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PSORIASIS (J WU, SECTION EDITOR)

Enteropathy in Psoriasis: A Systematic Review of Gastrointestinal Disease Epidemiology and Subclinical Inflammatory and Functional Gut Alterations

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Abstract

Purpose of Review Psoriasis in an inflammatory skin disorder associated with systemic inflammation. This systematic review summarizes the epidemiology, histology, and function of the gastrointestinal (GI) system in patients with psoriasis.

Recent Findings Although psoriasis patients are at higher risk for developing inflammatory bowel disease and celiac disease, estimates of their prevalence have varied and it is unclear whether psoriasis patients without GI symptoms may harbor subclinical inflammation.

Summary In a meta-analysis, the pooled prevalence of Crohn disease, ulcerative colitis (UC), and celiac disease among patients with psoriasis was 0.4, 0.5, and 2%, respectively. The pooled prevalence of psoriasis among patients with Crohn disease was 9.5% and among patients with UC was 6.6%. A significant proportion of psoriasis patients harbor lymphocytic infiltrates in the small and large intestine; 40–50% of the psoriasis patients demonstrate abnormal intestinal absorption based on fecal fat, D-xylose, and lactose tolerance tests. These results suggest that the inflammatory state of psoriasis may in some patients extend to the GI tract.

Keywords Psoriasis · Crohn disease · Ulcerative colitis · Celiac disease · Systematic review · Prevalence

Introduction

Psoriasis is a chronic inflammatory skin disease affecting approximately 2 to 4% of the US population [1••, 2]. Increasing evidence has shown that psoriasis involves systemic inflammation, with various studies demonstrating elevated levels of circulating inflammatory markers, such as C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1 in psoriasis

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patients [3–6]. Additionally, affected individuals demonstrate increased vascular inflammation as revealed by FDG-PET [7–10]. This systemic inflammation is reflected in the comorbidities that psoriasis patients are at increased risk of developing, including psoriatic arthritis, metabolic syndrome, diabetes, obesity, and atherosclerosis [11].

Tumor necrosis factor-α (TNF-α) has been implicated to play a key role in both psoriasis and inflammatory bowel disease (IBD). Anti-TNF-α antibodies such as adalimumab and infliximab have demonstrated efficacy in treating these inflammatory diseases [12–14]. Similarly, the IL12/23 inhibitor ustekinumab is approved for the treatment of both psoriasis and Crohn disease. Genetic links have been observed between psoriasis and IBD, with polymorphisms in or near *IRF5*, *IL12B*, *REL*, *TYK2*, *JAK2*, *ZMIZ1*, *PRDX5*, *SOCS1*, *STAT3*, *FUT2*, and *YDJC* shared between these diseases [15–17]. In addition, the *IL23R* gene has been implicated as a susceptibility locus for psoriasis, IBD, and celiac disease [18–20]. Thus, chronic inflammation in psoriasis and inflammatory GI disease have been proposed to operate along shared pathways.

This review aims to detail the association between psoriasis and three inflammatory diseases of the gut: Crohn disease, ulcerative colitis (UC), and celiac disease. Additionally, this review examines studies assessing inflammatory and functional changes in the GI tract of psoriasis patients to elucidate whether a subset of psoriasis patients without overt GI disease harbor subclinical intestinal inflammation.

Methods

Epidemiology of GI Disease Among Psoriasis Patients

A systematic review of MEDLINE and EMBASE health literature databases was examined for articles describing the epidemiology of GI disease among psoriasis patients. Articles published prior to October 31, 2017, were first screened by abstract and title for relevant information, and those that met inclusion criteria were further examined. Articles were included if subjects had physician-diagnosed psoriasis or psoriatic arthritis (PsA) and had either physician-diagnosed Crohn disease, UC, or celiac disease that described epidemiological data. Studies were excluded if they examined drug-induced psoriasis or GI disease, sampled non-human subjects, were of foreign language, or were not full publications (conference abstracts, commentaries, or letters to editor). Additionally, for robustness, we only included studies with a sample size of greater than 100 patients. Four reviewers (IS, EY, KB, CL) independently screened articles for inclusion (Figure S1), and discrepancies were resolved by an additional reviewer (WL). Study and participant characteristics as well as epidemiological results were extracted using a standardized data form designed for this review topic.

Subclinical GI Inflammatory and Functional Alterations

A separate systematic review of the literature was performed, using MEDLINE and EMB1ASE databases for observational studies of gastrointestinal biopsies in psoriasis patients or evaluation of malabsorption in psoriasis (fecal fat excretion, D-xylose, lactose tolerance test). Additional relevant articles were found by manually inspecting references. The included articles were limited to English language and human subject studies published before May 1, 2016. To be eligible for inclusion, the original studies needed to fulfill the following criteria: clinical trial, case-control, or cross-sectional design; and evaluation of gastrointestinal mucosal histology or architecture or absorption in conjunction with psoriasis. Two reviewers (WJ and RS) independently extracted the data and performed the review. Any discrepancies were adjudicated by WL. For each study included in the final analysis, the following were recorded: study design, geographic location, study size, methods used, and results.

Statistical Analysis

The frequencies were tabulated and data were analyzed using STATA Special Edition version 14.2 (College Station, TX). A random-effects meta-analysis was used to pool prevalence estimates of Crohn disease, UC, or celiac disease while accounting for variability. The DerSimonian-Laird random-effects method was used where counts for diseased and the sample size were provided. Statistical significance was ascertained if $p < 0.05$. To examine study heterogeneity, I^2 was used to characterize studies by the Higgins and Thompson classification for interpreting variability between studies, where low, medium, and high heterogeneity was determined by an I^2 of $\leq 25\%$, 50%, and $\geq 75\%$, respectively [21].

Results

Epidemiology of GI Disease Among Psoriasis Patients

An initial search of the literature describing the epidemiology of GI disease among psoriasis patients yielded 696 articles (Figure S1). After duplicates were removed, 483 publications were screened for inclusion by title and abstract. Finally, 24 reports were included for analysis, 12 of which were case-control studies, 7 cohort studies, and 5 cross-sectional studies (Table S1).

There were 16, 14, and 9 studies that described Crohn disease, UC, and celiac disease, respectively, among patients with psoriasis. IBD was unspecified in five studies [22, 23••]. Overall, there were 231,401 psoriasis patients and 7,881,207 total subjects from all studies; 1150 patients had Crohn disease, 1305 had UC, and 29,029 had celiac disease. Most studies were of adults, with only 3 studies including 34,816 total children, of which 2942 had psoriasis or psoriatic arthritis [24, 25••, 26••].

