The Prevalent Comorbidome at the Onset of Psoriasis Diagnosis

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ABSTRACT

Introduction: Psoriasis (PsO) is currently regarded as a systemic inflammatory disease with a growing burden of post-diagnosis associated comorbidities. To determine the initial burden of comorbiditis we evaluated the comorbidome at PsO onset.

Methods: In a matched case–control study, we extracted data on 57,228 patients and 125 morbidities from the Clalit Health Services Israeli insurance database. PsO cases were matched with control individuals by sex and age at enrolment. As pre-existing comorbidities, we considered all conditions already present in controls at the same age as the matched PsO case at the time of their diagnosis. To test for differences in the odds of comorbidities between the case and control groups, logistic regression analyses were run to calculate the odds ratio (OR) for each comorbidity, after which the comorbidome was graphically represented.

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Results: In this study we enrolled 28,614 PsO patients and 28,614 controls with an average age of 45.3 ± 19.6 years. At the time of diagnosis, PsO patients were more likely to be diagnosed with 2–4 comorbidities (28.8% vs 23.8%) and > 5 (19.6% vs 12.9%,). PsO patients' specific comorbidomes evidenced several pathological cores: autoimmune and inflammatory systemic diseases [i.e., hidradenitis suppurativa (OR 3.55, 95% CI 1.88–7.28) or polymyalgia rheumatica (OR 3.01 95% CI 1.96–4.77)], inflammatory bowel diseases [i.e., Crohn's disease (OR 2.99 95% CI 2.20–4.13)], pulmonary inflammatory diseases [i.e., chronic obstructive pulmonary disease (OR 1.81 95% CI 1.61–2.04)], hepatological diseases [i.e., cirrhosis (OR 2.00 95% CI 1.36–3.00)], endocrine diseases [dysthyroidisms (OR 1.82 95% CI 1.30–2.59)], mental disorders [i.e., depression (OR 1.72 95% CI 1.57–1.87)], and cardiovascular diseases (i.e., hypertension (OR 1.47 95% CI 1.41–1.53)].

Conclusion: The PsO-onset comorbidome may help health professionals plan more comprehensive patient management. By screening for these common PsO-linked conditions, early diagnosis and treatment may become more frequent, thus greatly benefiting patients on their medical journey.

Key Summary Points

PsO (psoriasis) patients in the vast majority of the cases are multimorbid and clinicians have to treat a complicated patient that needs a multidisciplinary approach.

Unhealthy lifestyle habits are also frequent risk factors at the onset of PsO.

Identifying these factors can help physicians better treat patients and provide appropriate therapy.

Proper education of patients could develop their awareness of the comorbidities that interact with the disease, helping them to manage their condition.

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INTRODUCTION

Psoriasis (PsO) is currently regarded as a chronic, systemic inflammatory disease [1] capable of causing several dermatologic and non-dermatologic comorbidities [2] that may influence its treatment and monitoring [2–4]. Our aging population and the spread of non-communicable diseases have made many of these comorbidities gain notoriety from a public health standpoint, due to their increasing prevalence. It is therefore important to study PsO-related multimorbidity in order to enable healthcare systems to address the growing complexities of our healthcare needs.

In a recent review by Bu and colleagues [5], the emergence of new PsO comorbidities (e.g., asthma, periodontitis, bullous diseases) was highlighted in relation to other associated pathologies (such as inflammatory bowel diseases, chronic kidney disease, and coronary artery disease). Understanding and monitoring such comorbidities, which is also known as the comorbidome, has become of paramount importance in order to choose the ideal

biological therapy and customize follow-ups. Indeed, both epidemiological studies and murine models indicate that comorbidities may influence PsO progression and vice versa [6, 7]. Multidisciplinary styles and interdisciplinary teamwork are thus essential when treating people with multiple comorbidities, in order to properly manage their illnesses [8].

Although several scientific studies have analyzed the increased odds of specific comorbidities in psoriatic patients (providing possible etiological explanations for their association with PsO), epidemiological studies on the specific characteristics of the PsO comorbidome are still lacking. The aim of this research was to compare the pre-existing multimorbidity profile of psoriatic patients with that of non-psoriatic matched controls.

