Psoriasis: Targets and Therapy

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REVIEW

Type 2 diabetes and psoriasis: links and risks

This article was published in the following Dove Medical Press journal:
Psoriasis: Targets and Therapy

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Abstract: Psoriasis (PsO) is one of the most common chronic inflammatory skin diseases with a world prevalence of 2%–4%. The increasing knowledge of the mechanisms driving PsO has raised focus on existing links to metabolic syndrome and type 2 diabetes (T2D). We reviewed the existing literature of the prevalence and risk of T2D in patients with PsO. The studies reviewed were mainly large retrospective cohort and case–control studies, showing an increased prevalence of T2D in PsO patients compared to controls, particularly in late onset (type 2) PsO. T2D prevalence did not correlate to patient age or severity of PsO in the reviewed studies. Conclusively, T2D was found to be more prevalent in patients with PsO compared to the background population. Several mechanisms involved in lipid transportation seem to be upregulated in PsO patients. Physicians play a key role concerning information about known comorbidity and promotion of early prophylaxis in patients with PsO.

Keywords: psoriasis, type 2 diabetes, association, risk, link

Introduction

Psoriasis (PsO) is a chronic inflammatory skin disease that affects 2%–4% of the global population.[1] The understanding of PsO as a systemic inflammatory disease along with the increasing knowledge of the mechanisms driving PsO has raised focus on existing links to metabolic syndrome and type 2 diabetes (T2D).[2] The association of PsO with inflammatory and metabolic diseases has been investigated in numerous cohort studies. In addition, earlier reviews of the literature have assessed the association between PsO and T2D.[3,4] However, the nature of the association between PsO and T2D is still ambiguous. In many studies it is unclear which disease came first, PsO or T2D. In addition, earlier studies did not group patients based on disease severity, which may have let to unclear conclusions about the true association between PsO and T2D. Herein we review studies examining the epidemiology of T2D in patients with PsO. Furthermore, we explore the possible pathophysiological links between PsO and T2D.

Study selection

We performed a search in PubMed using the keywords "psoriasis," "diabetes," "risk," "link," "association." Inclusion criteria were original, human studies written in English, focusing on the prevalence or risk of T2D in patients with PsO. Included study types were case reports, clinical studies, clinical trials, comparative studies, controlled clinical trials, multicenter studies, and randomized controlled trials. Exclusion criteria were animal studies, reviews, meta-analyses, comments on earlier publications, and studies not focusing on the direct relationship between PsO and T2D. Abstracts were read to

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Dovepress
http://dx.doi.org/10.2147/PTT.S159163

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evaluate the eligibility of the study. We intended to perform a complete and exhaustive review of the literature on T2D prevalence in PsO patients, focusing on major cohort studies.

The search in PubMed yielded a total of 1,357 hits. Exclusion of studies not written in English, animal studies, earlier reviews, and meta-analyses yielded 172 studies. All abstracts were evaluated, and 44 articles and abstracts were included (Supplementary material). The studies were published between 1995 and 2018 and included case–control studies (25/44, 56.8%), retrospective (14) and prospective (4) cohort studies (18/44, 40.9%), and a case series (1/44, 2.3%). We divided and described the studies based on their focus; epidemiological studies focusing on T2D and other comorbidities in PsO patients (40 studies), where some described pathophysiological features of PsO subtypes (7/40 studies), and mechanistic and genetic links between PsO and T2D (four studies).

T2D in PsO patients

A total of 15 studies were descriptive epidemiological cohorts, which included only PsO patients. The studies included on average 2,695 patients (range: 82–11,900) from ten different countries (Brazil,[5] Italy,[6] France,[7,8] Spain,[9,10] Thailand,[11] United Kingdom,[12] Czech Republic,[13] China,[14] Turkey,[15] and Romania[16]). Kwa et al[17] (USA) who used population registry-based admissions as a proxy measure for PsO was excluded from the analysis. The average prevalence of T2D across PsO cohorts was 11.6%, excluding Mihai et al[16] due to an inaccurate T2D prevalence measure.[16] Kimball et al,[18] who reported baseline disease characteristics in a prospective PsO cohort including 11,900 patients, was the largest non-population-based study included. They found a T2D prevalence of 11.4%, which agrees with the estimated average prevalence. Gisondi et al[6] only found a T2D prevalence of 7% in a prospective interventional study, including 10,539 PsO patients, whereas Baeta et al[5] performed a cross-sectional study on 190 Brazilian PsO patients and found a T2D prevalence of 15.4%, that is, three times that of the Brazilian background population. There was no apparent association between T2D prevalence and mean patient age (n=15, P=0.183) across the identified cohorts.