From the 19 articles that provided demographic information, the average age of study subjects was 46.1 years and 49% were male. 23.2% of the subjects were smokers among 7 studies, while the average proportion of patients with hypertension was 12.4% from 3 studies [23••, 24, 25••, 27, 28••, 29, 30••, 31••, 32••, 33]. Ethnicity was not commonly described, with only two articles reporting these data. Specifically, one US and Canadian study reported a majority of Caucasian (93.9%) and 3.3% Hispanic children [26••]. Another study in Israel noted an 88.6% Jewish and 11.4% Arabic population [32••]. Most studies were from Italy (36%), followed by the USA (21%), Canada, Germany, Israel, and Sweden (14% each, respectively) [22, 24, 26••, 27, 29, 30••, 32••, 33, 34, 35••, 36–40]. Other countries represented were Denmark, Ireland, Korea, Morocco, Netherlands, Scotland, Spain, and Taiwan [23••, 25••, 28••, 41••, 42–44]. The majority of publications were from the World Health Organization Region of Europe (67%) and the Americas (17%), while a minority were from the Western Pacific (8%) and Eastern Mediterranean (4%) [45].

The prevalence was reported for Crohn disease, UC, celiac disease, and unspecified IBD among psoriasis (Table 1). Combining the results in a meta-analysis, the pooled prevalence for Crohn disease was 0.4% (0.2–0.5%), for UC was 0.5% (0.2–0.7%), and for celiac disease was 2% (0.5–3.5%) (Fig. 1). The prevalence of IBD or celiac disease for the general population was reported by several studies, of which the pooled general prevalence for Crohn disease was 0.3% (0.1–0.4%), for UC was 0.4% (0.4–0.5%). One study reported the prevalence of celiac disease in general as 0.1% [37].

The pooled prevalence for psoriasis among Crohn disease was 9.5% (5.8–13.3%) and 6.6% for UC (3.0–10.2%). In a sensitivity analysis examining the impact of geographic region, the pooled prevalence of Crohn disease and UC among patients with psoriasis was unchanged when studies from the Western Pacific region were excluded.

The risk of having GI disease in psoriasis patients compared to non-psoriatic controls was examined among several studies. In Italy, the odds ratio (OR) for Crohn disease was 2.5 (1.7–3.6), adjusted for age and gender [27]. The reported risk ratio (RR) for Crohn disease was 5.2 (2.8–9.6) in the USA and 0.7 (0.5–0.9) in Taiwan [29, 42]. For UC, the adjusted OR was 1.6 (1.2–2.3) in Italy and the adjusted RR in the USA was reported as 1.7 (0.4–7.0) [27, 29]. The OR for celiac disease was 2.7 (1.6–4.5) in an Israeli study and in an Italian study the OR was 11.3 (1.4–90.1) [35••, 37].

Several studies reported the prevalence ratio (PR) to examine how GI disease differs in patients with psoriasis compared to those without psoriasis. In Germany, the PR for Crohn disease was noted as 2.1 (1.8–2.3) among adults and 3.7 (2.2–6.4) in children with psoriasis [24, 33]. In the USA, the PR for Crohn disease was 1.6 (1.4–2.0) [22]. For UC, the PR was 1.9 and 1.1 in psoriatic adults and children within Germany, respectively, and 1.3 in the USA [22, 24, 33]. Similarly, the PR for unspecified IBD was 1.4 (1.2–1.6) [22].

Some publications explored the association of psoriasis among patients with GI disease (Table S2). The pooled prevalence of psoriasis among patients with Crohn disease was 9.5% (5.8–13.3%) and 6.6% among UC (3.0–10.2%). In a sensitivity analysis, the removal of the outlier Augustin et al. study of children altered the pooled prevalence results for psoriasis among Crohn disease and UC (13.9% [4.8–23.0%] and 11.1% [3.5–18.7%], respectively). One Swedish study noted that the prevalence of psoriasis among celiac disease was 1.4% and the hazard ratio of developing psoriasis among celiac disease patients was 1.7 (1.5–1.9) among adults and 2.1 (1.6–2.6) among children and calculated an attributable risk of 42% [40].

There were four articles that exclusively examined GI disease among PsA patients [26••, 32••, 38, 39]; while several studies included additional data on PsA (Table 2) .[22, 23••, 28••, 29, 35••, 41••]. The prevalence of Crohn disease, UC, celiac disease, and unspecified IBD among PsA cohorts were 2.6, 0.9, 3.1, and 2.2%, respectively. One PsA study reported the prevalence of IBD or celiac in the general population for Crohn disease, UC, and celiac disease as 0.6, 0.4, and 0.2%, respectively [32••]. The adjusted OR was 2.2 for Crohn disease, 1.9 for UC, and 1.5 for celiac disease [32••]. The RR was 6.5 for Crohn disease in a US population-based study [29].

Interestingly, a few studies examined the temporality of psoriasis onset in comparison to GI disease. Psoriasis developed before IBD in 17 cases, developed at the same time in 4 patients, and developed after IBD in 2 persons [31••, 44]. Interestingly, the severity of psoriasis was different when the onset of psoriasis was prior to Crohn disease (62%) or UC (80%) compared to after the diagnosis of IBD (23%) [44]. When psoriasis preceded IBD, the Psoriasis Area Severity Index (PASI) score was significantly higher than when compared to controls without IBD (12.8 vs. 4.4, $p < 0.001$); however, there was no difference in psoriasis severity when psoriasis occurred after IBD onset (4.0 vs. 4.4, $p = 0.35$) [31••].

Histologic Appearance and Lymphocytic Infiltration of Intestinal Mucosa in Psoriasis

A total of 850 articles were identified from the initial search of subclinical GI inflammation. After reviewing abstracts, 36 full-text articles were further evaluated, and 23 articles were included for analysis.

