Psoriasis and Renal Disorders: A Large-Scale Population-Based Study in Children and Adults

Rivka Friedland^{a, b} Khalaf Kridin^{c, d} Arnon Dov Cohen^{e, f} Daniel Landau^{b, g}
Dan Ben-Amitai^{a, b}

^aPediatric Dermatology Unit, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; ^bSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; ^cLübeck Institute of Experimental Dermatology, University of Lübeck, Lübeck, Germany; ^dAzrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel; ^eDepartment of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel; ^fSiaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beersheba, Israel; ^gPediatric Nephrology Institute, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

Keywords

Pediatric patients · Kidney · Nephropathy · Psoriasis · Comorbidity

Abstract

Background: Psoriasis is a systemic disease with associated comorbidities. An association between renal diseases and psoriasis has previously been reported in adult patients, but little is known about renal diseases in pediatric patients. **Objective:** To determine whether there is an association between psoriasis and renal comorbidities in adult and pediatric patients. **Methods:** This cross-sectional study analyzed the database of the largest health care maintenance organization in Israel. Logistic regression was used to calculate odds ratios to compare 68,836 psoriatic patients and 68,836 controls with respect to renal comorbidities. **Results:** In adults, an inverse association emerged between psoriasis and dialysis (OR, 0.69; 95% CI, 0.58–0.83) and kidney transplantation (OR, 0.60; 95% CI, 0.43–0.83), a positive association with other kidney diseases (OR, 1.09; 95% CI, 1.05–1.13), and no association between psoriasis and chronic kidney disease (OR, 1.03; 95% CI, 0.98–1.09). Comparing 9,127 pedi-

atric patients and 9,478 controls, no association was found between psoriasis and renal comorbidities, chronic kidney disease (OR, 0.90; 95% CI, 0.33–2.48), dialysis (OR, 2.06; 95% CI, 0.19–22.69), kidney transplantation (OR, 0.34; 95% CI, 0.04–3.29), or other kidney diseases (OR, 0.98; 95% CI, 0.79–1.23), even after a multivariate analysis adjusting for putative confounders. **Conclusion:** As opposed to adult patients, pediatric patients with psoriasis were not shown at risk of kidney diseases.

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Introduction

Psoriasis is a chronic, inflammatory, immune-mediated, cutaneous disease that affects 2–3% of the world's population, with wide variability among countries and ethnic groups [1]. Approximately 1% of children and adolescents are affected with plaque psoriasis [2]. In 35% of adult patients, the disease initially occurs during the first

Rivka Friedland and Khalaf Kridin contributed equally to this work.

2 decades of life [2]. Along with skin manifestations, childhood psoriasis has been associated with a higher risk of developing comorbidities such as hyperlipidemia, obesity, hypertension, diabetes mellitus, arthritis, and Crohn's disease [2–4]. These associations are the basis for defining psoriasis as a systemic disease.

In adult patients, psoriasis has also been shown to be an independent risk factor for chronic renal disease and end-stage renal failure [5–11]. In addition, patients with end-stage renal disease on chronic hemodialysis have a greater risk of developing psoriasis [12]. These large cohort studies did not include pediatric populations.

Renal diseases, i.e., nephrotic syndrome and glomerulonephritis, were reported in small numbers of pediatric psoriatic patients [13–18].

Understanding the prevalence of renal comorbidities, if they exist in pediatric psoriatic patients, is crucial for managing this special population. It may also shed light onto the pathogenesis lying at the basis of these comorbidities.

Materials and Methods

Study Design and Database

We conducted a population-based cross-sectional study aimed at investigating possible associations between psoriasis and 4 renal comorbidities and outcomes: chronic renal failure, dialysis, kidney transplantation, and other kidney diseases.

The current study was based on the computerized data set of Clalit Health Services (CHS). CHS is the largest health care maintenance organization in Israel, providing a wide array of private and public health care services for 4.5 million enrollees as of October 2018 (57% of the general Israeli population). The computerized data set of CHS receives constant real-time input from medical, administrative, and pharmaceutical operating systems; it has proven effective for epidemiological studies [19]. The chronic disease registry, in particular, collects data from multiple sources, including primary care and hospital reports, and laboratory and imaging analyses, which are subsequently manually confirmed by primary care physicians. This registry has proven highly reliable and accurate [20].