METHODS

Clinical Data

This matched case–control study was conducted on 57,228 subjects, drawn from the Clalit Health Services Israeli database, recording all people registered to the insurance from 1 January 2002 to 31 December 2017. All patients diagnosed with PsO at the time of recruitment (December 2017) were defined as a case group and a random selection of control subjects, without a diagnosis of PsO at the same time, (1:1), previously matched for sex (gender at birth) and age, were selected.

Clalit is the Israeli state's largest health organization, charged with administering health services and funding its members. The database currently includes the healthcare records of 4.6 million patients collected over 14 hospitals and 1300 primary care clinics. Data collection captures demographic information (i.e., gender or date of birth) and diagnoses according to the methods previously described [9], including specific data related to these diagnoses. Differently from other dermatoses, PsO has its own label and its data extraction has been validated in the literature [10, 11].

Data on 125 comorbidities were also extracted from the same source, and were related to cardiovascular, endocrine, metabolic, gastrointestinal, hematologic, kidney, infection, mental health, musculoskeletal, nervous system, ocular, reproductive system, respiratory system, skin, rheumatic, autoimmune, and lifestyle related diseases and malignancies.

The current study focuses only on pre-existing comorbidities, considering all prevalent conditions that were present at the time of PsO onset. In controls, disorders that were present at the same age as when the matched psoriatic patients got their diagnosis were considered.

Statistical Analysis

Descriptive statistics on sex, age, and comorbidities were first obtained with categorical variables represented as frequencies. Means, medians, and standard deviation were applied to summarize continuous numerical variables (with SD).

The prevalence rates for each pre-existing morbidity were calculated as percentages together with their 95% binomial confidence intervals for proportions. Differences in comorbidity prevalence between case and control groups were then evaluated with a two proportion Z-test. Univariate logistic regression was performed to assess the odds ratio (OR) for each comorbidity in psoriatic subjects compared with non-psoriatic subjects. Results were considered statistically significant at 0.001, which takes into account the multiple tests performed.

The comorbidome was then plotted, graphically representing all comorbidities that had a statistically significant association with PsO onset ($p < 0.001$). The size of each bubble is proportional to the prevalence of the disease in the psoriatic cohort, while proximity to the center (psoriasis) expresses the strength of the association between the comorbidity and PsO diagnosis [this was numerically obtained as the inverse of the OR (1/OR)]. All circles relating to a disease with an increased occurrence in the psoriatic group fall inside the dashed orbit (1/OR < 1), while morbidities with a decreased prevalence are outside (1/OR > 1).

R 4.0.4 was used to conduct statistical analyses. Data preparation and visualization were performed in Python 3.8.8.

Ethical Approval Statement

The Human Investigation Committee (IRB) of Ben-Gurion University of the Negev, Beersheba, Israel, approved this study and granted an exemption from informed consent.

RESULTS

Demographic characteristics

PsO patients ($N = 28,614$) and controls ($N = 28,614$) were matched for age and gender. The mean age was 45.3 (SD ± 19.6) years, 50.5% of the subjects were male (see Table 1).

Table 2 reports comorbidity prevalence in PsO patients and controls. The prevalence analysis revealed that, of those diagnosed with PsO, 28.70% (28.17–29.22) were smokers, 28.40% (27.87–28.92) already had hyperlipidemia, 22.10% (21.65–22.62) had hypertension, and 16.10% (15.70–16.55) were obese. Diabetes was also found to be one of the most frequent comorbidities in psoriatic patients, at 11.34% (10.98–11.72).

The pathologies linked most strongly with PsO were arthritis (OR = 3.81, $p < 0.001$), hidradenitis suppurativa (OR = 3.55, $p < 0.001$), polymyalgia rheumatica (OR = 3.01, $p < 0.001$), sarcoidosis (OR = 3.00, $p < 0.001$), as well as Crohn's disease (OR = 2.99, $p < 0.001$), celiac disease (OR = 2.03, $p < 0.001$), and cirrhosis (OR = 2.00, $p < 0.001$); these all had odds ratios ≥ 2.00.