Table 1 Epidemiology of GI disease among psoriasis patients

Author, year	Study period	Country	Prevalence, % (95% CI)		Effect (95% CI)
			Psoriasis	General population	
Crohn disease					
Augustin 2010 [24]	2005–2005	Germany	0.92	0.45 (0.4–0.5)	PR, 2.06 (1.8–2.3)
Augustin 2010 (children) [33]	2005–2005	Germany	0.51	–	PR, 3.69 (2.2–6.4)
Cohen 2009 [27]	–	Italy	0.51; 20–39 years: 1.1, 40–59 years: 0.4, ≥ 60 years: 0.3	0.20 (0.1–0.3)	OR[a], 2.49 (1.7–3.6)
Egeberg 2016 [28••]	1997–2012	Denmark	0.22	0.20 (0.2–0.2)	IRR[a], 1.96 (1.7–2.3)
Eppinga 2017 [41••]	2009–2014	Netherlands	0.70 (0.4–1.3)	–	–
Li 2013 [29]	1996–2008	USA	0.50	0.23 (0.2–0.3)	RR, 5.2 (2.8–9.6); RR[a], 5.8 (3.1–10.6)
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 1.6 (1.4–2.0)
Park 2014 [31••]	1990–2012	Korea	0.04	–	–
Tsai 2011 [42]	2006–2006	Taiwan	0.10	–	RR, 0.66 (0.5–0.9)
Vanaclocha 2015 [23••]	2008–2012	Spain	0.2 (0.0–1.0)	–	–
Ulcerative colitis			–	–	
Augustin 2010 [24]	2005–2005	Germany	1.09	0.56 (0.5–0.6)	PR, 1.91 (1.7–2.1)
Augustin 2010 (children) [33]	2005–2005	Germany	0.12	–	PR, 1.13 (0.4–3.3)
Cohen 2009 [27]	–	Italy	0.48; 20–39 years: 0.4, 40–59 years: 0.5, ≥ 60 years: 0.5	0.28 (0.2–0.3)	OR[a], 1.64 (1.2–2.3)
Egeberg 2016 [28••]	1997–2012	Denmark	0.53	0.55 (0.5–0.6)	IRR[a], 1.73 (1.6–1.9)
Eppinga 2017 [41••]	2009–2014	Netherlands	0.80 (0.5–1.4)	–	
Li 2013 [29]	1996–2008	USA	0.15	0.31 (0.3–0.3)	RR, 1.6 (4.0–6.7); RR[a], 1.7 (0.4–7.0)
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 1.3 (1.1–1.6)
Park 2014 [31••]	1990–2012	Korea	0.05	–	–
Vanaclocha 2015 [23••]	2008–2012	Spain	0.80 (0.3–1.9)	–	–
Celiac disease					
Birkenfeld 2009 [37]	–	Israel	0.29; 20–39 years: 0.5, 50–59 years: 0.3, ≥ 60 years: 0.2, male: 0.2, female: 0.4	0.11 (0.1–0.1)	OR, 2.7 (1.6–4.5); OR[a], 2.7 (1.7–4.5)
De Bastiani 2015 [35••]	–	Italy	4.1; male: 4.5, female: 3.7		OR, 11.3 (1.4–90.1)
Kelati 2017 [25••]	2014–2016	Morocco	1.8	–	–
Kia 2007 [46]	2004–2005	USA	2.0	–	–
Ojetti 2006 [36]	–	Italy	3.6	–	–
Woo 2004 [43]	–	Ireland	2.3	–	–
Unspecified IBD					
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 1.4 (1.2–1.6)
Vanaclocha 2015 [23••]	2008–2012	Spain	1.3	–	–

CI confidence interval, *IBD* inflammatory bowel disease, *IRR* incidence risk ratio, *OR* odds ratio, *PR* prevalence ratio, *RR* rate ratio

[a] Adjusted for age and sex

Mucosal biopsies from psoriasis patients were obtained from the duodenum, jejunum, and ileocolon in 9, 11, and 3 studies, respectively. Mucosal classification of biopsies was based on an observer's assessment of stereomicroscopic and

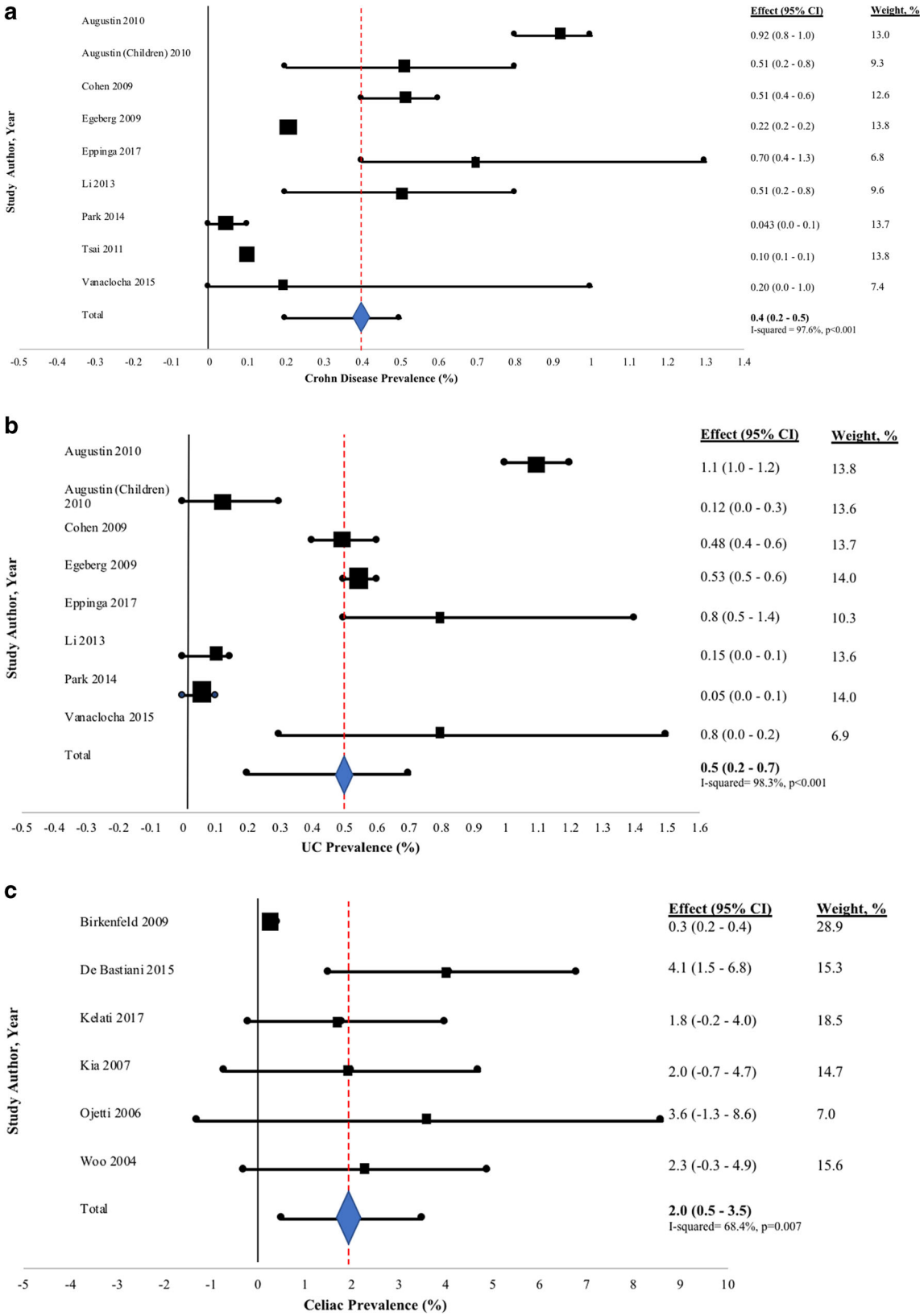

Fig. 1 Forest plot of GI disease prevalence in psoriasis. **a** Pooled prevalence of Crohn disease among psoriasis patients. **b** Pooled prevalence of UC among psoriasis patients. **c** Pooled prevalence of celiac disease among psoriasis patients. **d** Pooled prevalence of psoriasis among Crohn disease patients. **e** Pooled prevalence of psoriasis among UC patients