Study Population and Covariates

The data set of the CHS was systematically checked for cases with ICD-9 diagnostic code psoriasis between January 1, 2011, and December 31, 2017. Patients were defined as eligible for inclusion only if one of the following criteria was fulfilled: (i) documented diagnosis of psoriasis registered by a board-certified dermatologist or (ii) diagnosis of psoriasis in discharge letters of patients admitted to dermatological wards.

The diagnosis of renal outcomes was based on the chronic registry of CHS. Diagnostic codes constituting the diagnosis of "other kidney diseases" are detailed in supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000522228).

We additionally recruited a matching control group of 1 control subject lacking a diagnosis of psoriasis per each case of psoriasis. Controls were matched based on sex, age, and ethnicity, and were

ascertained to be alive and to have contributed longitudinal data to the CHS data set. Diagnoses of renal comorbidities and outcomes were based on the CHS chronic registry. Specifically, the diagnosis is based on the documentation of board-certified nephrologists and is eventually validated by the managing general practitioner.

The different subgroups were compared using the Charlson comorbidity index (CCI), a validated method of measuring comorbid underlying diseases which has been demonstrated to be a dependable predictor of mortality [21]. Pediatric study participants were <18 years of age at the onset of psoriasis regardless of the time in which renal diseases emerged. Socioeconomic status was defined according to the poverty index of the member's residence area as defined during the 2008 National Census. The population was divided into 3 categories according to their poverty index (low, intermediate, and high).

Statistical Analysis

Baseline characteristics are described using means and standard deviations (SD) for continuous variables, and percentages to describe categorical values. The distributions of clinical and sociodemographic factors were compared among psoriatic patients and controls using the χ^2 test and *t* test, as indicated.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to compare cases and controls with respect to the presence of renal comorbidities. Two-tailed *p* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software, version 25 (SPSS, IBM Corp., Armonk, NY, USA).

Results

Characteristics of the Study Population

The study population included 137,672 individuals; 68,836 were patients with psoriasis, and 68,836 age-, sex-, and ethnicity-matched control individuals. The mean (SD) age at the onset of psoriasis and recruitment of controls was 42.5 (21.1) years, and 50.0 and 83.3% of the study populations were females and Jewish, respectively. No significant variability in socioeconomic status was observed between the two groups. Compared to controls, patients with psoriasis had a higher prevalence of obesity (25.4 vs. 21.3%, respectively; *p* < 0.001) and smoking (37.4 vs. 34.3%, respectively; *p* < 0.001). The mean CCI was higher in patients with psoriasis than in the control participants (1.41 ± 2.06 vs. 1.32 ± 2.05 , respectively; *p* < 0.001; Table 1).

The current study population encompassed a subgroup of 9,127 pediatric patients with psoriasis and 9,478 age-, sex-, and ethnicity-matched pediatric controls. Pediatric patients with psoriasis had a higher frequency of obesity (19.4 vs. 15.5%, respectively; *p* < 0.001), whereas the socioeconomic distribution, frequency of smoking, and CCI were comparable between patients and controls (Table 1).

