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ORIGINAL ARTICLE

Gastrointestinal comorbidities in patients with psoriatic arthritis

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Abstract Comorbidities associated with psoriatic arthritis (PsA) include cardiovascular diseases, diabetes mellitus, and obesity. This study evaluated the association between PsA and common gastrointestinal (GI) diseases. A retrospective study was performed in Israel's largest health care provider database between 2002 and 2013. 3161 PsA patients were matched for age and sex with 31610 randomly selected patients. We searched these patients' records for the presence of peptic ulcer disease (PUD), reflux esophagitis, Crohn's disease, ulcerative colitis, irritable bowel syndrome (IBS) and celiac disease. T-test was used to compare continuous variables and a Chi-square test was used for categorical variables. Multi variate logistic regression models were used to assess the association between PsA and GI comorbidities. PsA was associated with Crohn's disease (OR 2.4, 95 %CI: 1.75–3.32, $p < 0.0001$), ulcerative colitis (OR 2.1, 95 %CI: 1.33–3.26, $p = 0.001$), reflux esophagitis (OR 1.6, 95 %CI: 1.44–1.78, $p < 0.0001$), PUD (OR 1.5, 95 %CI: 1.31–1.63, $p < 0.0001$) and IBS (OR 1.4, 95 %CI: 1.01–1.86, $p = 0.045$). After controlling for known risk factors, the association remained significant between PsA and Crohn's disease (OR 2.2, 95 %CI: 1.59–3.03, $p < 0.0001$), ulcerative colitis (OR 1.9, 95 %CI: 1.21–3.00, $p = 0.005$), reflux esophagitis (OR 1.5, 95 %CI: 1.31–1.63, $p < 0.0001$), and PUD (OR 1.3, 95 %CI: 1.12–1.47, $p < 0.0001$). No significant association was found between PsA and celiac disease. In the current study PsA was associated with gastrointestinal morbidities including Crohn's disease, ulcerative colitis, PUD and IBS. Physicians treating patients with PsA should be aware of these associations.

Keywords Gastrointestinal diseases · Spondyloarthritis · Psoriatic arthritis.

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Introduction

Psoriatic arthritis (PsA) is an inflammatory arthritis that, in addition to joint and skin manifestations, is associated with numerous comorbidities and extra-articular/cutaneous manifestations that reduce quality of life and life expectancy. Comorbidities include cardiovascular diseases including myocardial infarction, cerebrovascular disease, hypertension, diabetes mellitus, obesity, hyperlipidemia, fibromyalgia, depression and osteoporosis [1–5]. PsA belongs to the seronegative spondyloarthritis (SpA) group of arthritis [6], in which GI involvement in the form of ulcerative colitis and Crohn's disease has been described in 5–10 % of cases [7]. Subclinical involvement was described up to two-thirds of SpA patients [8], implying a possible association between PsA with inflammatory bowel diseases (IBD) [9]. Despite these significant figures, and the important role of the gut in PsA pathogenesis [10], published reports on the connection between PsA and common GI morbidity are scarce. Recognition of this possible association may benefit

PsA patient management and follow up, as well as prompt research into the possibility of common pathogenic pathways of the two entities [11]. The present study was carried out to determine the association between PsA and GI morbidity, utilizing a large health care provider database.

Materials and methods

The database maintained by Clalit Health Services (CHS), Israel's largest healthcare provider, enrolls approximately 4.3 million members, 52 % of the Israeli population. The system's database receives continuous real-time input from pharmaceutical, medical and administrative digital systems, and has been used in numerous studies [12–14]. Disease codes employ a modification of the International Classification of Diseases Ninth Revision (ICD-9) and medication use is coded according to ATC (Anatomical Therapeutic Chemical) classification. The PsA cohort was described in details in a previous study [15]. Briefly, patients diagnosed with PsA by a rheumatologist or with this diagnosis noted on their hospital discharge summary between January 2002 and December 2013 were included in the cohort. For each of the 3161 PsA patients in the registry, 10 patients of the same age and sex without a diagnosis of psoriasis, rheumatoid arthritis or ankylosing spondylitis were randomly selected from the database to serve as the control group. Demographic data collected for both group included age, sex, ethnicity, and socioeconomic status (SES), which was determined according to the CHS classification of the clinic where the patient was enrolled: low = 1, medium = 2, or high = 3. The CHS classification is defined by logistic and manual qualitative assessment and is highly correlated with the SES status assigned by the Israel Central Bureau of Statistics.