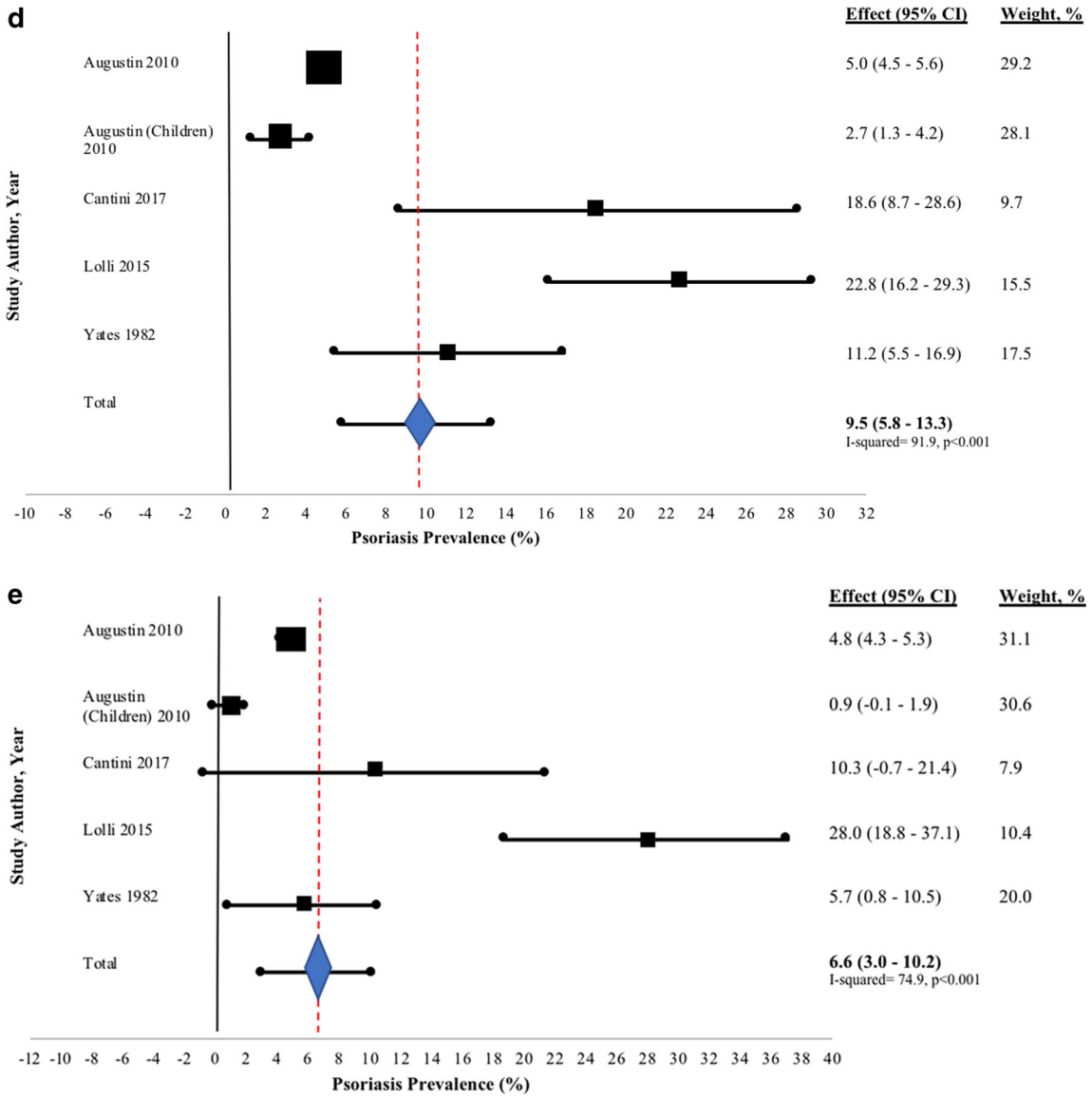

Fig. 1 (continued)

histologic appearance and is summarized as follows: (1) normal: predominantly fingers and narrow leaves; (2) abnormal (a) grade I: cylindrically shaped villi are solely present (b) grade II: leaf-shaped villi are also present (c) grade III: ridge-shaped villi are also present (d) grade IV: convolutions are also present in 21 of 23 studies (91%) reported psoriasis to be significantly associated with abnormal histologic appearance of intestinal mucosa (Table 3) [63]. Half of the psoriasis patients who had undergone duodenal biopsies had significant mucosal lymphocytic infiltration. Additionally, several studies noted an increased number of mast cells and eosinophils in duodenal mucosa of psoriasis patients, especially in those with concomitant psoriatic arthritis [37, 50, 53].

One jejunal study commented on the presence of mucosal lymphocytes, noting 100% of the psoriasis patients to have abnormally high lymphocytic infiltration. A separate study evaluated cell proliferation kinetics in jejunal epithelium and found significantly higher labeling indices in subjects with psoriasis compared to healthy controls ($p < 0.01$) [55].

Three studies examined ileocolic lymphocytic infiltration in patients with psoriasis. Combining all studies, only 30% of the psoriasis patients had significantly elevated levels. However, one study reported a significantly higher prevalence of microscopic inflammatory gut lesions in patients with psoriasis compared to controls [65].