Table 1. Descriptive characteristics of the study population

Characteristic	Patients (n = 68,836)	Controls (n = 68,836)	p value	Pediatric patients (n = 9,217)	Pediatric controls (n = 9,478)	p value
Age, years						
Mean±SD	42.5±21.1	42.4±21.2	0.380	10.1±4.8	10.0±4.8	0.240
Median (range)	40.3 (0.1–103.5)	40.2 (0.1–101.7)		10.4 (0.1–18.0)	10.4 (0.1–18.0)	
Male sex, n (%)	34,393 (50.0)	34,393 (50.0)	1.000	4,184 (45.4)	4,335 (45.7)	0.638
Ethnicity, n (%)						
Jews	57,348 (83.3)	57,358 (83.3)	1.000	6,637 (72.0)	6,859 (72.4)	0.584
Arabs	11,488 (16.7)	11,478 (16.7)		2,580 (28.0)	2,619 (27.6)	
Obesity, n (%)	17,466 (25.4)	14,630 (21.3)	<0.001	1,785 (19.4)	1,473 (15.5)	<0.001
Smoking, n (%)	25,746 (37.4)	23,636 (34.3)	<0.001	310 (3.4)	331 (3.5)	0.628
SES, n (%)						
Low	24,002 (34.9)	23,951 (34.8)	0.697	3,988 (43.3)	4,079 (43.0)	0.678
Intermediate	27,860 (40.5)	27,755 (40.3)	0.449	3,445 (37.4)	3,517 (37.1)	0.671
High	16,736 (24.3)	16,773 (24.4)	0.665	1,746 (18.9)	1,824 (19.2)	0.601
Charlson comorbidity score, mean ± SD	1.41±2.06	1.35±2.05	<0.001	0.11±0.36	0.10±0.33	0.123
Charlson comorbidity score (without age), mean ± SD	0.71±1.27	0.66±1.29	<0.001	0.11±0.36	0.10±0.33	0.123

SD, standard deviation; SES, socioeconomic status. Statistically significant p values are italicized.

Table 2. The association between psoriasis and kidney diseases in the general study population

Disease	Psoriasis (n = 68,836), n (%)	Controls (n = 68,836), n (%)	OR (95% CI)	Univariate p value	Adjusted OR (95% CI) ^a	Multivariate p value
Chronic renal failure	2,468 (3.59)	2,384 (3.46)	1.04 (0.97–1.10)	0.220	1.03 (0.97–1.11)	0.328
Dialysis	205 (0.30)	293 (0.43)	<i>0.70 (0.59–0.84)</i>	<0.001	<i>0.72 (0.59–0.87)</i>	<i>0.001</i>
Kidney transplantation	56 (0.08)	95 (0.14)	<i>0.59 (0.42–0.82)</i>	<i>0.001</i>	<i>0.62 (0.45–0.87)</i>	<i>0.006</i>
Other kidney diseases	4,749 (6.89)	4,385 (6.37)	<i>1.09 (1.04–1.14)</i>	<0.001	<i>1.10 (1.05–1.15)</i>	<0.001

OR, odds ratio; CI, confidence interval. Statistically significant results are italicized. ^a Multivariate logistic regression model adjusting for age, sex, ethnicity, and socioeconomic status and Charlson comorbidity index.

The Association of Psoriasis with Renal Comorbidities in the General Study Population

The overall prevalence of chronic renal failure was comparable between patients with psoriasis and controls (3.59 vs. 3.46%, respectively; OR, 1.04; 95% CI, 0.97–1.10). The lifetime prevalence rates of dialysis (0.30 vs. 0.43%, respectively; OR, 0.70; 95% CI, 0.59–0.84) and kidney transplantation (0.08 vs. 0.14%, respectively; OR, 0.59; 95% CI, 0.42–0.82) were lower among patients with psoriasis relative to controls. The prevalence of other kidney diseases, however, was higher among patients with psoriasis (6.89 vs. 6.37%, respectively; OR, 1.09; 95% CI, 1.04–1.14; Table 2).

Table 2 additionally demonstrates the findings of the multivariate logistic regression analysis adjusting for putative confounding factors. The associations of psoriasis

with dialysis (OR, 0.72; 95% CI, 0.59–0.87), kidney transplantation (OR, 0.62; 95% CI, 0.45–0.87), and other kidney diseases (OR, 1.10; 95% CI, 1.05–1.15) were not substantially affected in the analysis.

The Association of Psoriasis with Renal Comorbidities Age-Specific Analysis

In a subgroup analysis on the pediatric study population, no association was found between psoriasis and any of the renal comorbidities: chronic renal failure (OR, 0.90; 95% CI, 0.33–2.48), dialysis (OR, 2.06; 95% CI, 0.19–22.69), kidney transplantation (OR, 0.34; 95% CI, 0.04–3.29), or other kidney diseases (OR, 0.98; 95% CI, 0.79–1.23; Table 3).

