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Psoriasis, bone and bowel: a comprehensive review and new insights

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Abstract

Psoriasis is a chronic immune-mediated disorder affecting about 2% of the population worldwide which is associated with significant morbidity. The disease usually presents as raised, well-demarcated erythematous plaques with adherent silvery scales. Psoriasis can appear at any age but it has two peaks occurring at 15–20 and 55–60 years of age. It affects males and females equally. Despite the multitude of investigations about psoriasis and even development of drugs with satisfactory results, its pathogenesis is not fully understood yet and its course is unpredictable. Various environmental triggers, e.g., obesity, stress and drugs may induce disease in genetically susceptible patients. Although psoriasis was considered primarily as a disease of the skin, more investigations have been revealed its systemic nature. Psoriatic arthritis (PsA) may complicate up to one-third of cases of psoriasis vulgaris (PV). Also, the association between psoriasis and a variety of other immune-mediated disorders such as inflammatory bowel disease (IBD) and celiac disease (CD) has been confirmed in various studies. Moreover, a growing body of evidences indicates that psoriasis shares some common histological and phenotypical properties with the spectrum of osteoimmunological diseases such as Paget's disease of bone (PDB). Thus, exploring the common molecular and genetic mechanisms underlying psoriasis and related disorders is of paramount importance for better elucidating disease pathogenesis and designing more targeted treatments.

Keywords

Psoriasis, psoriatic arthritis, celiac disease, Paget's disease of bone, osteoprotegerin, antibodies, Dickkopf-1

Introduction

Psoriasis is a chronic immune-mediated disorder affecting about 2% of the population worldwide with significant emotional and socioeconomic burden and decreased quality of life. The common clinical variant referred to as plaque psoriasis or psoriasis vulgaris (PV) accounts for about 80% of psoriasis cases [1]. PV usually presents as raised, well-demarcated erythematous plaques with adherent silvery scales. It could

appear at any age but two peaks in the age of onset have been reported. The first peak occurs at 15 years to 20 years of age and the second smaller peak starts between 55 years to 60 years [2]. It affects males and females equally [3]. Both innate and adaptive immune systems have been implicated in the pathogenesis of psoriasis. Dendritic cells seem to have an important role in bridging the gap between innate and adaptive immunity through secretion of the interleukin-12 (IL-12) and IL-23 which are currently being targeted widely for therapeutic uses in psoriasis and inflammatory bowel disease (IBD) [1, 4, 5]. Although the exact pathogenesis is unknown but it has been found that various environmental triggering factors, e.g., obesity, stress, poor hygiene, low humidity and drugs may induce psoriasis in genetically susceptible patients [6]. Moreover, the important role of oxidative stress in initiating and maintaining psoriasis has been demonstrated [7, 8]. Although it was considered primarily as a disease of skin, more investigations revealed its systemic inflammatory nature [9]. Psoriatic arthritis (PsA) would complicate up to one-third of patients with PV [10]. Both psoriasis and PsA have a strong heritability rate [11]. Twin studies have shown a significantly higher concordance rate in monozygotic compared to dizygotic twins. However, none of these studies have reported a 100% concordance rate indicating the important role of environmental factors in addition to genetic predisposition [12]. Further, the association between psoriasis and a variety of other immune-mediated disorders such as IBD and celiac disease (CD) has been confirmed in various studies [11, 13, 14]. A large proportion of diseases which are epidemiologically bound to psoriasis may involve the gastrointestinal tract. The oral psoriasis is now widely accepted as psoriatic alimentary tract manifestations. Psoriasis-specific oral lesions are histologically identical to that psoriatic skin lesions and might precede cutaneous presentations [15].

Psoriasis and gastrointestinal tract

The first peak of psoriasis coincides with IBD peak of onset around 15–30 years [16]. The odds ratio for psoriasis development is higher in younger (< 30 years) than older (> 30 years) patients with IBD which further supports a common genetic background between IBD and psoriasis [17]. Both psoriasis and IBD affect the women and men equally in contrast to many other immune-mediated diseases [16, 18]. Regardless of the phenotype, a high frequency of microscopic gut inflammation in all subsets of spondyloarthritis (SpAs) has been found indicating a loss of intestinal barrier integrity in this spectrum [19]. Both IBD and psoriasis are characterized by gut dysbiosis in the form of decreased bacterial diversity [20, 21]. Additionally, in psoriatic patients, structural and functional abnormalities of the digestive system have been found throughout all segments [22]. Psoriasis and PsA inpatients showed the strongest association with IBD, CD and autoimmune hepatitis [23]. In a Mendelian randomization study (2022), genetically predicted Crohn's disease was associated with 42.5% increased risk of psoriasis [11]. Conversely, psoriasis was associated with a 35% increased risk of Crohn's disease. In addition, PsA was associated with about 32% increased risk of Crohn's disease and Crohn's disease mutually was linked to about 45% elevated risk of PsA. Hence, a bidirectional causal relationship between psoriasis/PsA and Crohn's disease was found. However, no mutual causal relationship between psoriasis/PsA and ulcerative colitis (UC) was seen in this study [11]. Moreover, combined IBD-psoriasis patients might have different phenotypic and genotypic features in comparison with individuals suffering from a single disease. For example, psoriasis was diagnosed significantly at a younger age in combined psoriasis-Crohn's disease individuals compared with psoriasis-only patients. Further, the extent of involvement in Crohn's disease and UC was larger in concomitant IBD-psoriasis patients than IBD-only patients. However, most psoriasis-IBD patients have mild psoriasis [24]. From a genetic perspective, seven common non-histocompatibility human leukocyte antigen (*HLA*) susceptibility loci between Crohn's disease and psoriasis were reported by Sun et al. [11] (2022) in addition to confirmation of four previously reported loci. Ellinghaus et al. [25] (2016) who investigated the genetic landscape of UC, Crohn's disease, psoriasis, primary sclerosing cholangitis and ankylosing spondylitis (AS) found significant temporal co-morbidity amongst these five diseases. They concluded that despite significant pleiotropy (shared risk alleles between two diseases) rather than heterogeneity (a subgroup of one disease has a higher burden of risk alleles of the other one), there was a clear distinction with respect to genetic markers for each disease. These findings challenge the