Intestinal Malabsorption Studies in Psoriasis

A total of 17 studies evaluating intestinal malabsorption in psoriasis patients were reviewed. Six measured fecal fat excretion, seven measured D-xylose tolerance, and four measured lactose tolerance (Table 4). Other less commonly

Table 2 Epidemiology of GI disease among psoriatic arthritis patients

Author, year	Study period	Country	Prevalence, %		Effect (95% CI)
			Psoriasis	General population	
Crohn disease					
Egeberg 2016 [28••]	1997–2012	Denmark	–	–	IRR, 3.40 (2.30–4.91); IRR[a], 3.40 (2.35–4.93)
Eppinga 2017 [41••]	2009–2014	Netherlands	1.97	–	
Kraishi 2011 [38]	2008–2010	Canada	6.70	–	SRR, 11.4 (1.4–21.3)
Li 2013 [29]	1996–2008	USA	0.09	–	RR, 6.5 (2.1–20.7)
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 2.1 (1.3–3.3)*
Zohar 2016 [32••]	2002–2013	Israel	1.5	0.62	OR, 2.4 (1.8–3.3); OR[a], 2.2 (1.6–3.0)
Ulcerative colitis					
Egeberg 2016 [28••]	1997–2012	Denmark	–	-	IRR, 2.45 (1.87–3.20); IRR[a], 2.42 (1.85–3.16)
Eppinga 2017 [41••]	2009–2014	Netherlands	0.99	–	–
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 2.0 (1.3–3.1)*
Zohar 2016 [32••]	2002–2013	Israel	0.73	0.35	OR, 2.1 (1.3–3.3); OR[a], 1.9 (1.2–3.0)
Celiac disease					
De Bastiani 2015 [35••]		Italy	4.65	–	–
Lindqvist 2002 [39]	1997–1999	Sweden	4.40	–	–
Zohar 2016 [32••]	2002–2013	Israel	0.35	0.23	OR, 1.5 (0.8–2.8)
Unspecified IBD					
Eppinga 2017 [41••]	2009–2014	Netherlands	3.0	–	–
Makredes 2009 [22]	2001–2002	USA	–	–	PR, 1.8 (1.3–2.5)*
Vanaclocha 2015 [23••]	2008–2012	Spain	–	–	OR and RR, 1.75 (0.98–2.98)
Zisman 2017 [26••]	2010–2013	USA, Canada	1.4	–	–
Zohar 2016 [32••]	2002–2013	Israel	2.2	–	–

CI confidence interval, *IBD* inflammatory bowel disease, *IRR* incidence rate ratio, *OR* odds ratio, *PR* prevalence ratio, *PsA* psoriatic arthritis, *SRR* standardized rate ratio

*Statistically significant at $p < 0.05$

[a] Adjusted for age and sex

reviewed tests include ^{51}Cr-labeled EDTA absorption, standard cellobiose/mannitol permeability, jejunal tissue aryl hydrocarbon hydroxylase (AHH) activity, sucrose tolerance, and folic acid absorption.

There was a total of 113 psoriasis patients for whom fecal fat excretion was measured. 43% had documented steatorrhea. Similarly, there were 6 D-xylose tolerance tests, accounting for 140 psoriasis patients with abnormal D-xylose excretion in 40%. Finally, a joint analysis of four lactose utilization studies resulted in 52% of the patients with significant lactose intolerance.

Testing of ^{51}Cr-labeled EDTA absorption and microsomal AHH activity revealed psoriasis patients to have less ^{51}Cr-labeled EDTA absorption and AHH activity [68, 70]. Additionally, 24% of the psoriasis patients were noted to have an abnormal cellobiose/mannitol recovery ratio, while 41% of the patients had impaired folic acid absorption [69, 71].

Discussion

The association of comorbidities among psoriasis has been well established; however, there have been few studies that synthesize studies reporting the prevalence or association of Crohn disease, UC, or celiac disease within psoriasis patients [73, 74•]. Though the mechanism of potential shared risk between psoriasis and GI disease remains unknown, factors such as shared genetics and similar intestinal microbiomes may play a role [17, 75].

Overall, the pooled prevalence of Crohn disease, UC, and celiac disease in psoriasis is greater than in the general

Table 3 Studies of intestinal mucosal structure in patients with psoriasis

Study	Study design	Region	Total number of study cases	Method of study; position of mucosa	Key results (number of patients from intestinal mucosal biopsy)
Lindqvist 2006 [47]	Case-control	Sweden	35 PsV patients 19 PsA patients 11 IBS patients	H, I Gastric and duodenal mucosa	32% (6/19) PsA patients had a highly significant increase of mononuclear cell in the epithelium (score ≥ 2–3). 42% (8/19) PsA patients had a slight increase (score 1–2). 53% (10/19) PsA patients had an increase of eosinophilic cells. 43% (12/28) AGA-positive PsV patients showed a slight increase in number of mononuclear cell infiltrates in the epithelium (score 1–2). 7% (2/28) anti-EMA-positive PsV patients showed a pronounced increase in lymphocytes (score 2–3).
Woo 2004 [43]	Cross section	UK	130 PsV patients	H Duodenal mucosa	3.8% (5/130) had elevated serum IgG AGA; 8.5% (11/130) had elevated serum IgA AGA; 7.7% (10/130) had elevated serum IgA TGA. 2.8% (3/130) had celiac disease. 11% (1/9) AGA-positive PsV patient had villous atrophy and increased intraepithelial lymphocytes. 100% (3/3) AGA-negative PsV patients had normal duodenal histology.
Ojetti 2003 [48]	Cross section	Italy	92 PsV patients	H Duodenal mucosa	7.6% (7/92) were AGA positive. 100% (7/7) AGA-positive PsV patients had an increased number of lymphocytes in the duodenal epithelium. 57% (4/7) AGA-positive PsV patients had villous atrophy.
Khardikova 2002 [49]	Cross section	Russian	20 PsV patients	H, E Duodenal bulb mucosa	20% (4/20) PsV patients had atrophic gastritis. 25% (5/20) PsV patients had chronic duodenitis. 10% (2/20) PsV patients had scary deformation of the duodenal bulb.
Michaëlsson 2000 [50]*	*Clinical trial*	Sweden	33 PsV patients (AGA-positive) 6 PsV patients (AGA-negative)	H Duodenal mucosa	45% (15/33) AGA-positive patients showed an increased number of lymphocytes in the duodenal epithelium, while no such increase was seen in 100% (6/6) of AGA-negative patients. 13% (2/15) of AGA-positive patients had villous atrophy. 0% of the AGA-negative patients had villous atrophy. Most patients had an increased number of mast cells and eosinophils in the duodenal stroma.
Michaëlsson 1997 [51]*	Cross section	Sweden	43 PsV patients (35 AGA positive and 8 AGA negative) 10 healthy controls	H, I Duodenal mucosa	35% (14/40) patients who underwent biopsy showed abnormal lymphocyte in filtration (score ≥ 1) in the intraepithelial duodenum. 65% (26/40) patients who underwent biopsy had normal lymphocyte infiltration (score < 1). 43% (16/37) patients who underwent biopsy had duodenal mast cell score ≥ 1. 57% (21/37) patients who underwent biopsy had duodenal mast cell score < 1.
Michaëlsson 1997 [52]*	Case-control	Sweden	37 PsV patients 19 IBS patients	H,I Duodenal mucosa	65% (24/37) PsV patients were AGA positive. 68% (25/37) PsV patients had a normal score (0 to <1), with no increase in mononuclear cells in the epithelium. 19% (7/37) PsV patients had a score of 1–2 and 13% (5/37) scored > 2–3.
Michaëlsson 1996 [53]*	Cross section	Sweden	39 PsV patients 8 IBS patients	H, I Duodenal mucosa	The mean number of EG2+ cells per section (94 +/− 55) in 36 PsV patients was significantly higher than the mean number of EG2+ cells per section (23 +/− 1 32) in 8 patients with IBS.
	Cross section	Sweden	39 PsV patients	H, I	36% (14/39) PsV patients had an IEL score > 1.