When investigating adult study participants, a significantly inverse association emerged between psoriasis and dialysis (OR, 0.69; 95% CI, 0.58–0.83) and kidney trans-

Table 3. The association between psoriasis and kidney diseases stratified by adult and pediatric study populations

	Pediatric population				Adult population			
	<i>n</i> (%) in psoriasis	<i>n</i> (%) in controls	OR (95% CI)	adjusted OR (95% CI) ^a	<i>n</i> (%) in psoriasis	<i>n</i> (%) in controls	OR (95% CI)	adjusted OR (95% CI) ^a
Chronic renal failure	7 (0.1)	8 (0.1)	0.90 (0.33–2.48)	0.89 (0.32–2.47)	2,461 (4.1)	2,376 (4.0)	1.03 (0.98–1.09)	1.04 (0.97–1.10)
Dialysis	2 (0.0)	1 (0.0)	2.06 (0.19–22.69)	1.18 (0.09–15.96)	203 (0.3)	291 (0.5)	<i>0.69 (0.58–0.83)</i>	<i>0.69 (0.57–0.82)</i>
Kidney transplantation	1 (0.0)	3 (0.0)	0.34 (0.04–3.29)	0.34 (0.04–3.28)	55 (0.1)	92 (0.2)	<i>0.60 (0.43–0.83)</i>	<i>0.59 (0.42–0.83)</i>
Other kidney diseases	155 (1.7)	162 (1.7)	0.98 (0.79–1.23)	0.96 (0.76–1.22)	4,594 (7.7)	4,223 (7.1)	<i>1.09 (1.05–1.13)</i>	<i>1.10 (1.04–1.15)</i>

OR, odds ratio; CI, confidence interval. Statistically significant results are italicized. ^a Multivariate logistic regression model adjusting for age, sex, ethnicity, and socioeconomic status and Charlson comorbidity index.

plantation (OR, 0.60; 95% CI, 0.43–0.83). Psoriasis displayed a positive association with other kidney diseases (OR, 1.09; 95% CI, 1.05–1.13), whereas no association was found between psoriasis and chronic renal failure (OR, 1.03; 95% CI, 0.98–1.09; Table 3). The outcome measures did not change substantially in both age subgroups following a multivariate analysis adjusting for putative confounders (Table 3).

Discussion

The current large-scale population-based study of 137,672 participants, of them 18,605 children, investigated the burden of renal diseases among patients with psoriasis. An age-stratified subgroup analysis found no association between pediatric psoriasis and renal diseases, including chronic renal failure, dialysis, kidney transplantation, or other renal diseases. The adult group demonstrated an association between psoriasis and kidney diseases, but an inverse association with dialysis and kidney transplantation.

In recent years, coexistence of psoriasis and renal diseases has increasingly been reported, resulting in the term “psoriatic nephropathy” [5–11, 22–32]. In adults, this term takes many forms. Different types of glomerulonephritis were described in adults with long-standing psoriasis [22–30]. Nephropathies and end-stage renal failure were reported in patients with acute forms of psoriasis such as generalized pustular psoriasis and erythrodermic psoriasis [31, 32]. Similar findings were reported in the pediatric psoriasis population, but in smaller numbers [13–18]. Deranged renal function and proteinuria were reported in adult patients with psoriasis, especially if they had concomitant psoriatic arthritis [33, 34], and a positive correlation to disease severity [35–37]. There are no similar studies to evaluate the prevalence of microalbu-

minuria and proteinuria in pediatric psoriatic patients. Several population-based studies demonstrated an increased risk of end-stage renal disease and chronic kidney disease in adult patients with psoriasis [5–11]. Moreover, patients with psoriasis have a higher risk of mortality, partially mediated by comorbidities, including renal diseases [38–41]. This association is also inversed, and patients treated with hemodialysis have a higher risk of developing psoriasis [12].