old paradigm in which a causal relationship between IBD and extra-intestinal manifestations being supposed, rather suggest the presence of a common pathophysiological pathway as the basis for the observed clinical concurrency by considering combined syndromes as genetically separated diseases [25]. At the molecular level, dysregulated cross-talking between dendritic cells and IL-17/IL-23 axis is currently regarded as the central mechanism in the pathogenesis of psoriasis and IBD [13]. IL-23 overexpression represents a disease model mimicking many features of SpAs, but its ultimate effect depends on the specific tissue microenvironment as evidenced by the lack of efficacy of IL-23 blocking agents in axial involvement in contrast to peripheral arthritis [19]. While IL-23 has a relatively consistent and unifying role in the pathogenesis of both psoriasis and IBD, inhibition of its downstream effector, namely IL-17A has led to different and paradoxical results in psoriasis and IBD [4]. For example, ustekinumab, a blocking agent of common subunit p40 of IL-12 and IL-23 showed effective inhibition of IL-12/IL-23 pathway and is now approved for plaque psoriasis, PsA, Crohn's disease and UC [16, 26, 27]. While IL-17 blocking agents, e.g., secukinumab and ixekizumab showed promising results in the treatment of psoriasis and PsA, they have the potential to exacerbate Crohn's disease [4]. These observations are consistent with Xi et al. [27] (2022) findings which demonstrated that in contrast to other 190 shared signature between psoriasis and UC, IL-17A was only evident in psoriasis transcriptome.

Moreover, there is considerable overlap between psoriasis and CD with respect to epidemiological, clinical and genetic characteristics. Psoriasis has been reported as the second most common cutaneous manifestations of CD as well as the second most prevalent immune-mediated disorder associated with CD after Hashimoto thyroiditis [28–30]. The risk of CD in psoriasis estimated to be two to three-fold in meta-analysis studies [31–33]. The association between CD and psoriasis is significant in all age groups but is decreasing with age [34]. In a large case-control study of children with biopsy-proven CD below the age of 20 years, the hazard ratio of developing psoriasis later in life was reported about two-fold with about 50% of cases attributed to the underlying CD [35]. Some authors indicated that some wheat proteins may act as psoriasis-specific antigen in a subgroup of patients with CD [36]. Moreover, elevated levels of immunoglobulin A (IgA) and/or IgG antibody (AB) anti-gliadin antibodies (AGAs) as well as anti-tissue trans-glutaminase (tTG) AB have been reported in psoriasis patients [37–42]. In some studies, the presence of tTG AB or AGAs has been associated with the severity of psoriasis and more need for second-line therapy [40, 43, 44]. In a Swedish study (2000) in patients with elevated levels of AGAs regardless of duodenal biopsy results (normal or consistent with CD), a three-month gluten-free diet (GFD) resulted in a highly considerable decrease in Psoriasis Area Severity Index (PASI) score as well as reduction in the AGAs level in 82% of patients whereas PASI score was exacerbated in the majority of AB-negative patients [14]. In a subsequent study led by the same author (2003), the clinical improvement of AGA-positive psoriasis patients who were on GFD was associated with significant histopathologic changes which did not achieve with treatments such as methotrexate (MTX) [45]. In another study, one year GFD led to 56% and 36% improvement in the PASI score in patients with very high and high levels of IgA AGAs, respectively [46]. According to a recent study (2020), IgG4-class AGAs were the only AB detected in the patients with severe psoriasis which were not detected in healthy controls thereby may serve as the potential serologic biomarkers for psoriasis diagnosis [47]. A genome-wide association study (2013) demonstrated 10 shared susceptibility loci between psoriasis and CD as well as 10 common susceptibility loci between psoriasis and Crohn's disease [48]. Surprisingly, five out of six newly discovered loci are involved in the innate immune pathway [48]. In terms of etiology, the results of a recent Mendelian randomization study are of paramount importance. Li et al. [49] (2022) found that CD serves as a causative factor for psoriasis and showed that each standard deviation of genetically determined increase in CD was associated with about 20% elevated risk of psoriasis whereas genetically determined psoriasis was not associated with the risk of CD. In addition, psoriasis variants other than PV have been also found to be associated with CD. Palmoplantar pustulosis (PPP) is a variant of psoriasis affecting about 18% of psoriatic patients [50, 51]. As opposed to PV, PPP is more frequently seen in females at the age of 50–70 years especially in the smokers without a positive family history [51–53]. In a Swedish study (1998), it was demonstrated that 8% of PPP patients had CD and 24% of whom showed raised levels of IgA AGAs [54]. In another study conducted by the same author (2007), 18% of PPP patients had IgA AGAs, 10% showed IgA tTG AB and 6% had CD with variable

