify seropositivity and may also be involved in modifying the genetic mechanism by which ACPA is produced. However, HRT is no longer recommended for long-term therapy due to the risk of serious side effects.

3. RA and bone loss

A major pathological RA manifestation is the reorganization of the synovial architecture, with immune cells infiltrating into the synovium, fibroblast-like synoviocytes (FLS) proliferation, synovial inflammation, and the pannus formation [20]. The FLS proliferation is induced by the inflammatory microenvironment and pro-inflammatory cytokines. The proliferated FLS consequently promote chronic damage to joint cartilage as well as bone loss [20,21]. The associated local-joint inflammatory state and the systemic one that follows, result in three radiographically identified forms of altered extra-articular-skeletal remodeling in RA patients [22–26]: a) periarticular bone loss, mainly caused by the proinflammatory cytokines from the inflamed synovium, which is in direct contact with bone. This varies with the disease severity; b) erosion of the subchondral bone, accompanied by mechanisms commonly associated with periarticular osteopenia; c) systemic/generalized osteopenia or osteoporosis (OP) involving the axial and appendicular skeleton.

Bone loss occurs in the very early course of RA, with the most significant rate of loss appearing early after disease onset. It has been shown that ~25% of patients with early RA show signs of osteopenia at the spine or hip before the beginning of therapy, and 10% have generalized OP, which is twice as high in comparison with the general population [27–31].

Each postmenopausal woman experiences physiological estrogen deficiency; however, the proportion of OP among these women has reached about 30% in the USA and Europe [32]. However, the prevalence of concurrent RA-OP in postmenopausal women is much higher than this number, reaching ~50% [24,33,34]. Interestingly, postmenopausal RA women were found to have a high frequency of OP (55.7%) in comparison with a relatively low frequency of OP in RA premenopausal women (18%) [33]. Several other studies are in agreement with these observations [24,34–38]. Moreover, the occurrence of hip and vertebral fractures is roughly doubled in postmenopausal RA, as compared with age-matched controls [39,40]. This may reflect, at least partially, a shared multifactorial etiology, with an added influence of factors unique to RA. The important question that arises in this connection is the nature of the one or more pathological mechanisms that cause such a dramatic elevation in OP prevalence in postmenopausal RA. This paper proposes potential mechanisms for explaining this phenomenon, in later sections.

4. Aging-related estrogen deficiency as a common cause for postmenopausal osteoporosis

Aging-related bone loss and osteoporosis affect millions of people worldwide [41] and in general, it is associated with substantial structural alterations in the skeleton, including a reduction in the trabecular bone volume, density, and strength [42]. With aging the number of osteoblasts decreases owing to a reduced number of their stem cells, defective proliferation and differentiation, a diversion of these progenitors toward the adipocyte lineage, as well as to increased apoptosis. Aging also significantly increases stromal/osteoblastic cell-induced osteoclastogenesis and promotes an expansion of the osteoclast precursor pool [43]. Advancing age is also associated with an initially subclinical proinflammatory state that has been termed 'inflamm-aging' [44], which is accompanied by an increase in oxidative stress. The hallmark of 'inflamm-aging' is the overproduction of proinflammatory (and often bone-resorbing) cytokines by macrophages. Over time, this impairs the antioxidant and repair potential of cells and promotes the generation of factors called AGEs (advanced glycation end products), a process that further stimulates the microenvironment to undergo a shift toward elevated proinflammatory cytokine levels in bone marrow and the serum [45–47].