

# Endocrine Comorbidities in Patients with Psoriatic Arthritis: A Population-based Case-controlled Study

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**ABSTRACT. Objective.** To investigate endocrine comorbidities in patients with psoriatic arthritis (PsA).

**Methods.** A retrospective, cross-sectional study was performed with the database of Clalit Health Services, the largest healthcare provider in Israel, between 2002 and 2014. Patients with PsA were identified and matched by age and sex to healthy controls. The following morbidities were analyzed: hypo/hyperthyroidism, hypo/hyperparathyroidism, hyperprolactinemia, Cushing disease, Addison disease, diabetes insipidus, diabetes mellitus (DM), pituitary adenoma, acromegaly, and osteoporosis. Descriptive statistics were applied. The associations between PsA and endocrine comorbidities were analyzed by univariable and multivariable analysis.

**Results.** The study included 3161 patients with PsA, 53.4% women, mean age  $58.4 \pm 15.4$  years, and 31,610 controls. Comparative analyses yielded higher proportion of hypothyroidism (12.7% vs 8.6%,  $p < 0.0001$ ), Cushing disease (0.3% vs 0.1%,  $p < 0.0001$ ), osteoporosis (13.2% vs 9.1%,  $p < 0.0001$ ), and DM (27.9% vs 20.7%,  $p < 0.0001$ ) in the PsA group compared with the control group. In the multivariable regression analysis, the following diseases were more frequent in the PsA group: hypothyroidism (OR 1.61, 95% CI 1.47–1.81), DM (OR 1.35, 95% CI 1.18–1.42), Cushing disease (OR 3.96, 95% CI 1.67–9.43), and osteoporosis (OR 1.56, 95% CI 1.37–1.78).

**Conclusion.** PsA is associated with a high frequency of hypothyroidism, osteoporosis, DM, and Cushing disease. Awareness of these comorbidities may help physicians provide the optimal medical care to patients with PsA. (First Release April 15 2017; J Rheumatol 2017;44:786–90; doi:10.3899/jrheum.161274)

## Key Indexing Terms:

ENDOCRINE

COMORBIDITY

PSORIATIC ARTHRITIS

Epidemiologic studies have shown that comorbidities occur frequently in patients with psoriatic disease<sup>1</sup>. Identifying

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these comorbidities is of the utmost importance to ensure optimal clinical outcome. Diseases of the endocrine system, including diabetes mellitus (DM)<sup>2</sup>, autoimmune thyroid disease<sup>3</sup>, obesity<sup>4</sup>, and osteoporosis<sup>5</sup>, are common in the general population. These disorders, which are partly immune-mediated, have been reported to occur more frequently with rheumatic diseases; for instance, a higher risk for hypothyroidism has been reported with rheumatoid arthritis (RA)<sup>6</sup> and psoriatic disease<sup>7</sup>. In patients with RA, inflammation both at disease onset and accumulated over time was found to be associated with and predict new comorbidity, including endocrine disease<sup>8</sup>. Little has been published on the prevalence of endocrine disorders affecting the thyroid, parathyroid, adrenal, and pituitary glands in large cohorts of patients with psoriatic arthritis (PsA). The purpose of our study was to investigate the frequency of and factors associated with various endocrine comorbidities in a large population-based cohort of patients with PsA.

## MATERIALS AND METHODS

Clalit Health Services (CHS) is Israel's largest healthcare provider. It serves 4.4 million enrollees — 52% of Israel's population. CHS maintains a database that receives continuous real-time input from pharmaceutical, medical, and administrative digital systems<sup>9</sup>. Designed for purposes of administrative and clinical management, the database is available for epidemiological studies. The current study was approved by the Institutional Review Board of Carmel Medical Center, Haifa, Israel (CMC-0014-14).

PsA cases diagnosed between 2002 and 2013 according to rheumatologists' records and/or hospital discharge records were included in the study. Validation of the diagnosis was estimated in another study and found to be high<sup>10</sup>, with a positive predictive value of 90.5%, and the cohort has been used in other published reports<sup>11,12</sup>. Demographic data were retrieved, including age, sex, ethnicity, smoking status (current or past smoking), and socioeconomic status (SES) at inception (determined according to the CHS categories of low, medium, and high; the classification is highly correlated with SES assigned by the Israel Central Bureau of Statistics). Other information collected was the presence of common endocrine comorbidities including DM, diabetes insipidus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Cushing disease, hypoparathyroidism, hyperparathyroidism, acromegaly, hyperprolactinemia, and osteoporosis. These diagnoses were reported in the database by the primary care physicians. A previous study described the validity of various comorbidities<sup>13</sup>. Although not all endocrine comorbidities were investigated in the study, the comorbidities investigated were recorded using the same medical system and database. Each patient was matched by age and sex to 10 controls without rheumatic disease or psoriasis and chosen from the CHS database.