villous atrophy [50]. Surprisingly, adhering to GFD led to nearly total resolution of lesions combined with normalization of the AB levels in both celiac and non-celiac patients. According to the authors, the presence of non-specific mild to moderate intraepithelial lymphocyte infiltration without evidence of villous atrophy which was seen only in those of positive AGAs, suggests a state of gluten sensitivity rather than necessarily CD in these subsets of patients [50]. However, the same results were not reproduced in a German, Italian and Australian studies probably in part due to ethnicity differences [55–57]. Indeed, in Europe, Germany has the lowest prevalence of CD whereas Sweden and Finland have the highest prevalence of the disease [58]. Moreover, an interesting case of recalcitrant acrodermatitis continua of Hallopeau, a relatively rare variant of PPP has been described in the literature (2014) with nearly complete resolution of skin lesions after adhering to GFD [59].

The term non-celiac gluten sensitivity (NCGS) was coined in 2012 to describe a new clinical entity [60]. NCGS is defined by the presence of morphological, functional and immunological disorders with good response to GFD without characteristic features of CD [61]. NCGS patients are usually young to middle-aged women with both intestinal and extra-intestinal manifestations. A family history of CD could be seen in 5% to 24% of them. Among the extra-intestinal presentations of NCGS, cutaneous manifestations such as psoriasis and eczema have been reported [57, 60]. The prevalence of *HLA-DQ2* and/or *HLA-DQ8* is 50% in NGCS patients compared to 40% of the general population but is much less than 99%, which is seen in celiac patients. About 25% to 50% of NGCS patients have elevated levels of AGAs, mainly IgG class. The duodenal biopsy in NGCS is normal or shows mild increased intraepithelial lymphocyte infiltration [60]. These features are consistent with the phenotypic, serologic and histologic findings of the PPP patients who described in the Swedish study [50].

Thus, it seems that a considerable proportion of PPP patients might be fall within the spectrum of NCGS, thereby would benefit from a GFD. Taken together, gluten could participate in the psoriasis pathogenesis either through inducing mixed innate and adaptive immune system responses in the setting of CD or by stimulation a dominant innate immune process in the background of NCGS. Thus, initiation of a GFD might be a viable therapeutic modality in the treatment of patients with psoriasis and PsA especially in the refractory cases.

Moreover, CD shares some other common features with psoriasis such as peripheral and axial arthritis as well as subclinical enthesopathy [62–66]. PPP is also an inseparable part of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. The acronym SAPHO stands for synovitis, acne, pustulosis, hyperostosis and osteitis which are not necessarily simultaneously being occurred [67]. SAPHO syndrome is a rare heterogeneous disease mainly affects individual at fourth to sixth decades of life with female preponderance [68–70]. The most common osteoarticular manifestation of the disorder is anterior chest involvement followed by spine [70]. PPP is the most frequent cutaneous manifestation of SAPHO syndrome which in some cases might occur as the only presentation [67, 70]. Of note, similar to PV the characteristic features of dermatoses associated with SAPHO syndrome are neutrophilic pseudo-abscesses highlighting the role of oxidative stress and the innate immune system. SAPHO syndrome also shares some common features with seronegative SpAs, especially PsA, e.g., synovitis, enthesitis, non-marginal syndesmophytes and bone erosions [70]. About 10% of SAPHO patients may be complicated with Crohn's disease, but more prevalence of *HLA-B27* has not been documented in SAPHO syndrome [70, 71]. However, there are some differences between SAPHO and PV. While PV demonstrates a strong association with the psoriasis susceptibility 1 (*PSORS1*) region (including *HLA-Cw6*), neither PPP nor SAPHO syndrome showed no linkage with this locus [72, 73]. Furthermore, PV often exacerbates with non-steroidal anti-inflammatory drugs (NSAIDs) but there is no report of *de novo* PPP lesions or exacerbation of previous lesions in SAPHO patients who most commonly treated with NSAIDs for musculoskeletal complaints. These findings further support the idea of considering SAPHO syndrome and PPP as distinct entities from PV [67, 74]. In conclusion, regarding the significant connection between PPP and CD/gluten sensitivity as well as established response to GFD and the fact that PPP is an inseparable component of SAPHO syndrome, it is reasonable to screen SAPHO patients for occult CD.