Clinical data represented by disease codes entered into the system by the treating family physicians and specialists included obesity (described also as BMI >30), smoking (current or past smoking) chronic obstructive pulmonary disease, bronchitis, diabetes mellitus, asthma, and scleroderma, and the presence of six common GI morbidities: irritable bowel syndrome (IBS), celiac disease, peptic ulcer disease (PUD), reflux esophagitis (GERD), Crohn's disease and ulcerative colitis (UC) were obtained for all participants.

Data regarding pharmaceuticals dispensed drugs during the study period included non-steroidal anti-inflammatory drugs (NSAIDS), subdivided into COX-1 inhibitors and COX-2 inhibitors; glucocorticoids; non-biological disease-modifying anti-rheumatic drugs DMARDS (hydroxychloroquine, sulfasalazine, methotrexate, azathioprine, leflunomide, cyclosporine A); and biological DMARDS (adalimumab, etanercept, infliximab and golimumab). Patients were included in the non-biological and biological DMARDS treatment groups after one or more drug prescriptions were dispensed during the study period. Steroid intake was divided into three groups: no drug dispensed during the study period, 1–2 steroid-containing preparations dispensed per year, and 3 or more steroid-containing preparations dispensed per year. COX-1 and COX-2 intake was compared between cases and controls based on dispensed prescriptions for the research period (mean and median).

Statistical analyses

T-tests was used to compare continuous variables and a Chi-square test was used for categorical variables. In the multivariable models, IBS was controlled for age and gender; PUD for glucocorticoids; COX-1 and COX-2 inhibitors dispensed, age and smoking; GERD for asthma, diabetes, obesity, scleroderma, smoking, COPD, and bronchitis; Crohn's disease for smoking, ethnicity and COX-1 usage; and ulcerative colitis for smoking, gender and COX-1 usage. The odds ratio (OR) and 95 % confidence intervals (CI) were calculated. All tests were 2-sided and $p \leq 0.05$ was considered significant. Data analysis was performed with the SPSS statistical package, version 22.0 (SPSS Inc., Chicago, IL, USA). The study was approved by the Institutional Review Board of Carmel Medical Center, Haifa.

Results

The PsA cohort consisted of 3161 patients 53 % female, with an average age of 58 ± 15 years, (Table 1).

Compared to the control group (Table 1), PsA patients had a higher socioeconomic status (25.2 % versus 20.5 %, $p < 0.0001$, respectively) and obesity (34.5 % versus 23.6 %, $p < 0.0001$).

In the univariable analyses (Table 2), the association between PsA and Crohn's disease (OR (95%CI) 2.4, (1.75–3.32), $p < 0.0001$) ulcerative colitis (OR 95 %CI: 2.1, (1.33–3.26,) $p = 0.001$), GERD (OR 1.6, 95 %CI: 1.44–1.78, $p < 0.0001$), PUD (OR 1.5, 95 %CI: 1.31–1.63, $p < 0.0001$), and IBS (OR 1.4, 95 %CI: 1.01–1.86, $p = 0.05$) was statistically significant (Table 2). No significant association was found between celiac disease and PsA ($p = 0.22$). This association was maintained in multivariable logistic regression models for Crohn's disease, ulcerative colitis, PUD and IBS (Table 2).

The association between disease severity and GI comorbidity (Table 3) was assessed by comparing the proportion of GI morbidities in 665 PsA patients who were never treated with DMARDS (biological or non-biological), and 2496 patients treated with DMARDS. No significant differences were found between these groups (Table 3).