The following pharmaceutical drugs during the study period were recorded: nonsteroidal antiinflammatory drugs, glucocorticoids, nonbiological disease-modifying antirheumatic drugs (DMARD; hydroxychloroquine, sulfasalazine, methotrexate, azathioprine, leflunomide, and cyclosporine), and biological DMARD (adalimumab, etanercept, infliximab, and golimumab). A patient who received 1 or more nonbiological or biological DMARD prescriptions was assigned to the respective group. Steroid intake was categorized as no drug dispensed during the study period, 1–2 steroid-containing preparations dispensed each year, and 3 or more steroid-containing preparations dispensed each year.

Descriptive statistics were used, including means with SD for continuous variables and frequencies (%) for categorical variables. The proportion of endocrine comorbidities was compared between groups, Student *t* tests for continuous variables and the chi-square test for categorical variables. To assess the association between PsA disease and endocrine comorbidity, univariable and multivariable conditional logistic regression models were applied, adjusted for age, sex, smoking (current or past), obesity (body mass index > 30), and steroid use. OR and 95% CI were calculated. All tests were 2-sided and  $p \leq 0.05$  was considered statistically significant. Data analysis was performed with the SPSS statistical version 21.0 (SPSS Inc.).

## RESULTS

There were 3161 patients with PsA identified in the CHS database. Table 1 compares the demographic data and disease characteristics of these patients at baseline and the control group of age- and sex-matched controls. The mean age of the patients with PsA was  $58.4 \pm 15.4$  years, and 53.4% were women. Patients with PsA were more obese than the controls (34.8% vs 26.3%,  $p < 0.0001$ ). SES and history of smoking were similar in the 2 groups (28.6% vs 27.7% for smoking,  $p = 0.26$ ). As expected, immunosuppressives and corticosteroids were prescribed more in patients with PsA as compared with the control group.

Endocrine comorbidities in patients with PsA are summarized in Table 2. Patients with PsA had more DM (OR 1.56, 95% CI 1.43–1.7), hypothyroidism (OR 1.62, 95% CI 1.44–1.81), osteoporosis (OR 1.69, 95% CI 1.49–1.92), and Cushing disease (OR 5.3, 95% CI 2.36–11.90) compared with controls. When accounting for confounding variables (Table 3), DM and osteoporosis were more prevalent in patients with PsA than controls with an OR of 1.35, 95% CI 1.18–1.42 and OR 1.56, 95% CI 1.37–1.78, respectively.

Hypothyroidism was also more prevalent with an OR of 1.61, 95% CI 1.47–1.81 when adjusting for age and sex. The OR of Cushing disease in the PsA group was 3.96, 95% CI 1.67–9.43, compared with the control group after adjusting for age, sex, and steroid use.

The prevalence of these conditions was not statistically different between the 2 groups: hyperthyroidism, hypo- and hyperparathyroidism, hyperprolactinemia, Addison disease, diabetes insipidus, pituitary adenoma, and acromegaly.

The estimated risk of disease burden or severity on various endocrine comorbidities was based on patients' treatment status, assuming that those who required DMARD had a more severe disease. The 665 of the 3161 patients with PsA who did not require any treatment with DMARD were considered to have a milder disease. Patients treated with DMARD had a higher estimated risk for osteoporosis of 1.37, 95% CI 1.04–1.78. Other endocrine comorbidities were not higher in patients with a more severe disease (Table 4).

## DISCUSSION

A high frequency of hypothyroidism, DM, osteoporosis, and Cushing disease was observed in our cohort of 3161 patients with PsA. Our finding of a high frequency of hypothyroidism is in line with Antonelli, *et al*'s report of a significantly higher frequency of thyroid autoimmunity (positive antithyroid peroxidase antibody, hypoechoic thyroid) in 80 patients with PsA, and of subclinical hypothyroidism in women with PsA than in the general population<sup>7</sup>. Autoimmune thyroid diseases (AITD) are T cell-mediated organ-specific autoimmune disorders that result from a dysregulation of the immune system leading to an immune attack on the thyroid. The prevalence of AITD is estimated to be 5% in the general population. The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction between genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease. Associations exist between AITD and other systemic immune-mediated disorders such as Sjögren syndrome, RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), cryoglobulinemia, and sarcoidosis<sup>14</sup>. In our study, a high frequency of hypothyroidism was reported with an OR of 1.56, 95% CI 1.4–1.75 compared with the general population, suggesting a possible shared immunopathogenic pathway or mechanism involving the adaptive immune system in AITD pathogenesis and PsA.