These comorbidities are summarized as a graphical comorbidome (Fig 1).

Table 1 Sample characteristics

Characteristic	PsO ($N = 28,614$) Value %	Control ($N = 28,614$) Value %	Total ($N = 57,228$) Value %
Age			
Mean ± SD	45.30 ± 19.60	45.30 ± 19.60	45.30 ± 19.60
Median (min–max)	47.00 (0–97)	47.00 (0–97)	47.00 (0–97)
Sex			
Male n (%)	14,464 (50.50%)	14,464 (50.50%)	28,928 (50.50%)
Female n (%)	14,150 (49.50%)	14,150 (49.50%)	28,300 (49.50%)
N. pre-existing morbidity			
Mean ± SD	2.48 ± 3.01	1.81 ± 2.62	2.15 ± 2.84
Median (min–max)	1 (0–25)	1 (0–23)	1 (0–25)
N. pre-existing morbidity (classes)			
0 n (%)	8980 (31.40%)	12,232 (42.70%)	21,212 (37.10%)
1 n (%)	5789 (20.20%)	5890 (20.60%)	11,679 (20.40%)
2–4 n (%)	8232 (28.80%)	6797 (23.80%)	15,029 (26.30%)
5 + n (%)	5613 (19.60%9	3695 (12.90%)	9308 (16.30%)

Table 2 Pre-existing comorbidity prevalence rates and odd ratios with 95% confidence interval (CI) in psoriatic subjects compared to non-psoriatics

Comorbidity	PsO (*N* = 28,614)		Control (*N* = 28,614)		OR* (95% CI)	
	n	Prevalence % (95% CI)	*n*	Prevalence % (95% CI)		
Autoimmune and inflammatory systemic diseases						
Arthritis	456	1.59 (1.45; 1.75)	121	0.42 (0.35; 0.51)	3.81	(3.13; 4.68)
Hidradenitis suppurativa	39	0.14 (0.10; 0.19)	11	0.04 (0.02; 0.07)	3.55	(1.88; 7.28)
Polymyalgia rheumatica	78	0.27 (0.22; 0.34)	26	0.09 (0.06; 0.13)	3.01	(1.96; 4.77)
Sarcoidosis	45	0.16 (0.12; 0.21)	15	0.05 (0.03; 0.09)	3.00	(1.72; 5.57)
Inflammatory bowel diseases						
Crohn's disease	155	0.54 (0.46; 0.63)	52	0.18 (0.14; 0.24)	2.99	(2.20; 4.13)
Celiac disease	95	0.33 (0.27; 0.41)	47	0.16 (0.12; 0.22)	2.03	(1.44; 2.90)
Ulcerative colitis	111	0.39 (0.32; 0.47)	60	0.21 (0.16; 0.27)	1.85	(1.36; 2.55)
Pulmonary inflammatory diseases						
Chronic obstructive pulmonary disease	772	2.70 (2.51; 2.89)	432	1.51 (1.37; 1.66)	1.81	(1.61; 2.04)
Asthma	1895	6.62 (6.34; 6.92)	1413	4.94 (4.69; 5.20)	1.37	(1.27; 1.47)
Hepatological disease						
Cirrhosis	74	0.26 (0.20; 0.33)	37	0.13 (0.09; 0.18)	2.00	(1.36; 3.00)
Chronic active/persistent hepatitis	160	0.56 (0.48; 0.65)	83	0.29 (0.23; 0.36)	1.93	(1.49; 2.53)
Hepatitis C carrier	202	0.71 (0.61; 0.81)	120	0.42 (0.35; 0.50)	1.69	(1.35; 2.12)
Reflux esophagitis/ gastritis/duodenitis	1683	5.88 (5.61; 6.16)	1255	4.39 (4.15; 4.63)	1.36	(1.26; 1.47)
Peptic ulcer	1241	4.34 (4.10; 4.58)	988	3.45 (3.24; 3.671)	1.27	(1.16; 1.38)
Endocrine diseases						
Hypo/hyperparathyroidism	91	0.32 (0.26; 0.39)	50	0.18 (0.13; 0.23)	1.82	(1.30; 2.59)
Hypothyroidism	1599	5.59 (5.33; 5.86)	1111	3.88 (3.66; 4.11)	1.47	(1.36; 1.59)
Gout	258	0.90 (0.80; 1.02)	158	0.55 (0.47; 0.65)	1.64	(1.35; 2.00)
Osteoporosis	1293	4.52 (4.28; 4.77)	1107	3.87 (3.65; 4.10)	1.18	(1.08; 1.28)
Mental disorders						
Depression	1635	5.71 (5.45; 5.99)	974	3.4 (3.20; 3.62)	1.72	(1.59; 1.87)
Anxiety	1210	4.23 (4.00; 4.47)	718	2.51 (2.33; 2.70)	1.72	(1.56; 1.89)
Neuroses	715	2.5 (2.32; 2.69)	575	2.01 (1.85; 2.18)	1.25	(1.12; 1.40)
Cardiovascular and metabolic diseases						
Carotid artery disease	273	0.95 (0.85; 1.07)	165	0.58 (0.49; 0.67)	1.66	(1.37; 2.02)