Table 1 Demographic and clinical characteristics of PsA patients and the control group

		PsA patients $N = 3161$	Control $N = 31,610$	P value
Age		58.29 ± 15.44	58.21 ± 15.99	$p = 0.61$
Gender	Male	1474 (46.63 %)	14,740 (46.63 %)	$p = 1.00$
	Female	1687 (53.37 %)	16,870 (53.37 %)	
Ethnicity	Jews	2801 (88.61 %)	26,307 (83.20 %)	$p < 0.01$
	Arabs	360 (11.39 %)	5303 (16.80 %)	
Socioeconomic status	Unknown	31(0.98 %)	699 (2.21 %)	p < 0. 01
	Low	1012 (32.02 %)	12,008 (38.00 %)	
	Medium	1320 (41.76 %)	12,436 (39.34 %)	
	High	798 (25.25 %)	6467 (20.46 %)	
Smoking[&]		904 (28.60 %)	8742 (27.66 %)	$p = 0.26$
Obesity	Family physician diagnosis	1091 (34.51 %)	7464 (23.61 %)	p < 0. 01
	Calculated BMI >30	1100 (36 %)	8315 (27.8 %)	
Non-biologic	Methotrexate	2161 (68.36 %)	113 (0.36 %)	p < 0. 01
DMARDS use*	Sulfasalazine	1312 (41.51 %)	67 (0.21 %)	p < 0. 01
	Azathioprine	159 (5.03 %)	124 (0.39 %)	p < 0. 01
	Hydroxychloroquine	471 (14.90 %)	179 (0.57 %)	p < 0. 01
	Cyclosporine	91 (2.88 %)	59 (0.19 %)	p < 0. 01
Biologic	Adalimumab	571 (18.06 %)	9 (0.03 %)	p < 0. 01
DMARDS use*	Etanercept	525 (16.60 %)	0 (0.00 %)	p < 0. 01
	Infliximab	305 (9.65 %)	20 (0.06 %)	p < 0. 01
	Golimumab	99 (3.13 %)	0 (0.00 %)	p < 0. 01
Steroid	No use	1059 (33.50 %)	19,667 (62.22 %)	P < 0. 01
use**	1–2	970 (30.69 %)	7570 (23.95 %)	$p < 0.0001$
	≥3	1132 (35.81 %)	4373 (13.83 %)	p < 0.0001
COX1 intake***	Mean ± std	13.87 ± 16.17	7.59 ± 10.60	P < 0. 01
	Median	9.00	4.00	p < 0. 01
COX2 intake***	Mean	4.44 ± 0.81	1.30 ± 3.12	p < 0. 01
	Median	2.00	0.00	p < 0. 01

[&] Defined as present or past smoker

*Use defined as number of patients ever having received a prescription

**Steroids usage was divided into three groups according to the number of steroid containing preparations dispensed per year

***COX1 and COX2 intake was compared between cases and controls based on pharmaceutical dispenses for the research period (mean and median)

Discussion

Our cohort consisted of 3161 PsA patients with some differences in socioeconomic status, weight and ethnicity characteristics compared to the randomized control group of 31,610 patients.

The slightly more females than males (53.4 % vs. 46.6 %) in our PsA group is in line with the male-to-female ratios reported in the literature ranging from 0.7:1 to 2.1:1 [16]. The tendency of our PsA patients to have a higher prevalence of obesity than the control group was expected and reported in the literature. It may be partially explained by alteration in adipocytokines level [17, 18].

