Review paper

The link between psoriasis and other diseases based on epidemiological and genetic analyses

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Abstract

Psoriasis is a chronic disease, which is associated with numerous genetic and environmental factors. The high prevalence of psoriasis worldwide (2–3% of the general population) and its various comorbidities lead to research on its pathogenesis. The aim of this article is to describe the current state of knowledge on the potential links between psoriasis and other diseases, such as inflammatory bowel diseases, uveitis, arthritis, hypertension, metabolic syndrome, diabetes mellitus, atherosclerosis, fatty liver disease, dyslipidaemia, sleep apnoea, celiac disease, lymphoma, erectile dysfunction, Parkinson's disease, osteoporosis, chronic obstructive pulmonary disease, psychiatric disorders and substance use. Further research in this area may lead to better treatment options in the future.

Key words: psoriasis, comorbidities, GWAS, epidemiology.

Introduction

Psoriasis has been linked to a vast number of different comorbidities. Classically it has been regarded as the disease limited to the skin; however, the more pathogenetic factors are being discovered, the wider the spectrum of its linked diseases becomes. What is undeniable is that the molecular pathways involved in psoriasis and those that lead to other diseases overlap significantly. Some of them are widely recognized by clinicians (i.e. psoriatic arthropathy, uveitis, inflammatory bowel diseases) as they share similar pathogenetic factors. Psoriasis has also been described as an independent cardiovascular risk aggravator due to chronic systemic inflammation. Some researchers even point to similar pathogenesis of the psoriatic plaque to the one found in atherosclerosis. Recent studies suggest an increased prevalence of non-alcoholic fatty liver disease, erectile dysfunction, sleep apnoea, celiac disease, lymphomas and psychological disturbances. The complete list of comorbidities is presented in Table 1. In this review we will consider possible genetic links between psoriasis and other diseases.

Table 1. Comorbidities of psoriasis

Classic – inflammatory diseases	Psoriatic arthritis Inflammatory bowel diseases Uveitis
Metabolic disorders	Metabolic syndrome Hypertension Diabetes mellitus Atherosclerosis Metabolic associated fatty liver disease Dyslipidaemia Sleep apnoea
Immune-related diseases	Celiac disease
Neoplasms	Lymphomata
Others	Erectile dysfunction Parkinson's disease Osteoporosis Chronic obstructive pulmonary disease
Psychological disorders	Psychiatric disorders, sleep disorders, depression, anxiety, suicidal behaviour Smoking habit, alcoholism

Psoriasis and classic inflammatory diseases

Psoriasis and inflammatory bowel diseases

The link between inflammatory bowel diseases (IBD) and psoriasis has been observed for decades. The research published in 2022 suggests that there is a link between IBD and both psoriasis and psoriatic arthritis (PsA). Patients with psoriasis have a greater risk of developing IBD that include Crohn's disease (CD) and ulcerative colitis (UC) [1]. Both diseases share similar

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treatment patterns and are often treated with immunosuppressants. Other common features are epidemiological characteristics, genetic susceptibility loci and immune mechanisms [2].

Frieder *et al.* found that biologics inhibiting the interleukin (IL) 17 (IL-17) pathway proved effective in treating psoriasis and PsA. However, concerns have been raised about their potential to exacerbate IBD symptoms [3]. Some authors report that these drugs may induce CD or UC [4, 5].

In 1990 Lee *et al.* suggested a genetic link between psoriasis and CD and proposed that extraintestinal symptoms of CD should include psoriasis [6]. Li *et al.* tested psoriasis sample sets for 5q31 variants associated with psoriasis and CD showing a strong relationship [7].