Table 2 continued

Comorbidity	PsO (N = 28,614)		Control (N = 28,614)		OR* (95% CI)	
	n	Prevalence % (95% CI)	n	Prevalence % (95% CI)		
Hypertension	6333	22.10 (21.65; 22.62)	4645	16.2 (15.81; 16.67)	1.47	(1.41; 1.53)
Peripherical vascular disease	519	1.81 (1.66; 1.98)	357	1.25 (1.12; 1.38)	1.46	(1.28; 1.68)
Diabetes	3247	11.40 (10.98; 11.72)	2339	8.17 (7.86; 8.50)	1.44	(1.36; 1.52)
Arrhythmia	1022	3.57 (3.36; 3.79)	736	2.57 (2.39; 2.76)	1.40	(1.28; 1.55)
Hyperlipidemia	8124	28.40 (27.87; 28.92)	6455	22.60 (22.08; 23.05)	1.36	(1.31; 1.41)
Ischemic heart disease	2355	8.23 (7.91; 8.56)	1778	6.21 (5.94; 6.50)	1.35	(1.27; 1.44)
Systemic/peripherical cerebrovascular accident	773	2.70 (2.52; 2.90)	619	2.16 (2.00; 2.34)	1.26	(1.13; 1.40)
Valvular cardiac disease	783	2.74 (2.55; 2.93)	629	2.20 (2.03; 2.38)	1.25	(1.13; 1.39)
Retinopathy	597	2.09 (1.92; 2.26)	482	1.68 (1.54; 1.84)	1.24	(1.10; 1.40)
Environmental and lifestyle-related conditions						
Obesity	4613	16.10 (15.70; 16.55)	2923	10.20 (9.87; 10.57)	1.69	(1.61; 1.78)
Smoking	8209	28.70 (28.17; 29.22)	6021	21.00 (20.57; 21.52)	1.51	(1.45; 1.57)
Other						
Deafness	487	1.70 (1.56; 1.86)	326	1.14 (1.02; 1.27)	1.50	(1.31; 1.73)
Malignancy	1515	5.30 (5.04; 5.56)	1209	4.23 (3.99; 4.47)	1.27	(1.17; 1.37)
Prostatic hypertrophy	1041	3.64 (3.42; 3.86)	871	3.04 (2.85; 3.25)	1.20	(1.10; 1.32)