Oxidative stress in psoriasis and related conditions

The imbalance between production and elimination of reactive oxygen species (ROS) leads to oxidative stress. ROS has been shown to have a critical role in the pathogenesis of both psoriasis and CD [8, 75]. ROS promotes inflammation through several signaling pathways including nuclear factor-kappa B (NF-κB) pathway [8]. Elevated levels of ROS have been reported in the skin, plasma and blood cells of psoriatic patients [8, 75]. Furthermore, increased risk of developing psoriasis in individuals carrying the polymorphism of genes encoding enzymes involved in oxidative stress has been reported in psoriasis [8]. For example, the 55 Methionine (M allele) > Leucine polymorphism of paraxonase-1 (*PON1*) gene poses a significant risk for psoriasis [8, 75]. PON1 is produced in the liver and its concentration has been shown to be reduced in the psoriatic patients treated with MTX. MTX exerts its anti-proliferative effects on keratinocytes through inducing oxidative stress [75]. It has been long understood that the hepatotoxic complications of MTX are disproportionally increased in psoriatic patients compared to other autoimmune diseases such as rheumatoid arthritis (RA) but the underlying cause remained unknown [76]. Thus, increased oxidative stress plus decreased level of *PON1* might explain the exaggerated hepatotoxic complications of MTX in psoriasis. Meanwhile, diets rich in antioxidants have demonstrated promising outcomes in the psoriasis treatment [77]. More importantly, several novel effective biologic drugs for psoriasis have been demonstrated antioxidant properties. Secukinumab which targets IL-17 pathway has been shown to reduce peripheral oxidative stress markers as opposed to MTX [7, 8]. Ustekinumab, an inhibitor of common p40 subunit of IL-23/IL-12 has demonstrated antioxidant properties by targeting Janus kinase 2/signal transducer and activator of transcription 3 (STAT3) pathway [8]. In addition, apremilast an inhibitor of phosphodiesterase-4 which has been approved for the treatment of psoriasis and PsA, inhibits oxidative stress and inflammation through modulating NF-κB pathway [7]. So, the remarkable efficiency of novel biologic drugs in psoriasis may in part be attributable to their antioxidative effects [8]. Similarly, impaired oxidative balance has been documented in both treated and untreated celiac patients. Gluten exerts its detrimental effects on enterocytes through either toxic or immunogenic mechanisms or both. A significant association between the severity of villous atrophy and the level of ROS has been found in the study conducted by Moretti et al. [78] (2018).

PsA and related disorders from an osteoimmunological perspective

Over the recent years, the role of autoimmunity in bone metabolism has been more investigated suggesting the direct and indirect interactions between autoantibodies and bone cells particularly osteoclasts (OCLs). Successful prevention of bone erosion in RA patients with drugs targeting B-cells further enforces this idea. In animal studies, it has been found that receptor activator of NF-κB ligand (RANKL) expression and subsequent bone erosion in the inflammatory arthritis are dependent only on the synovial fibroblstoid cells and B cells rather than T helper 17 (Th17) cells highlighting the important role of the innate and humoral immune system in bone destruction in these conditions [79]. Although, yet no single auto antigen has been identified in the so-called seronegative SpAs particularly PsA, however, specific AB against several bone regulators such as osteoprotegerin (OPG), noggin and sclerostin have been found in the sera of AS patients [80–83]. Circulating functional AB against OPG have been also detected in RA [80, 84]. The OPG/RANKL pathway is the key regulator of osteoclastogenesis and maintaining its balance is necessary for normal bone metabolism [80, 85]. OPG acts as a decoy receptor to RANKL thereby preventing the stimulation of receptor activator of NF-κB (RANK) receptor on the surface of OCLs leading to inhibition of OCLs differentiation [80]. Osteoblasts (OBLs) varies their degree of RANKL and OPG to regulate OCLs activity through modulation of RANK receptor [86]. Additionally, wingless-related integration site (Wnt) signaling pathway is the key mediator of osteoblastogenesis. Osteophytes may be regulated by inhibitory effect of Dickkopf-1 (DKK-1) on Wnt pathway independent from RANKL/OPG axis. There is a mutual inverse relationship between OPG and DKK-1 [87]. Mutations in *RANKL* gene leading to congenital bone diseases have not been detected in humans but mutations in the *OPG* and *RANK* genes leading indirectly to increased RANKL signaling have been identified that may lead to the high bone turn-over phenotypes of juvenile Paget's disease and familial expansile osteolysis, respectively [86]. Further, recent studies demonstrated that unbalanced OBLs and

OCLs activity induced by autoantibodies might have a more important role in the bone derangements seen in autoimmune diseases such as CD than secondary malnutrition [80]. Taranta et al. [88] (2004) studied two groups of celiac patients with and without adherence to GFD. The study demonstrated increased RANKL/OPG ratio in patients who were not adherent to GFD. Interestingly, they found that the sera of celiac subjects directly affect both OBLs and OCLs *in vitro*. While osteoclastogenesis was increased about 40 times after exposure to the sera of celiac patients compared to healthy controls, OBLs proliferation and alkaline phosphatase (ALP) activity were elevated up to three times at maximum. Despite increased levels of both RANKL and OPG, the level of RANKL was raised disproportionally resulted into increased RANKL/OPG ratio. After starting GFD, the sera of patients showed significantly lower osteoclastogenic activity compared to those who were not on a GFD and RANKL/OPG ratio returned to normal. The authors suggested that an unknown factor with immune cells origin might contribute to unbalanced RANKL/OPG ratio by directly affecting OBLs and OCLs activity [88]. The same pattern was found in celiac patients compared to controls by Fiore et al. [89] (2006). The authors concluded that the results might be secondary to persistent osteopenia despite of strict adhering to long-term GFD [89].