The higher frequency of diabetes in psoriasis and PsA in our study concurs with several studies that have shown increased prevalence of diabetes in psoriasis<sup>15</sup> and PsA<sup>16,17,18</sup>. Among diabetic patients, psoriasis is generally associated with higher rates of microvascular and macrovascular complications<sup>19</sup>, and in patients with PsA, metabolic syndrome and insulin resistance are highly prevalent and were found to be independently associated with the severity

**Table 1.** Demographic characteristics and drugs used in patients with PsA and controls. Values are n (%) unless otherwise specified.

Characteristics	PsA, n = 3161	Control Group, n = 31,610	p
Age, yrs, mean $\pm$ SD	58.36 $\pm$ 15.42	58.21 $\pm$ 15.99	NS
Male	1474 (46.6)	14,740 (46.6)	NS
Female	1687 (53.4)	16,870 (53.4)	NS
Socioeconomic status <sup>†</sup>			
Low	1012 (32)	12,008 (38)	< 0.0001
Medium	1320 (41.8)	12,436 (39.3)	
High	798 (25.2)	6467 (20.5)	
Smoking	904 (28.6)	8742 (27.7)	NS
Obesity, BMI > 30	1100 (34.8)	8315 (26.3)	< 0.0001
BMI, mean $\pm$ SD	27.5 $\pm$ 5.8	28.7 $\pm$ 5.9	< 0.0001
Methotrexate *	2161 (68.4)	113 (0.4)	< 0.0001
Salazopyrin*	1312 (41.5)	67 (0.2)	< 0.0001
Azathioprine*	159 (5)	124 (0.4)	< 0.0001
Plaquenil*	471 (14.9)	179 (0.6)	< 0.0001
Cyclosporine*	91 (2.9)	59 (0.2)	< 0.0001
TNF- $\alpha$ inhibitors*	975 (30.8)	23 (0.1)	< 0.0001
Systemic steroids**			
None	1059 (33.50)	19,667 (62.22)	< 0.01
1–2	970 (30.69)	7570 (23.95)	< 0.01
$\geq$ 3	1132 (35.81)	4373 (13.83)	< 0.01

<sup>†</sup> According to Clalit Health Services, correlated with Israel Central Bureau of Statistics. \* No. patients ever received the drug during the study period. \*\* Steroid usage was divided into 3 groups according to the no. steroid-containing preparations dispensed per year. PsA: psoriatic arthritis; BMI: body mass index; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; NS: not significant.

**Table 2.** Endocrine comorbidities in patients with PsA compared with controls (univariable analysis). Values are n (%) unless otherwise specified.

Comorbidities	PsA, n = 3161	Control Group, n = 31,610	Univariable Analysis		
			OR	95% CI	p
Diabetes mellitus	881 (27.9)	6545 (20.7)	1.56	1.43–1.70	< 0.0001
Diabetes insipidus	3 (0.1)	12 (0.04)	2.50	0.71–8.86	NS
Hypothyroidism	403 (12.7)	2705 (8.6)	1.62	1.44–1.81	< 0.0001
Hyperthyroidism	46 (1.5)	454 (1.4)	1.01	0.75–1.38	NS
Hypo/hyperparathyroidism	24 (0.8)	184 (0.6)	1.30	0.85–2.00	NS
Acromegaly	0 (0)	5 (0.02)			NS
Hyperprolactinemia	2 (0.1)	52 (0.2)	0.38	0.09–1.58	NS
Osteoporosis	416 (13.2)	2867 (9.1)	1.69	1.49–1.92	< 0.0001
Cushing disease	9 (0.3)	17 (0.1)	5.30	2.36–11.90	< 0.0001
Addison disease	4 (0.1)	13 (0.04)	3.33	1.07–10.33	0.037

PsA: psoriatic arthritis; NS: not significant.

**Table 3.** Endocrine comorbidities in patients with PsA compared with controls (multivariable analysis). Values are n (%) unless otherwise specified.

Comorbidities	PsA, n = 3161	Control Group, n = 31,610	Multivariable Logistic Regression Model		
			OR	95% CI	p
Diabetes mellitus*	881 (27.9)	6545 (20.7)	1.35	1.18–1.42	< 0.0001
Hypothyroidism**	403 (12.7)	2705 (8.6)	1.61	1.47–1.81	< 0.0001
Osteoporosis <sup>†</sup>	416 (13.2)	2867 (9.1)	1.56	1.37–1.78	< 0.0001
Cushing disease <sup>‡</sup>	9 (0.3)	17 (0.1)	3.96	1.67–9.43	0.002

\* Adjusted for risk factors age, sex, smoking, obesity, and steroids use. \*\* Adjusted for risk factors age and sex.