Psoriasis and uveitis

The association between psoriasis and eye disorders has been observed for a long time, especially in the case of PsA. In 1976, the relationship between uveitis and PsA was first described by Lambert and Wright [8]. Uveitis is the inflammation of the uvea, which consists of three areas: the iris, the choroid and the ciliary body. The coexistence of inflammation is also observed in uveitis with psoriasis regardless of arthritis [9]. Uveitis is most common in patients with PsA and its concomitance with pustular psoriasis is often observed [10]. The HLA-B*27 is a common risk locus for PsA and uveitis [11]. HLA haplotypes such as the HLA-B51 gene were found in patients with psoriasis and uveitis [12]. Chandran *et al.* found a prevalence of uveitis in 2% of patients with psoriasis, regardless of the severity of the dermatosis [13]. Durrani *et al.* suggest the isolation of a separate clinical entity – the so-called psoriatic uveitis [14]. Paiva *et al.* reported that 67% of patients with PsA and uveitis were HLA-B27 positive [15]. Therefore, certain cytokines play a role in the pathogenesis of psoriasis and uveitis: tumor necrosis factor α (TNF-α), IL-17, IL-23, IL-22, IL-12, IL-6, and helper T cells (Th1, Th17) [16, 17]. Köse *et al.* found that psoriasis-associated uveitis can be chronic, bilateral, with heavy progression and a high relapse rate. Thus, the dermatologists must be vigilant and refer their psoriasis patients to an ophthalmologist for periodic checkups even if they exhibit no ocular symptoms [18].

Psoriasis and metabolic disorders

Psoriasis and atherosclerosis

The relationship between psoriasis and increased risk of cardiovascular events has been well documented. The issue was addressed in European guidelines on cardiovascular disease prevention [19]. Due to common pathogenetic pathways involving chronic inflammation and Th1 and Th17 activation, a link between the two comorbidities is observed [20]. The IL-23 gene rs2066808 polymorphism was associated with an increased incidence of psoriasis [21] and premature coronary artery disease [22]. On the other hand, a SNP rs11209026 G/A in IL-23R (with reduced receptor signal transmission) was described to be protective against atherosclerosis progression [23].

In 2021 Su *et al.* identified common differentially expressed genes (DEGs) of atherosclerosis and psoriasis in gene expression profiles downloaded from the Gene Expression Omnibus (GEO) database, which pointed out 16 hub genes in the pathogenesis of both conditions – LYN, CSF2RB, IL1RN, RAC2, CCL5, IRF8, C1QB, MMP9, PLEK, PTPRC, FYB, BCL2A1, LCP2, CD53, NCF2 and TLR2 [24].

Psoriasis and obesity

The link between obesity and psoriasis has been long observed. Recent meta-analyses proved that a higher body mass index (BMI) increased the odds ratio of psoriasis occurrence. Moreover, obesity itself exacerbated psoriasis severity and was linked to lower response in patients treated with anti-TNF-α agents. Reduction in one's body mass results in reduction of skin lesion severity [25].

According to one study, BMI of > 35 kg/m^2 was associated with an increased odds ratio (OR) of 2.69 of psoriasis development in women [26]. Obesity is associated with higher blood serum leptin and resistin levels; interestingly, obese psoriatic patients had higher levels of the two hormones compared to obese non-psoriatic individuals [27].

In 2016 Greb *et al.* as well as Naito and Imafuku performed an epidemiological study on the association between the two [28, 29], which was later identified as causality in a Mendelian Randomization Study performed by Ogawa *et al.* in 2019 [30].

In 2022 Kisielnicka *et al.* found an association between psoriasis and obesity in the population of Polish patients; polymorphisms of 11 different genes were identified to have an impact on the patients' BMI, namely seven of them (rs1558902 in the FTO gene, rs696574 in CALCRL gene, rs10968110, rs4551082, rs4609724, rs9320269, and rs2338833 in unidentified genes) may cause an increase in BMI among all psoriatic patients and four genetic variants (rs1556519 in ITLN2 gene, rs12972098 in AC003006.7 gene, rs12676670 in PAG1 gene, and rs1321529) may decrease the BMI value [31]. The FTO gene was associated with a higher risk of obesity and higher PASI score in patients with psoriasis [32]. The polymorphisms of TNF-238G/A, TNF-308G/A, IL10-1082G/A, TNFAIP3, and MC4R genes were linked to a higher obesity rate in both control and psoriatic groups and with a higher risk of PsA in the latter [33]. Moreover, alleles of leptin, leptin receptor, adiponectin and omentin were linked to earlier psoriasis onset and its higher severity [34].