In both studies, only the OPG level was measured but searching for OPG AB was not addressed. It could be hypothesized that the missing agent in the Taranta et al. [88] and Fiore et al. [89] studies was uncovered by Riches et al. [90] (2009) in their innovative and groundbreaking discovery of OPG AB in a 40-year-old man with occult CD who had presented with severe refractory osteoporosis and a phenotype very similar to juvenile Paget's disease. Because of the refractory osteoporosis and high bone turn-over status despite maintaining GFD and intake of supplemental calcium and vitamin D, the investigators suspected another cause other than secondary malabsorption to CD. It was confirmed that neutralizing AB against OPG is responsible for this phenotype [90]. It is noteworthy to say that AB with the greatest affinity for OPG was detected in this patient which may explain such an extreme phenotype [81].

In conclusion, one possible explanation for increased RANKL/OPG ratio in favor of RANKL in the studies led by Fiore et al. [89] (2006) and Taranta et al. [88] (2004) is the presence of functional neutralizing AB against OPG in the sera of celiac patients leading to disproportionally decreased levels of OPG relative to RANKL. As a result, the balance shifted towards the osteoclastogenesis while unopposed OPG molecules maintained their osteoblastic function. So, it could be expected that the sera of celiac patients would demonstrate both osteoblastic and osteoclastic properties with osteoclastic superiority.

In the study conducted by Real et al. [81] (2015), they found that in at least half of celiac patients, epitope-specific AB against OPG would develop. This study shed more light on the previous studies and further supported the important role of functional AB against OPG in bone pathogenesis of CD. Hauser et al. [82] (2017) screened a cohort of patients with established AS for existence of OPG AB and found OPG AB in about eight percent of AS patients.

Up to 30% of patients with psoriatic skin lesions will develop PsA in the future. On average, psoriasis precedes the onset of PsA by 8 years to 10 years [10, 91]. PsA affects both peripheral and axial skeleton without any gender predilection [92]. The development of PsA is the result of a complex interplay between genetic background and environmental triggers such as biomechanical stress [93]. PsA have marked phenotypic differences with RA and other SpAs. While axial involvement in RA is uncommon and it tends to involve the joints symmetrically with distal interphalangeal (DIP) joints sparing, PsA often asymmetrically involves the peripheral (including DIP) and axial joints. Dactylitis and enthesitis are common characteristic features of PsA which are not typically observed in RA. RA is considered as a purely erosive disease of peripheral joints with little evidence of bone formation whereas PsA shows a markedly different pattern including mixed pattern of bone resorption and formation in peripheral and axial joints [10]. As opposed to RA, in PsA periarticular bone mineral density is often preserved with new bone formation in the form of periostitis and severe ankyloses [94, 95].

In contrast to bone resorption, underlying molecular mechanisms of new bone formation in PsA are poorly understood. However, Wnt/DKK-1 axis, IL-17 and IL-22 have been proposed [87, 96]. Even in asymptomatic psoriatic patients, there are evidences of subclinical bone formation at the entheseal sites

[93]. The important role of tumor necrosis factor-alpha (TNF-α) and IL-17/IL-23 axis have been demonstrated in PsA pathogenesis. While the beneficial effects of IL-17 blocking agents such as secukinumab on excessive bone formation have been observed in PsA, TNF-α blocking agents have not produced comparable effects on bone formation suggesting the dominant destructive effect of TNF-α in PsA [93, 96]. Despite of convincing evidences that peripheral enthesitis is IL-23 dependent, the drugs targeting IL-23 showed no satisfactory outcomes in axial enthesitis (Table 1) [93, 97].

Table 1. Summary of the cells and mediators involved in the PsA pathogenesis

Mediators/Cells	Effect
RANKL	Osteoclastogenesis ↑
OPG	Decoy receptor of RANKL: osteoclastogenesis ↓
	Regulates the DKK-1 expression through a feedback loop
	Vascular calcification ↓
DKK-1	Natural inhibitor of Wnt: bone formation ↓
	Inhibition of DKK-1: circulating OPG ↑; osteoclastogenesis ↓
Wnt pathway	Osteoblastogenesis ↑
TNF-α	RANKL ↑: bone erosion
	DKK-1 ↑: bone erosion
IL-22	OBL ↑ differentiation of mesenchymal stem cells: bone formation ↑
	RANKL ↑ on FLS: osteoclastogenesis
IL-17	RANKL ↑: osteoclastogenesis
	Wnt ↓: inhibition of new bone formation
	Exacerbating enthesitis through stimulation of mesenchymal stem cells
IL-23	Peripheral enthesitis
	Key mediator of Th17 expansion and maintenance
Innate γδ T cells	Production of IL-17 independent from IL-23: OBLs proliferation ↑
Th17	Production of IL-17
Th22	Production of IL-22 in the absence of IL-17A