The pediatric population was not evaluated for psoriatic nephropathy; however, our study harbingers the investigation of renal comorbidities in this population. In contrast to adults, a difference in the burden of renal disease between children with psoriasis and age- and sex-matched controls without psoriasis was not established. The reason for this finding might be related to the severity of the disease. As mentioned above, adults with severe psoriasis were found to have a significantly higher prevalence of renal failure than their age- and sex-matched controls (OR, 1.59%; 95% CI, 1.09–2.32), but this trend disappeared in patients with mild psoriasis [9]. The majority of children have mild disease [2], therefore explaining the lack of increased risk for kidney diseases.

Systemic inflammation is considered to be responsible for the connection between psoriasis and several comorbidities in both adults and children, including obesity, diabetes mellitus, dyslipidemia, arterial hypertension, and inflammatory bowel disease [3, 4]. The term “psoriatic march” relates to the long-term complications of long-standing, chronic inflammatory states, such as atherosclerosis and cardiovascular disease, affecting adults but not children [42]. Renal dysfunction may be a part of the “psoriatic march” spectrum, also appearing as a late complication, thus not expected to be found in young patients. This is also reflected in the higher CCI we found in psoriatic patients compared with controls, but not in the

pediatric patient group, i.e., indicating the higher comorbidity burden in adult compared to pediatric patients.

Another conjecture for age-related risk of renal impairment in psoriasis is the pathogenesis of the renal injury. There are studies that show an increased risk of subclinical microalbuminuria in adult patients with severe psoriasis in the absence of comorbid cardiovascular or metabolic disease [43, 44]. It is suggested that small vessel rather than large vessel inflammation is responsible for this subclinical malfunction that may in time cause irreversible damage to renal function [5]. Further studies in the pediatric population are needed to determine whether renal functions are also impaired in children with psoriasis.

It is noteworthy that the mechanism underlying the link between psoriasis and nephropathies is not fully understood. Numerous reports of various types of glomerulonephritis suggest an immunological pathogenesis such as T-cell dysregulation and increased levels of immune complexes [11, 26, 36, 45]. Therefore, it is not surprising that glomerulonephritis was reported in both adults and children with psoriasis [13–18, 22–31]. Lately, interleukin-17, a proinflammatory factor detected in high levels in psoriasis patients, was found to also play a role in various renal diseases [46, 47]. High levels of interleukin-17 in psoriasis may induce renal inflammation, resulting in glomerulonephritis and other renal injuries [7].

Two unexpected findings are the equal risk of chronic renal failure for psoriatic and nonpsoriatic patients, and the inverse correlation between psoriasis, and dialysis and kidney transplantation. Although previous studies support these findings [48, 49], they included small numbers of patients; therefore selection bias might have resulted in an underestimation of kidney diseases. Our study includes a large sample size, as it is grounded on a computerized database of 4,927,000 enrollees; thus, it is less susceptible to selection and ascertainment bias. Lack of data concerning severity and duration of disease could affect the results. The study population is not stratified by severity; thus, conditions which are correlated with disease severity might not be represented. In addition, this study included only Israeli patients, therefore further observational studies on populations of different ethnicities are necessary. Given the cross-sectional design, we could not identify the temporal relationship between investigated diseases, which interferes with drawing firm conclusions regarding the presence of causality. Given the low number of positive outcomes, a Poisson model might have provided tighter CI.

In conclusion, our population-based large-scale study demonstrates that psoriasis is associated with kidney diseases, but in pediatric patients this association is not es-

tablished. Further studies are needed to establish these findings in order to solidify guidelines for comorbidity management in pediatric patients with psoriasis.

Key Message

As opposed to adults, an increased risk of kidney diseases is not established in pediatric psoriasis.

Statement of Ethics

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Ben-Gurion University of the Negev, Beersheba, Israel, approved this study and granted an exemption from informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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No funding was received for this study.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rivka Friedland and Khalaf Kridin. The first draft of the manuscript was written by Rivka Friedland, and all authors commented on previous versions of the manuscript. All authors read and approved the final paper.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding author (Rivka Friedland) upon reasonable request.

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