<sup>†</sup> Adjusted for risk factors age, sex, smoking, and steroid use. <sup>‡</sup> Adjusted for risk factors age, sex, and steroid use.

PsA: psoriatic arthritis.

Table 4. Endocrine comorbidities in patients with PsA treated with DMARD compared with patients with PsA not treated with DMARD\*. Values are n (%) unless otherwise specified.

Comorbidities	PsA Not Treated with DMARD, n = 665	PsA Treated with DMARD, n = 2496	OR	95% CI
Diabetes mellitus	194 (29.2)	687 (27.5)	0.9	0.8–1.1
Hypothyroidism	80 (12.0)	32 (12.9)	1.1	0.8–1.4
Hyperthyroidism	6 (0.9)	40 (1.6)	1.8	0.8–4.2
Hyperparathyroidism	4 (0.6)	20 (0.8)	1.3	0.5–3.9
Hyperprolactinemia	0 (0)	2 (0.1)	1.0	1.0–1.0
Cushing disease	1 (0.2)	8 (0.3)	2.1	0.3–17.1
Diabetes insipidus	1 (0.2)	2 (0.1)	0.5	0.1–5.9
Addison disease	0 (0)	4 (0.2)	1.0	1.0–1.0
Osteoporosis	70 (10.5)	346 (13.9)	1.4	1.0–1.8

\* Nonbiological DMARD: hydroxychloroquine, sulfasalazine, methotrexate, azathioprine, leflunomide, and cyclosporine; and biological DMARD: adalimumab, etanercept, infliximab, and golimumab. PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drug.

of underlying PsA<sup>20</sup>. Several mechanisms could explain the association between PsA and diabetes, including the unhealthy lifestyle of patients with psoriatic disease<sup>21</sup>, the inflammatory cytokine milieu<sup>22,23,24</sup> that drives insulin resistance, and the shared susceptibility genetic loci for psoriasis and diabetes<sup>25,26,27</sup>. The association of PsA with diabetes in our study was statistically significant and was demonstrated even after controlling for potential confounders, including age, obesity, and steroid treatment. The important therapeutic implications of this association are likely to become clear with studies that examine the effects of antidiabetic drugs on psoriasis<sup>28,29</sup>.

Patients with inflammatory rheumatic diseases, including RA<sup>30</sup>, ankylosing spondylitis<sup>31</sup>, SLE<sup>32</sup>, SSc<sup>33</sup>, dermatomyositis, polymyositis, and vasculitis are known to have an increased risk for low bone density and fragility fractures<sup>34</sup>. Skeletal manifestations of PsA are complex and consist of both new bone formation manifesting with bone ankylosis, periostitis, and syndesmophytes, as well as bone resorption in the form of erosions. Less is known about the frequency of osteoporosis in PsA, and reviews of the literature regarding bone mineral density in PsA show inconsistent and conflicting results<sup>35,36,37</sup>. Our study suggested an increased frequency of osteoporosis in patients with PsA, and an even higher risk in patients with severe disease, suggesting a possible effect of disease severity or concurrent treatment on osteoporosis. Increased risk for osteoporotic fracture could herald higher risk for morbidity and mortality because the 3-year survival rate after a fracture has been reported to be 53%<sup>38</sup>.

Whether our finding of an increased frequency of Cushing disease in PsA reflects a true association or is related to a selection bias requires confirmation in observational, longitudinal studies. No suggestion of such an association was found in the literature. We speculate that such an association might appear after the successful treatment of endogenous hypercortisolism, which is occasionally followed by symp-

toms of unrelated immunologically mediated conditions. However, our data did not provide temporal relationships.

The major strength of our study lies in its population-based methods followed in a highly accurate database. Some limitations of our study must be mentioned. Because of the retrospective design in analyzing database variables, it may be underpowered in detecting associations with comorbidities for which the overall frequency in our sample is low, especially the comorbidities that require a high index of suspicion for the diagnosis. Thus, the results should be considered hypothesis-generating for prospective studies. Moreover, the lack of information on disease activity and the low reliability of the data on disease onset precluded evaluating the relationship between disease burden and the comorbidities, in particular the temporal relationship between them.

Nonetheless, our study demonstrated a higher association with major comorbid disease in patients with PsA compared with control patients, which may have implications for morbidity and mortality risks. Several less well-characterized comorbid associations were also recognized and might warrant further research. Physicians should be aware of these comorbidities and screen for DM, hypothyroidism, and osteoporosis to provide optimal medical care to their patients with PsA. Further studies are needed to determine whether more aggressive screening of asymptomatic patients with PsA improves diagnosis and outcomes. The recommended screening tests and schedule should also be investigated in future studies.

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