↑: increased; ↓: decreased; FLS: fibroblast-like synoviocytes

DKK-1, a negative regulator of Wnt signaling pathway, which is upregulated by TNF-α, has a crucial role in inhibition of new bone formation [93]. At least, part of the destructive effect of TNF on joints is mediated through DKK-1 [87]. DKK-1 is significantly expressed in the synovium of RA patients and its highest serum levels were seen in RA compared to other inflammatory arthritis. In fact, in RA, bone formation is hampered by TNF-α-mediated expression of DKK-1, whereas bone resorption is enhanced through increased RANKL activity by TNF-α that finally lead to net resorptive phenotype of RA [87, 96, 98]. In contrast, AS patients show the lowest levels of DKK-1 with nearly pure osteoblastic activity [98]. Interestingly, Diarra et al. [87] found that in addition to relieving the suppressive effects of DKK-1 on Wnt signaling, DKK-1inhibition by neutralizing AB could lead to OPG overexpression that altogether could result in net excessive bone formation mimicking bone phenotype of AS (Table 2). Thus, it could be hypothesized that co-existence of functional AB against DKK-1 and OPG may be responsible for the characteristic phenotype of simultaneous excessive bone formation and resorption status in at least a subgroup of PsA patients which is mediated through potentiating effect of Wnt on osteoblastogenesis as well as by neutralizing the inhibitory effect of OPG on RANKL.

More interestingly, there are considerable common characteristics between PsA and PDB with respect to the histopathology and pattern of bone involvement which are not seen in other rheumatologic diseases. PDB is the second most common metabolic disease of bone affecting about 3 percent of individuals older than 55 years. PDB is rare below the age of 50 years but doubles each decade thereafter. It occurs equally in men and women [99–101]. The clinical manifestations of PDB are highly variable depending on the affected bone with a predilection for axial skeleton involving most frequently the pelvis, lumbosacral spine, skull and long bones of lower extremities [102, 103]. It is characterized by increased bone formation coupled

Table 2. Profile of bone biomarkers in RA, CD, PsA and Paget's disease of bone (PDB)

Biomarkers	RA	CD	PsA	PDB
sRANKL	↑↑	↑↑	↑↑	↑
OPG	NL/↑	↑	↑	↑
OPG AB	NL/↑	↑	N/A	N/A
DKK-1	↑↑	N/A	↑/↓	NL/↑
DKK-AB	N/A	N/A	N/A	N/A

sRANKL: soluble RANKL; ↑: elevated; NL/↑: both normal and elevated levels reported; ↑↑: significantly elevated; N/A: data not available; ↑/↓: both increased and decreased levels reported

with increased and disorganized bone resorption [104]. OCLs are the primary cells involved in PDB demonstrating significant increase in number and size. RANKL is highly expressed in the bone marrow stromal cells of PDB similar to synovial tissues of PsA and RA patients. Also, elevated numbers of circulating OCLs precursors have been identified in PsA and PDB [94, 105, 106]. Excessive osteoblastic activity in PDB is reflected in the elevated serum levels of ALP which has been reported in 85% of patients [105]. Interestingly, among SpAs the serum level of bone ALP is only consistently elevated in PsA very similar to PDB [105, 107, 108]. PDB is highly localized and new lesions almost never develop in the course of disease. Instead, lesions increase in size rather than spreading to new sites and do not cross the bone boundaries, a finding similar to the skipping non-marginal syndesmophytes in PsA [105, 109]. OCLs in PDB are characterized by hypermultinucleation (up to 100 nuclei per cells) compared to 3 to 10 nuclei in normal OCLs [105]. Similarly, large OCLs with high nuclearity (more than 20 nuclei per cell) have been observed in PsA at the bone-pannus junction [94, 110]. Increased tissue vascularity is the hallmark of PDB [111]. Likewise, markedly increased vascularity and vessel tortuosity are seen in the psoriatic synovial tissue which are distinguishing features of PsA from RA [4, 94, 110]. Similar changes also have been observed in psoriatic skin tissues [110]. Analogous to psoriasis, increased arterial calcification is more common in PDB than in healthy subjects [111, 112]. OPG also acts as an inhibitor of vascular calcification. So, it is expected that neutralizing AB against OPG to facilitate excessive ectopic calcification in both PsA and PDB (Table 3) [113].