*Reference control group, p-value < 0.001

Pathologies that were not statistically associated ($p \geq 0.001$) with PsO were: oncology diseases (breast cancer, urine bladder cancer, kidney cancer, ovarian cancer, oral cancer, esophageal cancer, thyroid cancer, lung cancer, Hodgkin's lymphoma, liver cancer, chronic leukemia, melanoma, benign brain tumor, bone cancer, prostate cancer, cancer of genitalia, gastric cancer, laryngeal cancer, neck cancer, myeloma, sarcoma, neurofibromatosis, acute leukemia, polycythemia vera, lymphoproliferative cancer, colon cancer, myelodysplastic syndrome), chronic renal failure, aortic aneurism, irritable bowel syndrome, infertility, joint replacement, Behcet's disease, chronic heart failure, hepatitis B carrier, muscular dystrophy, cardiomyopathy, hyperthyroidism, congenital anomalies, pemphigus vulgaris, pulmonary embolism, pulmonary hypertension, familial Mediterranean fever, head of femur fracture, syphilis/gonorrhea, hereditary neurological disease, Parkinson's disease, myasthenia gravis, dialysis, disability, tuberculosis, motor neuron disease, epilepsy, Wilson disease, systemic lupus erythematosus, glaucoma, scleroderma, psychoses, Gaucher disease, Addison's disease, cerebral palsy, multiple sclerosis, bronchiectasis, dementia, Alzheimer's disease, amyloidosis, idiopathic hypertrophic sub-aortic stenosis, hyperprolactinemia, pneumothorax, blindness, acromegaly, retinitis, pigmentosum, cystic fibrosis

DISCUSSION

The present study indicates that the vast majority of psoriasis cases are multimorbid and thus, at the time of PsO diagnosis, clinicians are already having to treat a complicated patient needing a multidisciplinary approach. The conditions most associated with PsO onset were autoimmune and inflammatory diseases (i.e., rheumatoid arthritis, hidradenitis suppurativa, polymyalgia rheumatica, sarcoidosis, and Crohn's disease), followed by pulmonary
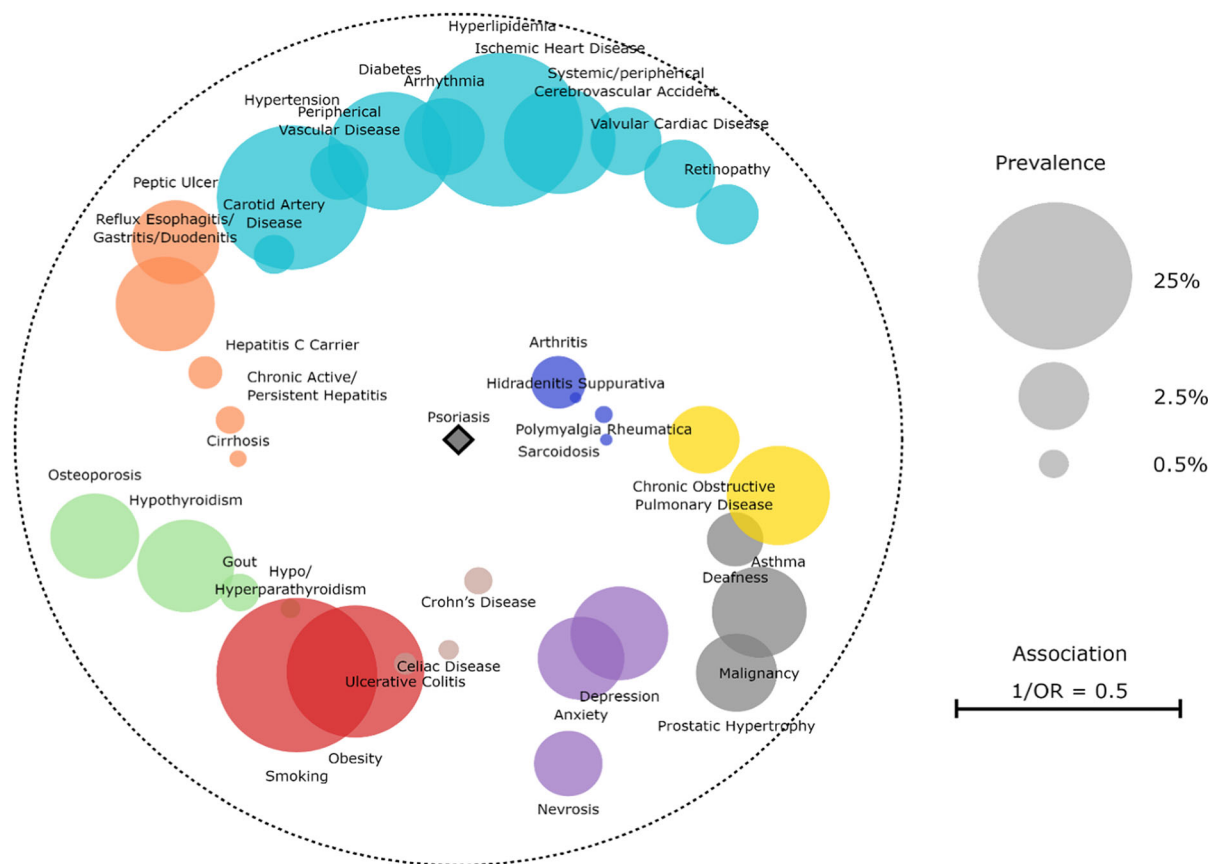
Fig. 1 The PsO comorbidome. The size of each *bubble* is proportional to the prevalence of the disease. The proximity to the center expresses instead the strength of the association between the morbidity and the PsO diagnosis and is the inverse of the OR. The *dashed orbit* corresponds to a radius OR = 1. All *circles* relating to a disease with an increased occurrence among the psoriatic group fall inside that orbit (1/OR < 1); vice versa, morbidities with a decreased prevalence are outside (1/OR > 1)