Psoriasis and hypertension

Some nation-wide studies have been performed in order to properly address the issue of hypertension in patients with psoriasis. The meta-analysis performed by

Armstrong *et al.* found the OR of developing hypertension to be 1.49 for severe and 1.30 for mild psoriasis compared to individuals without the disease [35]. Another population study by Kim *et al.* showed the OR to be 1.54 (and 1.18 when adjusting the results for comorbidities of dyslipidaemia, diabetes, antihypertensive medication, nonsteroidal anti-inflammatory drug use and sociodemographic factors) [36]. A French observational study showed that 26% of patients with psoriasis had hypertension [37].

Psoriasis and fatty liver disease

Up to 65% of patients with psoriasis were reported to suffer from non-alcoholic (or metabolic associated) fatty liver disease (NAFLD) [38]. A meta-analysis performed in 2022 addressed an OR of 2.03 for development of NAFLD compared to patients without psoriasis, however, no causality could be proven [39].

Psoriasis and diabetes mellitus

Patients with type 2 diabetes mellitus (T2DM) were found to be more insulin resistant than non-diabetics [40]. Wan *et al.* conducted an epidemiological study of patients with psoriasis and compared it to the control group. Comprising a group of 280 individuals with diabetes and psoriasis and 1867 with diabetes and without skin lesions, having adjusted the groups for age, sex and body mass index, the odds ratios (with 95% CI) for developing diabetes were 1.21 (1.01–1.44), 1.01 (0.81–1.26), and 1.64 (1.23–2.18) in the ≤ 2% BSA, 3–10% BSA, and > 10% BSA groups, respectively [41]. The common genetic background of psoriasis and T2DM were found in several loci related to psoriasis – to name PSORS2, PSORS3, and PSORS4 [42]. A single nucleotide polymorphism in the CDKAL1 gene was associated with a higher diabetes incidence and higher risk of psoriasis [43]. Other studies proved a link between some variants of IL-12B, IL-23R, IL-23A and higher susceptibility to both diseases [44]. An interesting study found a link in their common pathogenesis; a group of researchers led by Xiaohong investigated the STING-IRF3 pathway in mice and found a link between its upregulation and the development of psoriasis and diabetes mellitus [45]. Pleiotropy refers to a phenomenon based on the influence of a single gene on different phenotypes or various diseases. A fine example in psoriasis is the IL23R gene polymorphism. Single nucleotide polymorphisms (SNPs) at the 1p31.3 region were detected within the locus of the IL23R gene encoding the IL23 receptor p19 subunit [46], which were associated with an increased risk of psoriasis, CD, PsA and ankylosing spondylitis [47]. Chen *et al.* [48] found the association between IL-23R gene polymorphisms and idiopathic dilated cardiomyopathy, as well as left ventricular hypertrophy in the Chinese population [49]. It is worth noting that IL-23 is a heterodimer composed of a distinct p19 subunit and a p40 subunit that is shared with IL-12 [50]. The receptor complex for IL-12/IL-23 is expressed on natural killer (NK) and T cells, as well as on cells of the myelomonocytic lineage which includes dendritic cells [51]. The role of the IL-12/IL-23 pathway is proven by effectiveness in treatment of psoriasis with human monoclonal antibodies targeted against these cytokines (ustekinumab) [52]. The role of the aforementioned TNFAIP3 (TNF-α-induced protein 3) gene has been discovered in psoriasis and type 1 diabetes [53], rheumatoid arthritis [54], coronary artery disease [55], celiac disease [56], IBD [57], systemic lupus erythematosus (SLE) [58] and chronic sinusitis [59]. However, each of these units correlates with a different polymorphism within TNFAIP3. The aforementioned TRAF3IP2 was also found to be linked with higher susceptibility for PsA [60].

Psoriasis and sleep apnoea

Both psoriasis and sleep apnoea are considered to be inflammation-mediated conditions and are linked with general higher mortality [61]. A nation-wide Danish study assessed the incidence rate ratios (IRRs) between psoriasis and sleep apnoea. The IRRs (with 95% confidence intervals) for sleep apnoea were 1.30 (1.17–1.44), 1.65 (1.23–2.22), and 1.75 (1.35–2.26) for patients with mild, severe psoriasis and PsA, respectively [62]. In a review based on numerous observational studies the prevalence of the sleep apnoea syndrome in psoriatic patients varied between 36% and 81.8%, compared with a ratio of 3-7% in the general population [63].