Table 3 (continued)

Study	Study design	Region	Total number of study cases	Method of study; position of mucosa	Key results (number of patients from intestinal mucosal biopsy)
Michaelsson G 1995 [54]*			33 AGA-positive 6 AGA-negative	The duodenum distal to the papilla of Vater	21% (8/39) PsV patients had an IEL score > 1–2, 10% (4/39) PsV patients had an IEL score > 2–3 and 5% (2/39) PsV patients had an IEL score > 3. 100% (14/14) of patients with IEL score > 1 were AGA positive.
Hendel 1984 [55]	Case-control	Denmark	5 PsV patients 5 healthy controls	H, F Jejunal mucosa	Significantly higher small intestinal LI in PsV patients vs. health controls group ($p < 0.01$).
Hendel 1982 [56]	Cross section	Denmark	15 PsV patients	H, DM Jejunal mucosa	27% (4/15) PsV patients had increased fecal fat excretion. 40% (6/15) PsV patients had abnormal D-xylose absorption. 38% (5/13) PsV patients who underwent jejunal biopsy had abnormal surface (grade 3) appearance under dissection microscope. 46% (6/13) PsV patients who underwent jejunal biopsy had abnormal histological appearance.
Bansal 1980 [57]	Cross section	Indian	23 PsV patients	H, DM Jejunal mucosa	43% (10/23) PsV patients had abnormal gross appearance of jejunal mucosa under dissecting microscope (grades I and II). 78% (18/23) PsV patients had abnormal histopathological appearance (grades I–III).
Bedi 1974 [58]	Case-control	Indian	5 patients with pustular psoriasis 19 PsV patients	H Jejunal mucosa	21% (4/19) PsV patients with extensive psoriasis had abnormal jejunal histology. 100% (5/5) pustular psoriasis patients had normal jejunal histology.
Madanagopalan 1973 [59]	Case-control	Indian	14 PsV patients 15 Other patients	H, DM Jejunal mucosa	100% (14/14) PsV patients had abnormal mucosal appearance under a dissection microscope (grades II–III). 71% (10/14) PsV patients had abnormal histological appearance (partial villous atrophy).
Barry 1971 [60]	Case-control	England	22 PsV patients 20 healthy controls 15 ill controls	H, S Jejunal mucosa	45% (10/22) PsV patients had abnormal mucosal appearance (grades III and IV). 45% (10/22) PsV patients had abnormal mucosal appearance (grade II). 70% (14/20) controls had grade II appearance. 15% (3/20) controls had grade III or IV appearance.
Roberts 1971 [61]	Cross section	Germany	14 PsV patients	H, DM The level of the ligament of Treitz or from the first loop of jejunum	43% (6/14) PsV patients had abnormal jejunal mucosal morphology (blunted villi).
Themann 1970 [62]	Cross section	Germany	10 PsV patients	H, E Jejunal mucosa	40% (4/10) PsV patients had grade III abnormal histological appearance on light microscopy (partial villous atrophy/blunted villi). 40% (4/10) PsV patients had grade III; 10% (1/10) PsV patients had grade II; 50% (5/10) PsV patients had +abnormal histological appearance on electron microscopy.
Shuster 1967 [63]	Cross section	England	42 PsV patients	H, S Proximal loop of the jejunum and the fourth part of the duodenum	42% (12/26) PsV patients who underwent biopsy were frankly abnormal with a convoluted appearance and partial villous atrophy. 15% (4/26) PsV patients who underwent biopsy had equivocal appearance.
Ojetti 2006 [36]	Case-control	Italy	55 PsV patients (12 of these also had PsA) 65 healthy controls	H Ileac and colonic mucosa	60% (33/55) PsV patients had altered D-xylose absorption. 3% (2/65) healthy controls had altered D-xylose absorption. 50% (6/12) of PsA patients had altered D-xylose absorption.

Table 3 (continued)

Study	Study design	Region	Total number of study cases	Method of study; position of mucosa	Key results (number of patients from intestinal mucosal biopsy)
					3% (1/33) patients with altered D-xylose absorption were AGA positive—had normal histological appearance. 6% (2/33) patients with altered D-xylose absorption were EmA positive—both had abnormal histological appearance. 12.5% (1/8) PsV patients who underwent biopsy showed prominent tissue eosinophilia and hyperemia of the ileal terminal mucosa. 87.5% (7/8) PsV patients who underwent biopsy had normal ileoscopy and colonoscopy.
Scarpa 2000 [64]	Cross section	Italy	15 PsV and PsA patients 10 controls	H Colonic mucosa	100% (15/15) patients showed microscopic changes (hypercellular LP and lymphoid aggregates). 60% (9/15) patients showed macroscopically abnormal colonic mucosa. 100% (10/10) controls had no abnormal changes.
Schatteman 1995 [65]	Case-control	Belgium	64 PsA patients 354 spondyloarthropathies 37 articular controls 28 intestinal controls	H Cecum, ileocecal valve, terminal ileum and colorectum	11% (7/64) PsA patients had macroscopic inflammatory gut lesions. The prevalence of microscopic inflammatory gut lesions was significantly higher in PsA (10/64; 16%) than in articular controls (1/37; 3%) and intestinal controls (0/28; 0%).
Preger 1970 [66]	Cross section	American	8 PsV patients	H, E Jejunal mucosa	Unable to detect any abnormality in the structure or function in the small bowel.
Marks 1970 [67]	Case-control	England	55 PsV patients 48 controls	S The first part of the duodenum and the first 20 cm of the jejunum	26% (14/55) PsV patients had convolutions present; 7% had convolutions as predominant feature. 21% (10/48) of controls had convolutions present; 8% (4/48) had convolutions as predominant feature. No significant difference in PsV vs. control groups.