inflammatory diseases and endocrine diseases. Looking at overall PsO, the most prevalent cluster of comorbidities included metabolic and cardiovascular diseases.

Previous research has already investigated the relationship between psoriasis and other systemic inflammatory diseases, highlighting the existence of a common pathogenic pathway in which chronic inflammation and proinflammatory cytokines play a significant role [12, 13] (as summarized in *The Mosaic of Autoimmunity* by Shoenfeld [14]). In line with the scientific literature, our data showed that a cluster of systemic inflammatory diseases (including arthritis, hidradenitis suppurativa, polymyalgia rheumatica, and sarcoidosis) had

the strongest overall association with PsO. A quality study by Wu and colleagues [15] also confirmed this correlation, reporting an OR of 3.6 (95% CI [3.4–3.9]), which is close to the 3.81 found in our study. These inflammatory pathways may also be key in the pathogenesis of hidradenitis suppurativa (HS). In a Danish study that compared patients with and without this disorder, patients with HS had an OR of 2.99 (95% CI [2.04–4.38]) of having PsO. The author found that both PsO and HS show increased levels of IL-12/23 and TNF-α, which are known important hallmarks of inflammation [16]. Moreover, it has been demonstrated that psoriasis may share susceptibility genes with sarcoidosis due to the existence of polymorphisms

in the IL23R gene [17, 18]. Since the TH1 and TH17 pathways are thought to play a role in many inflammatory cutaneous disorders (including psoriasis, sarcoidosis, and hidradenitis suppurativa), this association between PsO and HS may be explained by this common pathway [19, 20].

Inflammatory bowel diseases are also associated with PsO in situations such as Crohn's disease. A previous review recognized that PsO is strongly associated with inflammatory bowel disease because of genetic anomalies, immune dysfunction, systemic inflammation, and dysregulation of the gut microbiota [21]. Moreover, it has been reported that PsO and inflammatory bowel disease share genetic susceptibility loci on chromosome 6p21, which corresponds to PSORS1 in psoriasis and IBD3 in inflammatory bowel disease [22].

Our data also highlight a strong association between COPD and the onset of psoriasis. Similar to the other inflammation-related diseases previously discussed, findings by Wang and colleagues [23] confirm that patients with COPD (as well as those with psoriasis) exhibit an imbalance between T17 and Treg. Levels of IL-1, IL-6, IL-8, and C-reactive protein (CRP) are highly elevated in COPD and are associated with the severity of the disease, a finding which is also seen in psoriasis [24]. Genetic susceptibility may also influence pulmonary-related diseases, with findings from previous research suggesting that loci for asthma and psoriasis may be partially overlapped [25–28]. Furthermore, the smoking habits of PsO patients, which are statistically higher than in the control group, could also directly trigger or worsen COPD, since PsO patients display subclinical airway inflammation [29].