T2D in PsO patients compared with controls

The prevalence of T2D in PsO patients compared to controls was examined in eleven studies. All the eleven studies showed an increased prevalence of T2D compared to controls. Four studies used different outcomes, including impaired glucose tolerance,[19] microvascular affection,[20] waist-to-height ratio,[21] and the risk of PsO in T2D patients.[22] The studies included a median of 906 (range: 40–48,523, mean 5,579) patients and 1,230 (range: 40–208,187, mean: 24,788) controls. The mean T2D prevalence was 10.3% in patients and 6.2% in controls. Of note, Parisi et al[23] compared 48,523 PsO patients with 208,187 controls in a large case–control study and found a slightly increased prevalence of T2D in PsO patients compared to controls (5.78% vs 4.69%). Other studies showed a significant difference in T2D prevalence between cases and controls; however, a large variation in prevalence was observed between studies. Bang et al[24] reported T2D in 18.1% of patients and 12.3% of controls, whereas Sommer et al[25] reported T2D in 11.7% of patients and 5.8% of controls, both in large cohorts. The heterogeneous findings complicate a reliable estimate of the true prevalence of T2D in patients with PsO and controls but support a significantly increased prevalence of T2D in PsO patients compared to healthy individuals. Ucak et al[19] used oral glucose tolerance test instead of a diagnosis of T2D to estimate this association showing significantly impaired glucose tolerance in PsO patients, which offers a more objective para-clinical measure when comparing cohorts.

T2D and PsO severity

Earlier studies have suggested that T2D prevalence may be correlated to the severity of PsO, suggesting that lack of stratification by severity may have impacted the conclusions in earlier studies on the association between the two conditions. However, across the PsO cohorts included herein, we found no evidence supporting a correlation between T2D prevalence and mean Psoriasis Area and Severity Index (PASI) (n=5, P=0.188), suggesting that PsO is a marker for increased risk of T2D independently of its severity. Despite this finding, Lee et al[26] described that, in addition to an overall increased risk of T2D in PsO patients, the risk is modulated by both PsO severity, comorbidities and concomitant medication in a large Taiwan cohort. Also, while overt T2D is seemingly not related to severity of PsO, intermediate phenotypes underlying the risk of T2D such as insulin resistance, fasting blood glucose and hemoglobin A1C may still be associated with the severity of PsO.[27] Naldi et al[28] concluded that the association found between PsO and T2D in other studies might have been confounded by lifestyle, smoking, overweight, or long disease duration, somewhat disagreeing with Lee et al.[26] However, Mahé et al[29] showed that patients with adult onset PsO had significantly more comorbidities compared to childhood onset patients. Therefore, long duration of disease may

not be a risk factor as much as lifestyle. Supporting these findings, Karoli et al[30] suggest that otherwise healthy PsO patients should take preventive measure toward modifiable risk factors, since the prevalence of systemic comorbidities is higher regardless of age of onset, however, associated with lifestyle choices.