Immune-related diseases

Psoriasis and celiac disease

Many studies have attempted to find a link between psoriasis and celiac disease, but the results have not been conclusive. Acharya *et al.* conducted a systematic review with meta-analysis of available reports to assess the relationship between psoriasis vulgaris and celiac disease. In patients with psoriasis, the occurrence of celiac disease is determined by the OD of 2.16, while in patients with celiac disease, the occurrence of psoriasis is determined by the OD of 1.8. They found a significant association between psoriasis and CD. Therefore, in patients with psoriasis, who report gastrointestinal complaints, there are indications for including celiac disease in the differential diagnosis [64].

Researchers emphasize that a gluten-free diet may be helpful in some patients with psoriasis. In people with celiac disease, a gluten-free diet does not only relieve gastrointestinal symptoms, but also reduces the severity of psoriasis [65].

Psoriasis and cancers

Psoriasis and lymphoma

Patients with psoriasis are at increased risk of several types of lymphomas.

Researchers found a significantly higher risk of Hodgkin lymphoma (HL) and cutaneous T-cell lymphoma (CTCL) in patients with psoriasis. However, the absolute risk of developing lymphoma associated with psoriasis is low [66]. CTCL affects approximately 0.4–1.0/100,000 individuals per year [67–69] and HF about 2–3 in 100,000 people [70, 71].

In the United States as well as in Europe, there have been many previous studies on the risk of lymphoma in patients with psoriasis [72, 73]. Trafford *et al.* conducted a meta-analysis assessing the impact of psoriasis, especially severe psoriasis, on the development of cancer. The most specific locations of neoplastic processes in patients are: colon (RR = 1.18), colorectum (RR = 1.34), kidney (RR = 1.58), larynx (RR = 1.79), liver (RR = 1.83), oesophagus (RR = 2.05), oral cavity (RR = 2.80), and pancreas (RR = 1.41). The study also found that mortality from carcinomas of the liver, pancreas and oesophagus was elevated in people with severe psoriasis [74]. The co-occurrence with other forms of blood neoplasms has also been brought into attention [75]. It is hard to deduct whether it is psoriasis itself or common psoriasis treatments, such as UVR and immune-suppressing medications that may be associated with a higher risk of cancer.

Others

Psoriasis and erectile disorder

Potency disorders or impotence are most often defined as the inability to obtain and maintain an erection sufficient for a satisfactory sexual intercourse. The low incidence of psoriatic lesions in the genital area does not explain the dangerous prevalence of sexual dysfunction [76]. Gupta *et al.* (1997) found that erectile dysfunction was present in 40.8% of patients with psoriasis [77]. Patients with psoriasis are more likely to experience depression, decreased libido and low self-esteem [78]. Kędra *et al.* investigated to what degree psoriasis, its severity, location and extent of skin lesions affect sexual dysfunction. They showed that the use of approved scales in dermatology (such as DLQI – Dermatology Life Quality Index, IIEF – International Index of Erectile Dysfunction, PASI – Psoriasis Area and Severity Index) should contribute to the quick identification of patients with sexual dysfunctions [79].

The researchers analysed data from 28 studies involving more than 52,520 patients with psoriasis and 1,806,022 million people without psoriasis. Five of eight studies have shown an association between erectile dysfunction and psoriasis [80].

Psoriasis and Parkinson's disease (PD)

For this purpose, the Parkinson's risk database was analysed during the 5-year observation period after the diagnosis of psoriasis, using population data from Taiwan. The researchers identified 4,885 patients with psoriasis and randomly selected 24,425 patients as a control cohort. Compared to the general population, psoriasis patients had a hazard ratio of 1.74 regardless of the patient's sex. Limitations of the study included the lack of information on the severity of psoriasis or on specific factors such as smoking, body mass index, alcohol consumption and dietary patterns [81].

In 2022, Li *et al.* found that psoriasis accelerates the overall progression of PD and increases the risk of depression and dementia associated with PD. The aim of the investigators was to assess the causal role of psoriasis in the progression of PD in a Mendelian randomization study [82].