The association found between both types of IBD and PsA (OR 2.4 and OR 2.1) are consistent with those of Makredes et al. [19], in a retrospective survey using a database of 11 million patients in Boston, MA, USA, aimed at determining whether patients with PsA carry a higher autoimmune disease burden than those with cutaneous psoriasis only. These authors found an association between PsA and Crohn's disease (OR 2.1 95 %CI: 1.3–3) and ulcerative colitis (OR 2.0 95 %CI: 1.3–3.1) similar to ours (OR 2.4 and OR 2.1 respectively). The similar association rates in these two studies, despite Makredes et al.'s control group of healthy individuals and ours of patients without PsA, and the difference in the populations (one American

Table 2 Gastrointestinal comorbidities in PsA patients compared to the control group

	PsA patients $N = 3161$	Control $N = 31,610$	Univariable model			Multivariable model*		
			Odds ratio	CI 95 %	P value	Odds ratio	95%CI	*P* value
Irritable bowel syndrome**	47 (1.48 %)	345 (1.10 %)	1.37	1.01–1.86	P = 0.05	1.37	1.01–1.86	*P* = 0.05
Celiac disease***	11 (0.35 %)	74 (0.23 %)	1.49	0.79–2.81	*P* = 0.22			
Peptic ulcer disease@	308 (9.74 %)	2135 (6.75 %)	1.49	1.31–1.69	P < 0.01	1.28	1.125–1.47	*P* < 0.01
Reflux esophagitis#	463 (14.64 %)	3061 (9.68 %)	1.60	1.44–1.78	P < 0.01	1.46	1.31–1.63	P < 0.01
Crohn's disease$	47 (1.48 %)	197 (0.62 %)	2.41	1.75–3.32	P < 0.01	2.20	1.59–3.03	P < 0.01
Ulcerative colitis&	23 (0.73 %)	111 (0.35 %)	2.08	1.33–3.26	*P* = 0.01	1.91	1.21–3.00	P = 0.05

*Logistic regression was performed separately for each item in the multivariable logistic regression model

**Irritable bowel syndrome – adjusted for risk factors: age and gender

***Celiac disease – no risk factors for adjustment were found

@ Peptic ulcer disease – adjusted for risk factors glucocorticoids, COX1 inhibitor and COX2 inhibitor consumption, age and smoking

Reflux esophagitis – adjusted for risk factors asthma comorbidity, diabetic comorbidity, obesity, scleroderma comorbidity, smoking and COPD/bronchitis comorbidity

$ Crohn's disease – adjusted for risk factors smoking, ethnicity and cox1 consumption

& Ulcerative colitis – adjusted for risk factors smoking, gender and COX1 consumption

and the other Israeli), demonstrate the trustworthiness of the association.

Several studies have reported the association between IBD and PsA, without, however, demonstrating a clear connection [20]. One possible explanation is that a common pathway such as dysregulation of gut microflora propagates both conditions. Research has established that patients with PsA have a lower relative abundance of multiple intestinal bacteria compared to healthy subjects, a phenomenon that can be seen in IBD patients [21, 22]. Another possible explanation is that gut inflammation permits exogenous factors to enter the body, and promote articular inflammation by activating an inflammatory cascade [23]. A team from Belgium demonstrated a close relationship between gut and locomotor inflammation in SpA in a study of 49 patients: clinical remission of articular disease was always associated with normal gut histology, and chronic lesions in the gut were associated with more advanced radiologic signs of SpA and with more destructive peripheral arthritis [24–26]. In another study by this group, ileocolonoscopy disclosed inflammatory gut lesions in 10 of 64 PsA patients (16 %). All 10 of these patients presented clinically with oligoarthritis or axial involvement but not with polyarthritis, and 60 % of them that exhibited gut lesions harbored the HLA-B27 antigen [27]. These phenomena were demonstrated on an animal model and in other studies in human as well [28]. These findings further illustrate that SpA is associated with gut inflammation more than is the skin condition itself. Additional evidence comes from a study in which 60 Crohn's patients and their relatives, demonstrated high intestinal permeability [29, 30].