Regarding liver diseases, the etiopathological link between these conditions and PsO is still not entirely clear, but a recent mouse model suggests a potential mutual influence in terms of flares [30]. It has also been previously reported that hepatic injury biomarkers and inflammatory biomarkers such as GM-CSF, iNOS, and ICAM-1 are increased in psoriatic inflammation [7]. Moreover, since PsO and hepatitis C virus (HCV) share pathophysiological factors, it is possible that the overproduction of TNF-α in

HCV may trigger the onset of psoriasis [31]. Indeed, a study by Chun et al. [32] emphasized that patients with PsO and hepatitis C have higher levels of cutaneous inflammatory genes than patients with psoriasis alone. Compared with HCV-negative psoriatic patients, those with HCV infection have higher levels of cathelicidin, TLR9, and are IFNcofHCV-positive, suggesting that HCV infection may increase the risk of developing PsO.

Hypothyroid and parathyroid diseases were also found to be associated with PsO in our study, a finding that appears consistent with several previous studies. Indeed, one study showed that psoriatic patients have higher levels of thyroid peroxidase antibodies and thyroglobulin antibodies [33]. Psoriasis has also been successfully treated with propylthiouracil (an antithyroid preparation) on both the local [34] and systemic levels [35]. Other researchers found that patients with unbalanced thyroid function had a more severe form of PsO than those with euthyroid psoriasis. This may be due to direct or indirect effects of thyroid hormones on PsO, as well as the fact that excessive production of thyroid hormones could aggravate PsO due to their proliferation-promoting effects [36]. Similarly, there have been reported cases of generalized PsO associated with hypoparathyroidism, in which patients have benefited from calcium and vitamin D5 treatment [4, 37, 38]. These hormonal imbalances that influence the onset and development of psoriasis, although rare, have not yet been fully explained.

The association between PsO development and osteoporosis, although statistically significant, appears to be on the weak side in our cohort of patients. Limited studies have analyzed this association, and the results are controversial [18, 39]. Data from our study suggest that osteoporosis could be a facilitating factor for the development of PsO. Similarly, previous research has suggested that a lack of vitamin D (a vitamin which helps the body absorb calcium) could affect the development of PsO due to its impact on the immune chain as well as proliferative modulative effects [40, 41]. It should be noted that both psoriasis and osteoporosis have been proven to be associated with TNF-α and IL-6 dysregulation, as well as with

metabolic syndrome [40, 42, 43]. These findings may suggest a common pathogenetic pathway underlying these two conditions.

Continuing further with this PsO/inflammation link, our data also suggest an association between PsO and mental disorders. Indeed, it has been found that a pre-existing diagnosis of major depressive disorder is a significant risk factor for the diagnosis of PsO [44]. One hypothesis is that a systemic inflammatory component is involved in the etiology of depression in both humans and mice. Proinflammatory cytokines such as interleukin IL-1 and IL-6 are elevated in subjects with depression, suggesting that the inflammatory process contributes to these psychological comorbidities rather than psoriasis itself causing these disorders [45]. This means that psychiatric disorders may be triggered by PsO duration, where a state of systemic inflammation persists for a long time.

Similarly, both PsO and vascular disease are characterized by chronic inflammation and proinflammatory cytokines [46]. A number of pathogenic features shared by cardiovascular disease and PsO (including immunological processes, inflammation, and proinflammatory cytokines) contribute to the development of psoriatic lesions as well as to atherosclerotic plaques [47]. Triggered by local and systemic inflammatory cells as well as the release of proinflammatory cytokines, psoriatic lesions are a common symptom of PsO [48, 49].

Overall, hyperlipidemia, hypertension, diabetes, and obesity emerged as the most frequent comorbidities among the psoriatic patients in our study. While these comorbidities are also classically associated with systemic inflammation, other possible links seem to be possible as well. In a Japanese study by Shiba et al., diabetes mellitus, hyperlipidemia, hypertension, and myocardial infarction were more prevalent in patients that had psoriasis [50]. Another study showed that patients with cardiovascular disease who use beta-blockers and angiotensin-converting enzyme inhibitors have an increased risk of developing PsO (or to have a worsening of the disease) [51]. An association between PsO and the ACE insertion/deletion polymorphism (which is associated with a myriad of disorders,

including diabetes and heart disease) was also observed in a case–control study [39]. These studies indicate that there may be an indirect correlation between the use of drugs targeting these pathways and PsO onset.