T2D in patients with PsO and psoriatic arthritis (PsA)

Concomitant PsA is seen in up to 30%[31] of PsO patients and represents a systemic affection of psoriatic inflammation. This inflammatory upregulation possibly characterizes part of the metabolic component that links PsO to increased risk of T2D. In a large case–control study Dubreuil et al[32] showed that PsO and PsA are both associated with risk of diabetes when adjusted for obesity and lifestyle factors, which agrees with Solomon et al[33] who found an increased incidence rate of T2D in PsO + PsA as well as rheumatoid arthritis (RA) patients compared to controls, supporting the systemic nature of PsO. Despite the lack of correlation between PsO severity and risk of T2D, a study by Edson-Heredia et al[34] found that patients with mild PsO were less affected by comorbid conditions than severe PsO patients. In addition, PsO patients were generally less affected than PsA patients. However, several studies showed no difference in the risk or prevalence of T2D in patients with PsA + PsO compared to patients with PsO alone.[35,36] Dubreuil et al[32] found that increased risk of diabetes in PsA was partially explained by obesity and lifestyle factors (alcohol and smoking) and that PsA and PsO were associated with the risk of diabetes when adjusted for obesity and lifestyle factors. This supports that the presence of PsA in patients with PsO mainly indicates a surplus of systemic inflammatory involvement, since autoimmune disorder prevalence, including T1D, does not differ between PsO and PsO + PsA patients.[36] Husted et al[36] also suggest that increased cardiovascular (CV) risk in patients with PsA is mainly attributable to hypertension and not diabetes. A certain overlap may exist and supposedly studies need to consider a larger number of related conditions with relevance to the metabolic syndrome and CV disease to properly assess the correlation with PsO.

Other metabolic complications in PsO patients

PsO is associated with several other metabolic complications, including hypertension, the metabolic syndrome, and overt heart disease. Understanding these associations play a significant role in optimizing treatment, comorbidity prophylaxis, and patient education. Karoli et al[30] compared 96 PsO patients with 100 controls and found that the prevalence of comorbidities associated with the metabolic syndrome (T2D, hyperlipidemia, and hypertension), including diagnosis of metabolic syndrome as a whole, was significantly increased in PsO patients (40% vs 22%).[30] Agreeing with these findings, Phan et al[7] found increased prevalence of hypertension, T2D, and dyslipidemia in French PsO patients compared to the general population. Karoli et al[30] suggested preventive measures in otherwise healthy PsO patients, whereas Wan et al[37] only suggested T2D prevention efforts in PsO patients with a body surface area of PsO >10%. However, Parisi et al[23] found that despite significantly higher BMI in patients with PsO compared to controls, PsO was not associated with CV events, when adjusting for comorbidities.

Bang et al[24] state that PsO predicts new-onset atrial fibrillation, proposing how studies should delineate this association and determine the need for screening. However, Parisi et al[23] found neither PsO nor severe PsO to be associated with risk of major CV events over 3–5 years after adjusting for known CV risk factors.[23] Whether this is due to a relatively short follow-up period is unclear, but Mehta et al[38] support the CV risk by a significantly more prevalent history of stroke and myocardial infarction in patients with PsO compared to controls. In addition, Karoli et al[30] found that carotid thickness was associated with PsO, hypertension, T2D, and insulin resistance, all comprising the metabolic syndrome. This supports the presence of not only CV risk factors in PsO patients but also clinically measurable CV disease. Given that PsO manifests as a multisystem disease, Baeta et al[5] suggest a comprehensive and multidisciplinary approach. The documented association with CV comorbidities may occur due to various factors such as the chronic inflammatory state of the disease, genetic susceptibility, and environmental factors and/or related to the quality of life or effects of drugs used for systemic therapy. Thus, prevention of risk factors associated with CV disease, especially in patients with severe disease and long disease duration, is recommended.[15,39] In addition, Gisondi et al[6] stress the importance of how choice of treatment should be weighed against the benefit and risks for each patient to ensure optimal management of symptoms and minimize acute and cumulative toxicities.

T2D and sub-types of PsO

Non-pustular PsO can be categorized as type 1 or type 2 based on the age at onset (early or late-onset).[40] These subtypes and their respective immunological profiles as well as their differ-