Method of study: H = histopathology; I = immunohistochemistry; E = electron microscopy; F = fluoroscopy; S = stereomicroscopy; DM = dissection microscope

PsV psoriasis vulgaris, *PsA* psoriastic arthritis, *AGA* antigliadin antibody, *anti-EMA* anti-endomysial antibody test, *IEL* intraepithelial lymphocyte infiltration, *IBS* irritable bowel syndrome, *LI* labeling index (labeling indices were calculated by counting labeled cells in all crypt cross sections through the entire proliferative compartment)

*Overlapping patients studied

Table 4 Studies of intestinal mucosal function in patients with psoriasis

Study	Study design	Region	Size/population	Malabsorption studies	Key results
Ojetti 2006 [36]	Case-control	Italy	55 PsV patients 65 healthy controls	D-xylose absorption	33/55 (60%) PsV patients had significantly lower D-xylose serum levels than that measured in controls. 2/65 (3%) healthy controls had altered D-xylose absorption.
Humbert 1991 [68]	Case-control	France	15 PsV patients 15 healthy controls	^{51}Cr-labeled EDTA absorption test	Differed significantly between PsV patients (2.46 ± 0.81%) and controls (1.95 ± 0.36%) ($p < 0.05$).
Hamilton 1985 [69]	Case-control	England	29 PsV patients 55 healthy controls	A standard cellobiose/mannitol permeability test	21% (6/29) PsV patients had abnormal cellobiose/mannitol recovery ratio. Did not differ significantly from controls.
Hendel 1982 [56]	Cross section	Denmark	15 PsV patients	Fecal fat excretion D-xylose absorption. Lactose tolerance test Sucrose tolerance test	27% (4/15) patients excreted more than 7 g of fat per day. 40% (6/15) PsV patients had abnormal D-xylose excretion. 8% (1/13) PsV patients tested exhibited lactase deficiency. 8% (1/13) PsV patients tested exhibited sucrase deficiency.
Chapman 1980 [70]	Case-control	England	43 PsV patients 73 healthy controls	Epidermis and Jejunal mucosa AHH activity	Basal and induced AHH activity in PsV patients were significantly less than in controls, $p < 0.001$ in epidermis and jejunal mucosa.
Bedi 1974 [58]	Case-control	Indian	5 patients with pustular psoriasis 19 PsV patients	Fecal fat excretion D-xylose absorption	100% (5/5) patients with pustular psoriasis had steatorrhea and abnormal D-xylose excretion. 42% (8/19) patients with extensive psoriasis showed D-xylose excretion. 68% (13/19) patients with extensive psoriasis had steatorrhea.
Barry 1971 [60]	Case-control	England	22 PsV patients 20 healthy controls 15 ill controls	Fecal fat excretion D-xylose tolerance tests Lactose utilization test	9% (2/22) PsV patients had steatorrhea. 9% (2/22) PsV patients had abnormal D-xylose excretion. In 100% (15/15) PsV patients studied by means of the lactose utilization test, the mean 2-h excretion rate of radiocarbon dioxide was 6.29% ± 2.37 which was significantly lower than the normal controls (8.22% ± 1.99;) $p < 001$.
Roberts 1971 [61]	Cross section	Germany	14 PsV patients	D-xylose absorption Lactase tolerance test Sucrose tolerance test	43% (6/14) PsV patients had reduced lactase activity. 43% (6/14) PsV patients had reduced sucrase activity. 21% (3/14) PsV patients had abnormal D-xylose excretion.
Summerly 1971 [71]	Cross section	England	22 PsV patients	Fecal fat excretion Folic acid absorption	50% (10/20) PsV patients had steatorrhea. 41% (9/22) PsV patients had impaired folic acid absorption.
Themann 1970 [62]	Cross section	Germany	10 PsV patients	Lactose tolerance test Sucrose tolerance test	50% (5/10) PsV patients demonstrated reduced lactase. 50% (5/10) PsV patients had a reduction of sucrase.
Shuster 1967 [63]	Cross section	England	42 PsV patients	Fecal fat excretion D-xylose absorption	58% (15/26) PsV patients tested excreted more than 5 g. of fat a day. 40% (4/10) PsV patients tested had abnormal D-xylose excretion.
Knowles 1963 [72]	Cross section	England	14 PsV patients	Folic acid absorption	43% (6/14) PsV patients found to have folic acid deficiency.
Preger 1970 [66]	Cross section	American	8 PsV patients	Fecal fat excretion D-xylose absorption	Unable to detect any abnormality in the structure or function in the small bowel.

Cr chromium, *EDTA* ethylenediaminetetraacetic acid, *PsV* psoriasis vulgaris

population reported in the studies, as supported by the pooled prevalence of GI disease among the general population and by previously conducted population-based studies. Of note, the pooled prevalence of celiac disease was much greater than the reported prevalence in the general population (2 vs. 0.1%). The pooled prevalence of GI disease among psoriasis patient was highest for celiac disease (2%) compared to Crohn disease (0.4%) or UC (0.5%), and correspondingly, the pooled prevalence for Crohn disease and UC was similar. The differences seen among celiac disease from IBD could possibly be related to the possibility that celiac disease is more common than IBD. Large population-based studies have predicted the global prevalence of celiac disease as 0.5 to 1%; specifically, 0.7 to 1% in the USA, 0.5 to 1% in Europe, 0.5% in Latin America, 0.5% in Asia, and 0.3 to 0.8% in the Middle East [76–87]. The prevalence of Crohn disease and UC reported from nationally representative studies ranged from 0.2 to 0.3% and 0.2 to 0.5%, respectively [88, 89]. Our review demonstrated a larger discrepancy between the prevalence IBD and the celiac disease in psoriasis patients compared to the baseline prevalence estimates.

Interestingly, the pooled prevalence of psoriasis among Crohn disease and UC was much higher (9.5% and 6.6%, respectively) than for the prevalence of Crohn disease or UC among psoriasis (0.4% and 0.5%, respectively). Awareness of the high occurrence of this comorbidity provides implications for IBD management and further supports overlap in inflammatory pathways. Fortunately, this overlap can be addressed using several systemic therapies that have efficacy in both IBD and psoriasis.