Table 3 Gastrointestinal comorbidities in PsA patients treated with DMARDS compared to PsA patients not treated with DMARDS*

	PsA patients not treated with DMARDS $N = 665$	PsA patients treated with DMARDS $N = 2496$	Univariable model		
			Odds ratio	CI 95 %	*p* value
Irritable bowel syndrome	11	36	0.87	0.44–1.72	$p = 0.69$
Celiac disease	3	8	0.71	0.19–2.68	$p = 0.71$
Peptic ulcer disease	74	234	0.83	0.63–1.09	$p = 0.18$
Reflux esophagitis	94	369	1.05	0.83–1.35	$p = 0.67$
Crohn's disease	7	40	1.53	0.68–3.43	$p = 0.30$
Ulcerative colitis	5	18	0.96	0.36–2.59	$p = 0.93$

* DMARDS- including non-biological disease-modifying anti-rheumatic drugs DMARDS (hydroxychloroquine, sulfasalazine, methotrexate, azathioprine, leflunomide, cyclosporine A); and biological DMARDS (adalimumab, etanercept, infliximab and golimumab)

A prospective study conducted on 174,476 American women from the Nurses' Health Study found a risk ratio of 6.5 (95 % CI 2.07–20.65) for PsA patients having Crohn's disease, much higher than the OR 2.2 found in our study. This discrepancy can be attributed to different statistical methods: we measured the number of patients associated with diseases while the Nurse's Health Study measured disease association in terms of person years [31].

Interestingly, we found a strong association (OR 1.5, $p < 0.0001$) between GERD and PsA. This association has not been addressed in the literature, despite research showing that SpA is characterized by inflammation of the enthuses, and the cruras of the diaphragm, being tendinous tissue, might be an active site of inflammation that causes loosening of the cruras, subsequently leading to GERD [32].

The association we found between PUD and PsA was lower in the multivariable than in the univariable model due to the fact that we controlled for use of COX inhibitors and glucocorticoids, which are frequently prescribed for PsA treatment (OR =1.3) [33]. Duodenal and gastric ulcers are slightly different from one another; but, the pathophysiology of both involves a combination of inflammation, protective deficiencies, and moderate amounts of acid and pepsin [34]. The inflammatory process present in PUD is associated with overproduction of cytokines IL-1-β, IL-6, IL-8 and TNF-α, some of which are identical to those overproduced in PsA, though we could not find the same pattern in both diseases [35]. We do not know of any research group that has found this association. Its clinical significance is even higher if the use of NSAIDS and steroids, additional well-known risk factors for PUD, in patients with PsA is taken into account.

No association was found between PsA and celiac disease (OR 1.5, $p = 0.22$, Table 2). A Canadian study of 590 celiac patients reported an association between celiac and psoriasis (OR 1.7, 95 % CI, 1.54–1.92), but no association between PsA or SpA and celiac [36]. Other studies reported an association between psoriasis and celiac, but none of them addressed the issue of PsA association directly [37–39], leaving unanswered the reason for the association of celiac with psoriasis and not with PsA.

The relative association found between IBS and PsA (OR 1.4, $p = 0.05$, Table 2) has not been previously reported. IBS is not an inflammatory disease and is categorized by absence of inflammatory process on intestinal biopsy. The association of IBS with a rheumatologic disease was described, in a study in with fibromyalgia was present in 20 % of patients with IBS [40]. Fibromyalgia is present in 17.2 % of PsA patients, which can explain the indirect association between IBS and PsA [41].

Study limitations include the retrospective analysis of the database, without analyzing the time relation of both diseases presentation due to the limited data on symptoms onset recorded in our system and the estimated calculation of drug intake as appreciated by pharmaceuticals dispensed drugs. The lack of information on PsA severity, which precluded directly correlating disease activity and GI comorbidities, was partially overcome by taking treatment and treatment modalities (biological and non-biological DMARDS) as an indicator of its severity. Since no association was found, we assume that the association between GI comorbidities and PsA is linked to its presence and not its severity.

In conclusion, the present study suggests a broader spectrum of GI comorbidities in PsA patients, including Crohn's disease and ulcerative colitis, GERD, PUD and IBS, than previously known. Further investigations of the new associations are required to determine their frequency and contributing factors. The identification and characterization of such comorbidities can improve the timely treatment, management and follow-up in PsA patients.

Compliance with ethical standards

Conflict of interest The authors declared no conflict of interest.

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