ent risks of T2D have been examined in seven of the included studies. Henseler and Christophers[40] compared almost 3,000 PsO patients with other dermatological inpatients and found that diabetes, as well as obesity and heart failure, was more frequent in PsO compared to age-matched controls. In addition, they found increased resistance to cutaneous bacterial infections in early onset PsO patients and that cutaneous immune disorders such as contact and atopic dermatitis (AD) and urticaria are underrepresented in PsO patients, compared to control subjects with other dermatological conditions. They proposed that this resistance to infection was due to Cw6-haplotype (type 1, early onset). This agrees with the findings by Christophers[41] who found that early onset PsO was dominated by certain leukocyte antigens (Cw6, B13, and Bw57), whereas late-onset PsO showed a different profile (Cw2 and B27) suggesting that PsO, immunologically, is not a single disease. Both Sommer et al[25] and Mahé et al[29] showed greater risk of T2D in type 2 PsO compared to type 1, and Ucak et al[19] showed impaired glucose tolerance mainly in type 2 PsO patients. Phan et al[8] found that early onset of PsO in the elderly was associated with comorbidities. Theodorakopoulou et al[42] found type 2 PsO to be associated with T2D. Lastly, Xu et al[14] found that metabolic disorders related to lipids were predominant in T1D, whereas type 2 PsO showed higher prevalence of T2D. Type 1 and type 2 PsO show certain differences with T2D prevalence as the most apparent. Further research is warranted on the immunological diversities between PsO subtypes.

The similarities and differences between PsO and related diseases have also been the focus of other studies. Radtke et al[43] found several diseases including asthma, vitiligo, and attention deficit/hyperactivity disorder to be more prevalent in AD compared to PsO, whereas diseases included in the metabolic syndrome were higher in PsO patients. These findings support newer pathomechanistic knowledge on the difference between PsO and AD, where barrier protective interleukins are downregulated in AD, but upregulated in PsO.[44,45]

Mechanistic links between PsO and T2D

Mechanistic and genetic links between PsO and T2D have been described in several smaller studies.

Cheung et al[46] analyzed and compared miRNA in lesional with non-lesional skin in a small case series of seven PsO patients. They found miRNA related to cholesterol efflux upregulated in lesional skin, believed to serve as a mechanistic link between psoriatic skin inflammation and comorbidities. Levels of the lipid transportation protein clusterin was compared between 15 moderate–severe PsO patients and controls by Buquicchio et al,[47] who found increased levels in PsO patients. Both the studies support how certain relevant metabolic mechanisms differ from healthy controls, though the significance of this is uncertain. The knowledge on what role these findings play in PsO and associated metabolic comorbidity is not yet understood, however, different studies agree that patients with PsO show upregulation of metabolites associated with increased CV risk.[48]

Theodorakopoulou et al[42] compared type 1 to type 2 PsO patients based on demographics and phenotypes and found an increased lymphocytic infiltration in T1D patients. In addition, they showed that CD4+:CD8+ lymphocyte ratio was highest in T2D patients. The immunological differences between subtypes warrant further research. Lastly, Mihai et al[16] included 82 Chinese PsO patients for genetic expression analysis. They measured levels of a panel of single-nucleotide polymorphisms (SNPs) in cytokine encoding genes and compared the levels to disease severity, though without any significant findings. Still, two SNPs were associated with T2D, one of which has been associated with PsO and PsO severity in a Chinese cohort.[49] They concluded that certain variants in cytokine encoding genes influence multiple organ systems, which should stimulate research about the development of metabolic syndrome in PsO patients.

The knowledge of the genetic mechanisms involved in systemic complications and comorbidities in PsO patients is sparse. Now when the pathomechanisms of PsO are described in increasingly more detail and with the disease being controlled well with biological therapies, the management of complications and comorbidities is the next challenge. Therefore, knowledge of mechanistic links between PsO and T2D should be investigated, focusing on possible therapeutic targets. In addition, continuous knowledge on PsO comorbidities are important to track and adjust preventive efforts.

Conclusion

It is well established that T2D is more prevalent in patients with PsO compared to the background population. However, the systemic inflammatory nature of PsO is believed to include multiple organ systems, accounting for the metabolic diseases associated with PsO. The exact mechanistic links between the two conditions are not entirely understood and warrant further research. However, an increasing amount of literature has investigated both metabolic and genetic links believed to connect these diseases. Physicians play a key role in concerning information regarding known comorbidity risk and promotion of early prophylaxis in patients with PsO.

Disclosure

The authors report no conflicts of interest in this work.

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