The sequestosome 1/polyubiquitin-binding protein p62 (*SQSTM1/P62*) gene encoding *SQSTM1* which is involved in the TNF and RANKL signaling pathways has an important role in the development of classic PDB and is currently the only recognized susceptibility loci predisposes to classic PDB [102, 105, 114]. Mutations in this gene result in increased expression of RANKL-NF-κB signaling pathway in OCLs by unknown mechanisms [114]. In addition, the role of *SQSTM1/P62* gene in neutralizing the chemical and oxidative stress in the cells has been confirmed [115]. It also has a crucial role in autophagy allowing specific molecules to undergo selective degradation. Autophagy is more activated in increased oxidative stress circumstances such as aging emphasizing the more important role of p62 in these conditions. The peak of PDB onset at the age of 55 years and over as well as the predilection for involvement of bones undergoing biomechanical pressure underscores the role of cumulative oxidative and biomechanical stress in the pathogenesis of PDB. Indeed, oxidative or mechanical stress might accelerate genetic susceptibility in PDB [114]. Further, new advances in the understanding of bone remodeling in SpAs have found that factors other than inflammation, especially biomechanical stress can play a major role in the development of erosive bone phenotype in these groups of diseases [116]. One of the characteristic features of PsA is the involvement of entheses which are transition zones between tendons/ligaments and bones that transduce mechanical forces from muscles to bones. Enthesitis is very common in PsA and could be induced by even low mechanical strain which most frequently occurs at the lower limbs. In addition, the onset of PsA about 10 years after the skin manifestations (over 45 years) points towards the important role of cumulative biomechanical stress in genetically predisposed individuals. There are strong histologic evidences of long-standing micro damage to entheses which are the typical upfront locations in PsA. Larger enthesophytes in the calcaneus-cuboid metatarsal and Achilles tendon of SpAs patients further supports the prominent role of biomechanical loading in the site-specific origin of arthritis or enthesitis in PsA. Further, the risk of developing PsA or transition from PV to PsA is increased with obesity in proportion to the magnitude of body mass index (BMI) suggesting the essential role of biomechanical stress [93].

Table 3. Comparison of epidemiologic and clinical characteristics of PDB and PsA

Characteristics	PsA	PDB
Age of onset, years	> 45	> 50
Gender	F = M	F = M
Familial history	Positive	Positive
Vascular calcification	Is present	Is present
Involvement of weight—bearing bony architecture	Lower extremity enthesitis (obesity)	Lower-extremities (long-bones)
	Pelvis	Pelvis
	Axial spondylitis	Axial skeleton
Bone ALP	↑↑	↑↑
CD association	Yes	Possibly
OCLs morphology	Hypermultinucleated	Hypermultinucleated
Oxidative stress	↑	↑
Tissue vascularity	↑↑	↑↑
Pattern of bone involvement	Asymmetric	Asymmetric
	Skipping non-marginal- syndesmophytes	Not crossing bone boundaries
Deep Koebner phenomenon	Confirmed	?
Daily trauma-related sites	DIP joints	Skull
	Ray distribution	
	Dominant-hand thumbnail	
	Obesity	
Environmental factors	Streptococcus/Drugs/Stress	Measles virus
Prevalence	Increased	Decreased

F: female; M: male; ↑: elevated; ↑↑: significantly elevated; ?: undetermined

The Koebner phenomenon, namely the elicitation of skin lesions at the sites of skin trauma has been well recognized in the cutaneous psoriasis [117]. Surprisingly, nail, scalp and intergluteal regions which their involvement harbors the highest risk for developing PsA, are sustained to the most of trauma burden in daily activities [74]. Severe and more prevalent involvement of the thumb nail of dominant hand as well as more prevalence of DIP joint involvement are characteristic features of PsA which might be explained by Koebner phenomenon [10, 74]. Interestingly, the clinical observations have found that psoriasis plaque fail to develop in denervated skin [118]. An enigmatic pattern of bone involvement, the so-called "ray distribution" has been described in PsA characterized by involvement of all joints of one finger while the adjacent joints might completely spare, as opposed to the involvement of joints of the same level on both sides in RA [119]. These unusual patterns of joint and skin involvement in psoriasis further support the prominent role of site-specific involvement rather than systemic factors only [10]. More importantly, deep Koebner phenomenon defined as triggered episodes of arthritis after trauma is well-recognized in PsA in contrast to other SpAs [120]. Moreover, the propensity of PDB for involvement of the skull and weight-bearing bony structures might be in part due to recurrent daily trauma, a feature similar to deep Koebner phenomenon in PsA.

Because of the lack of a classical and highly reproducible animal model with the ability to mimic all characteristic features of PsA, utilizing animal models of PDB is promising with respect to the above-mentioned similarities between the PsA and PDB [121].

Furthermore, it has been found that the beneficial effects of third-generation bisphosphonates in the treatment of PDB are not limited to their osteoclastic inhibitory properties. Indeed, it appears that OBLs are required for the optimal response to bisphosphonates [106]. Moreover, there are promising evidences regarding the successful treatment of cutaneous and osteoarticular presentations of SAPHO syndrome with bisphosphonates [70, 122, 123]. However, there are limited data about the efficacy of bisphosphonates in PsA which merit further investigation [124].

Additionally, there is a growing body of evidences concerning the association of both psoriasis and PDB with CD [48, 81]. Celiac may predispose patients to psoriasis through various mechanisms. Several common