Psoriasis and osteoporosis

There are few studies showing a possible link between psoriasis and reduced bone mineral density. A relationship between the two is based on common inflammatory factors in their pathogenesis, specifically TNF-α and IL-6.

In 2009, Dreiher *et al.* were the first to assess the relationship between psoriasis and osteoporosis. The incidence of osteoporosis was significantly higher in men with psoriasis compared to the control group (3.1% vs. 1.7%, OR = 1.86, $p < 0.001$), whereas no such relationship was found in women [83].

Pietrzak *et al.* discovered increased levels of TNF-α in patients with active psoriasis lesions, just as there was a correlation between serum TNF-α concentration and PASI score [84]. It has been found that TNF-α can stimulate the development of osteoclasts, thereby enhancing bone resorption. In addition, bone resorption is also stimulated by IL-6 [85]. Another factor that suggests a possible relationship between the two is osteopontin [86]. Some researchers suggest that anti-psoriatic therapy may have an impact on the course of osteoporosis. UVB phototherapy leads to improvement of the local skin condition, increases serum vitamin D concentration, but also has a beneficial effect on the bones by increasing bone mineral density [87]. Patients with PsA had significantly lower mineral density compared to people with psoriasis without arthritis [88].

Psoriasis and chronic obstructive pulmonary disease

Psoriasis and chronic obstructive pulmonary disease (COPD) are caused by similar factors. Some drugs (phosphodiesterase 4 inhibitors) are used in psoriasis, PsA and COPD alike [89].

In 2008, Dreiher *et al.* reported that COPD is more common in patients with psoriasis than in the control group (5.7% vs. 3.6%) [90].

In 2016, Ungprasert *et al.* showed that for patients with psoriasis the risk of developing COPD is 1.45 times higher than in the control group by evaluating a total of 7 studies and 331,347 patients [91].

Li *et al.* analysed 13,000 patients from four observational studies that also showed this association, but the risk was higher, particularly among patients with severe psoriasis [92].

In 2016, Balci *et al.* analysed spirometric parameters in patients with psoriasis compared to the control group. The mean ratio (FEV1/FVC) and FEF25–75% (forced expiratory flow) were significantly lower in patients with psoriasis than in the control group [93].

Psychological disorders

Psoriasis and psychiatric disorders, depression and anxiety

The link between chronic stress and exacerbations or development of many different diseases has been long observed [94] and up to 72% of patients with psoriasis experience a major psychological stress around 1 month prior to the onset of psoriatic lesions [95].

Truzzi *et al.* reports the following psychiatric conditions among psoriatic patients: sleep disorders (average prevalence of 62.0%), sexual dysfunction (45.6%), personality (35.0%), anxiety (30.4%), adjustment (29.0%), and depressive (27.6%) disorders [96]. An elevated risk of suicidal behaviour has also been described [96, 97].

Some studies show an increased prevalence of schizophrenia in psoriatic patients and a higher tendency to develop psoriasis among patients with schizophrenia [98–100]. The cumulative risk of developing psoriasis was 2.82% in patients with schizophrenia compared to 1.17% in those without the disease [101].

Another study assessed the risk for patients with schizophrenia-spectrum disorders to develop psoriasis or PsA and found no correlation between them [102].

The review conducted by Stewart *et al.* assessed a probable association between different measures of psychological stress, as well as onset, recurrence and severity of psoriasis [103], however, due to the scarcity of large population studies, the link between psyche and soma in psoriasis needs to be evaluated in further research.

Psoriasis and addictions

A study performed in Germany by Schielein *et al.* [104] shows that psoriasis patients share a greater tendency of several addictions compared to their peers without the dermatosis; that includes daily smoking (30.3% vs. 15.1%), alcohol dependence (8.6% vs. 3.1%), pathological gambling (1.2% vs. 0.2%), and legal or illegal drug abuse (6.0% vs. 3.2–5.2%) [105].

Conclusions

Psoriasis is a multidisciplinary disease not only affecting the skin, but also nearly all systems of the human body. The increased risk of psoriasis patients to develop different systemic disorders encourages dermatologists to look beyond the skin, whereas physicians of other specialties should efficiently refer patients with psoriasis to a dermatologist to properly address the patient's needs.

Conflict of interest

The authors declare no conflict of interest.

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