Many of these metabolic issues are often related to lifestyle and environmental factors, some of which are also known risk factors for PsO onset [52]. Our data showed a very strong association between PsO and obesity, followed by smoking. Again, this can be traced back to inflammation — according to several studies, pro-inflammatory adipokines such as TNF-α, IL-6, leptin, and adiponectin secreted by adipose tissue contribute to the pathogenesis of PsO [3, 53]. Another prospective study on female nurses in the US confirmed that higher BMI and weight gain are risk factors for incident psoriasis [54]. Recent studies have also shown that obesity increases IL-17A, IL-22, and Reg3 in mice, possibly contributing to the occurrence of psoriasiform dermatitis [55], and that weight loss can be a possible method for reducing PsO severity in overweight individuals [56]. Similarly, common cytokine pathways may also explain the relationship between PsO and gout [57], where increased levels of Th1 and Th17 cytokines (as well as high serum levels of uric acid) were found in both PsO [58] and gout [59] patients. However, a convincing etiopathological explanation of the strong association between these two conditions has not yet been provided [57].

Other environmental factors can also contribute to PsO. Indeed, oxidative stress induced by air pollutants, including ultraviolet radiation, polycyclic aromatic hydrocarbons, volatile organic compounds, oxides, particulate matter, ozone, and cigarette smoke, have been identified as determinants of several human skin diseases [60]. Our study shows that approximately one out of four patients (28.7%) with PsO is a smoker. PsO is particularly common among heavy smokers as well as those who have smoked for a long time, according to a recent review and meta-analysis of 16 case–control studies [61]. A cross-sectional study in Italy also revealed that patients who smoke more than 20 cigarettes a day are twice as likely to present

severe PsO compared with those who smoke less than ten cigarettes per day [62].

With regard to the association of malignancies (cancerous growths) with PsO, it has been hypothesized that immune check point inhibitors and molecular inhibitors may alter the immune system and, therefore, lead to the development of psoriasis [3]. Moreover, psoriasis can also be triggered by biologic drugs targeting tumor necrosis factor TNF-α, interleukin (IL)-23, or IL-17, through a paradoxical reaction that is thought to occur as a consequence of a cytokine imbalance caused by the blockage of immune signaling pathways [3]. Lastly, our study showed an association between deafness and PsO, suggesting that there may be a common pathogenetic pathway underlying these two diseases. To our knowledge, however, no previous scientific literature has investigated this hypothesis, leaving this as an area for future research. Another area of further investigation is a possible common pathway between prostatic hypertrophy and psoriasis, owing to recent scientific research showing that patients with prostatic hypertrophy could benefit from treatments with TNF-antagonists [63, 64].

Limitations and Strengths

Our study is based on an Israeli population that is split into Jewish and Arabic sub-populations, so future data will need to confirm our results in other patient subsets. Administrative data is usually collected for purposes other than research investigations, and thus could be less accurate than clinical data. Nevertheless, the use of such databases does have a major benefit, in that the use of routinely collected data minimizes the risk of selection bias, thus providing a useful insight into psoriasis in the general population.

CONCLUSION

Our current study describes the comorbidome found in PsO patients when they are first diagnosed with PsO. Psoriasis can be induced or exacerbated by a variety of factors, including genetics, comorbidities, and lifestyle.

Identifying these factors can assist clinicians in better counselling patients about PsO, while simultaneously providing clues as to the pathogenesis of the disease. Due to the wide range of therapies associated with this comorbidome, all systemic PsO treatments should account for every individual's ongoing drug prescriptions, lifestyle, and comorbidities. Lastly, by understanding the importance of major PsO comorbidities, while also being aware of their clinical interactions with PsO itself, patients could become active and well-informed participants in the management of their condition.

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