genetic susceptibility loci have been described in psoriasis and CD [48]. Furthermore, long-standing untreated CD has been shown to result in various immune-mediated disorders such as psoriasis probably through chronic antigenic stimulation or inducing oxidative stress [49, 125–127]. There are also evidences for the PDB and CD association. The phenotype of *OPG*-knockout mice has revealed the important role of OPG in the regulation of bone remodeling in the cortical and trabecular part of long bones as well as the skull which are the most involved bones in PDB [128]. More importantly, the discovery of neutralizing high-affinity AB against OPG in a patient with occult CD who presented with a phenotype very similar to juvenile's Paget's disease is very interesting and could shed more light on the pathogenesis of classic PDB and CD bone abnormalities. The majority of Juvenile Paget's disease cases are caused by mutations in the tissue necrosis factor receptor superfamily member 11B *(TNFRSF11B*) gene, which encodes OPG. The disease has a striking similarity with classic PDB but involves severely the entire skeleton in infancy or early childhood [129–131]. This mutation may also predispose individuals to classic PDB [132]. In fact, functional OPG AB produced by CD in this case, acted like a loss-of-function mutation in the *TNFRSF11B* gene resulted in a phenotype similar to juvenile Paget's disease. This event might also be true for classic PDB and could improve the understanding of the novel mechanisms underlying its pathogenesis and other related osteoimmunological disorders such as PsA. So, addressing these three potentially interrelated disorders in large prospective trials in order to better delineate their shared phenotypic and genotypic backgrounds as well as common molecular mechanisms is an unmet need.

Accordingly, a recently published case report introducing a 64-year-old man with advanced early-onset polyostotic PDB and concurrent psoriasis and elevated levels of anti-tTG AB may be instructive [133]. This case further underscores the probable causative role of CD in the premature development of PDB and its catastrophic complication namely, blindness (the third decade of life in this case) as well as psoriasis development and highlights the complex interplaying between PsA, PDB and CD.

Conclusions

The important role of the OPG/RANKL axis has been well realized in the bone abnormalities of PsA, PDB, RA and CD. The fact that RANKL expression and subsequent bone erosion in the inflammatory arthritis are dependent only on the synovial fibroblstoid cells and B cells rather than Th17 cells is very important and underscores the important role of the innate and humoral immune system in these conditions. Discovery of disease-specific AB like AB against OPG in the sera of CD patients which might serve either as loss-of-function or gain-of-function mutations of relevant genes is of paramount importance which have significant clinical implications. In the other words, targeting the humoral immunity could be a promising area of research for the drug designing and development in the treatment of psoriasis and especially PsA. Furthermore, despite the confirmed role of RANKL/OPG and Wnt/DKK-1 axis dysfunction in the pathogenesis of PsA, it is still unknown how these abnormalities would lead finally to the characteristic bone phenotype of PsA. Discovery of novel epitope-specific AB against other bone modulators such as sclerostin and noggin in AS is promising and may explain the extreme phenotypic differences observed in this spectrum.

Besides, due to the confirmed role of OPG AB in developing PDB-like phenotype and evidences of DKK-1 pathway dysregulation in both PsA and PDB and by taking into account their significant common bone features, it could be hypothesized that at least in a sub-population of PsA, simultaneous production of AB against OPG and DKK-1 molecules may contribute to the simultaneous increased catabolic and anabolic bone activities which is specific to PsA, either directly by psoriasis itself or indirectly through an underlying disease such as CD. Thus, searching for specific AB against OPG and DKK-1 in the sera of PsA patients deserves further investigation for better elucidation of disease pathogenesis. Also, screening of psoriasis, PsA and PDB patients for an occult CD by serologic markers is recommended.

Regarding the epidemiologic, clinical and genetic interrelations between PsA, psoriasis and IBD, screening of psoriatic patients with gastrointestinal symptoms via stool calprotectin is reasonable. Likewise, in patients with newly diagnosed CD, it is recommended to search thoroughly for the mucosal and dermatologic evidences of psoriasis in addition to requesting plain radiography for the clues of PDB in the

skull and lower extremities as well as occult psoriatic spondylitis or sacroiliitis. Also, owing to reported efficacy of bisphosphonates in the treatment of PDB as well as SAPHO syndrome, further investigation of the role of bisphosphonates in the treatment of cutaneous and articular manifestations of psoriasis is suggested.

Finally, due to marked similarities observed between bone phenotypes of PsA and PDB, the animal models of PDB might be a good candidate for investigating PsA pathogenesis.

Abbreviations

AB: antibody

AGAs: anti-gliadin antibodies

AS: ankylosing spondylitis

CD: celiac disease

DIP: distal interphalangeal

DKK-1: Dickkopf-1

GFD: gluten-free diet

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

IgA: immunoglobulin A

IL-12: interleukin-12

MTX: methotrexate

NCGS: non-celiac gluten sensitivity

NF-κB: nuclear factor-kappa B

OBLs: osteoblasts

OCLs: osteoclasts

OPG: osteoprotegerin

PASI: Psoriasis Area Severity Index

PDB: Paget's disease of bone

PON1: paraxonase-1

PPP: palmoplantar pustulosis

PsA: psoriatic arthritis

PV: psoriasis vulgaris

RA: rheumatoid arthritis

RANK: receptor activator of nuclear factor-kappa B

RANKL: receptor activator of nuclear factor-kappa B ligand

ROS: reactive oxygen species

SAPHO: synovitis, acne, pustulosis, hyperostosis, osteitis

SpAs: spondyloarthritis

Th17: T helper 17

TNF-α: tumor necrosis factor-alpha

tTG: tissue trans-glutaminase

UC: ulcerative colitis

Wnt: wingless-related integration site

Declarations

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Author contributions

FS: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. The author read and approved the submitted version.

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The author declares that there is no conflicts of interest.

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