In the present study, case-control or cohort data were not robust enough to conduct a pooled analysis for IBD or celiac disease risk. Only a few studies provided epidemiological estimates to determine risk associations such as OR or RR. Italians with psoriasis have 2.5 times the odds of developing Crohn disease compared to those without psoriasis and slightly increased odds of 1.6 for developing UC [27]. A similar significant odds for developing celiac disease of 2.7 was found in Israel [37]. However, a 11.3 greater odds of developing celiac disease was found in a large Italian study [35••]. A previously published meta-analysis estimated the risk of developing celiac disease among psoriasis patients as 3.1 times greater than for those without psoriasis [90•]. In the USA, psoriasis patients have a 5.8 significantly increased risk of developing Crohn disease and 1.7 insignificantly increased risk of UC [29]. Inconsistently, psoriasis was reported as significantly protective against developing Crohn disease in Taiwan [42]. The protective effect of psoriasis on Crohn disease risk could be influenced by differences in genetics or diet, lifestyle, and culture. IBD is significantly less prevalent in China than it is in the USA [91]. This is also supported by the recognized lower prevalence of IBD in Asia compared to global estimates [89]. Moreover, when Chinese psoriasis patients have Crohn disease, they are more likely to seek out traditional Chinese medicine therapies than in the West [92]. Therefore, the influence of psoriasis on IBD might be confounded if IBD were under-reported due to psoriasis patients receiving therapy from traditional Chinese medicine practitioners.

Select studies investigated the temporality of developing IBD with psoriasis. More individuals were noted to develop psoriasis before the onset of IBD. In addition, the psoriasis severity was increased in those patients developing psoriasis before IBD. This suggests that patients with severe psoriasis may harbor skin-specific factors that promote cutaneous inflammation over gastrointestinal inflammation.

In addition, we reviewed studies that assessed structural abnormalities in psoriasis patients from three intestinal regions: the duodenum, jejunum, and ileocolon. On average across all regions, 60% of the psoriasis patients in these studies had a significant increase in mucosal lymphocytic infiltration. The increase in lymphocytes was also seen in patients with psoriatic arthritis, but was not related to the presence of antigliadin antibody (AGA) or severity of skin disease [47]. Furthermore, abnormal mucosal histology and ultrastructure were also reported in a majority of studies. These results provide evidence for potential subclinical gastrointestinal inflammation in psoriasis patients. How these abnormalities are related to the degree of skin involvement, however, is not clearly established. One study reported 11 psoriasis patients to have 26–50% skin involvement and eight patients to have 51–75% skin involvement [57]. Of the group with less than 50% skin involvement, 73% showed grade I and II histologic changes. Of the group with greater than 50% skin involvement, 50% of the patients exhibited grade II changes. Alternatively, several studies did not report a relationship between the degree of mucosal histologic abnormality and the severity of psoriasis [58, 60, 63].

Structural and/or functional small bowel abnormalities can impair nutrient absorption, giving rise to a malabsorption syndrome [36]. Among functional studies in psoriasis, steatorrhea is a common finding that further supports previous scientific observations of psoriasis in the context of dermatogenic enteropathy. Review of the literature revealed 43% of the psoriatic subjects tested to have abnormal fecal fat excretion. The relationship between the degree of functional small bowel abnormalities and extent of skin involvement is better defined than that for structural abnormalities reported earlier. Several studies have shown that the incidence, frequency, and severity of steatorrhea are related to the extent of skin involvement [63, 93]. Furthermore, treatment of psoriasis coincides with a reduction in fecal fat excretion [63]. These results suggest that steatorrhea in these patients may be secondary to active psoriasis. The D-xylose test is another well-established tool to detect malabsorption in clinically asymptomatic individuals [36]. Our review of the literature suggests that a large

percentage of psoriatic patients have abnormal D-xylose absorption or lactose intolerance. One study additionally investigated whether these functional changes are associated with psoriasis severity and reported lactose intolerance to be significantly correlated with degree of skin involvement [60].

The included epidemiological studies are fairly representative of the national population. Based on our quality criteria, all publications had robust samples and most were from large population-based cohort studies, reflective of previously reported national estimates in the literature. Another notable strength of the included articles is a well-defined classification of diseases as established by a physician.

There are several limitations that may have affected our results. Differences in the study design and global populations examined may make some estimates difficult to compare. This was evidenced by the detection of heterogeneity in our meta-analyses.In addition, the small number of patients identified with GI disease from a large population may further contribute to imprecision. However, sensitivity analyses exploring removal of outlier studies revealed that this heterogeneity did not greatly impact the overall IBD and celiac disease estimates. Not all estimates were adjusted for age and sex, so some results may be influenced by confounders. However, the adjusted effects reported from several studies were not significantly different from the unadjusted effects.

Conclusions

Our systematic review investigated the worldwide prevalence of Crohn disease, UC, and celiac disease among psoriatic patients in order to explore the burden of GI inflammation. To our knowledge, our review is the first to summarize GI inflammatory disease epidemiology among psoriasis patients and to describe its contributing pathophysiological subclinical factors. Overall, there appears to be an increased prevalence and association of GI disease among psoriasis patients, as well as an increased prevalence of psoriasis in patients with GI disease. The highest prevalence of GI disease among psoriasis patients was found for celiac disease in comparison to the prevalence of IBD. Conversely, the prevalence of psoriasis among GI disease was much higher, suggesting a common susceptibility pathway. When the onset of psoriasis preceded that of GI disease, which tends to occur more frequently than vice versa, patients tended to experience more severe psoriasis.

Intestinal mucosal histology, ultrastructure, and function were investigated among psoriasis patients with mild or absent gastrointestinal symptoms. Review of the literature suggests that subclinical abnormalities in gastrointestinal structure and function are present in a significant percentage of psoriatic patients. It is unclear whether these underlying intestinal abnormalities in patients contribute to or are the result of cutaneous pathology. Although studies that examined the presence or absence of steatorrhea in psoriasis suggest that these intestinal changes may be secondary to cutaneous pathology, studies examining the relationship of other intestinal abnormalities and degree of skin involvement were less conclusive. Therefore, the complex relationship between the skin and the gut warrants further investigation.

Practitioners should be aware of the association of GI disease among psoriasis patients. Dermatologists should query psoriasis patients for the presence of GI symptoms and refer to a GI specialist when warranted. Similarly, gastrointestinal providers should inquire about skin findings. Patients should be educated on the link between psoriasis and gastrointestinal disorders so that they can be alert to early symptoms.

Compliance with Ethical Standards

Conflict of Interest IS, WJ, EY, RS, KB, CL, LA declare that they have no conflict of interest.

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