The risk of IgA nephropathy and glomerular disease in patients with psoriasis: A population based cohort study

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Dear Editor

Psoriasis, particularly when moderate to severe, is associated with an increased risk of incident chronic kidney disease (CKD)[1], although specific renal diseases observed in psoriasis patients remain poorly defined. Of special interest is IgA nephropathy (IgAN), which presents with episodic macroscopic hematuria and can lead to CKD and end-stage kidney disease. Several case reports link psoriasis to IgAN as well as elevated serum levels of IgA-containing immune complexes[2–4], however, no large-scale epidemiological studies have evaluated this association. Other forms of glomerular disease (GD) in psoriasis have also been reported, with cross-sectional studies yielding mixed findings[3,5,6] and one population-based cohort study finding psoriasis to be associated with an increased risk for glomerulonephritis without elucidating specific renal etiologies of glomerular damage[7]. Further understanding of the relationship between psoriasis and glomerular disease is thus warranted.

We conducted a population-based cohort study investigating incident IgAN and GD in psoriasis patients using data from The Health Improvement Network (THIN) from 1994–2014. THIN is a broadly representative electronic medical records database in the United Kingdom that has been previously validated for studying psoriasis[8]. Diagnostic codes were used to identify psoriasis patients (exposed) and the primary outcomes of IgAN and GD. Prescription codes for phototherapy or systemic medications identified patients with moderate-to-severe psoriasis. Algorithms to match psoriasis patients to patients without psoriasis (unexposed), define psoriasis severity, and identify start and end of follow-up time have previously been described[1]. Subjects with IgAN or GD prior to start of follow-up were excluded.

Risk factors for IgAN and GD were assessed as potential confounders in initial multivariable models for both outcomes. Covariates were measured on or before start date and included

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age, sex, body mass index, smoking and drinking habits, socioeconomic status (Townsend score), NSAID use, hypertension, diabetes, hyperlipidemia, cardiovascular disease, arthritis, and CKD.

Statistical analyses were performed using STATA 13.0 (StataCorp, College Station, TX, USA). Patient characteristics were summarized and compared using the Chi-square test and two-sided t-test for categorical and continuous variables, respectively. We obtained hazard ratios (HR) for the outcomes in exposed vs. unexposed patients using Cox proportional hazards regression. Initial multivariable models included covariates thought a priori to be confounders and those significant in univariable analyses (p   0.05). Starting with the highest p value >0.05, covariates were sequentially removed and eliminated if the exposure HR did not change   10%. Log-log survival plots verified that the proportional hazard assumption was met. Two-sided p values <0.05 determined statistical significance.

This study was consistent with the STROBE guidelines, Declaration of Helsinki, and approved by the IRB at University of Pennsylvania.

We identified 205,815 psoriasis patients (mild: 193,013; moderate-to-severe: 12,806) and 1,019,140 patients without psoriasis. Table 1 summarizes baseline cohort characteristics. The most common therapies for moderate-to-severe psoriasis were oral systemics (78.60%), specifically methotrexate (69.13%).

Patients with moderate-to-severe psoriasis had higher incidence rates of IgAN and GD (Table 1). In fully adjusted models (Table 2), both mild and moderate-to-severe psoriasis groups were more likely to develop IgAN; however, this risk was only statistically significant for moderate-to-severe psoriasis (HR 4.75, 95% CI 1.92–11.76). In fully adjusted analyses, only patients with moderate-to-severe psoriasis were at a statistically significantly increased risk for developing GD (HR 2.05, 95% CI 1.10–3.84). The excess risk of IgAN and GD attributable to moderate-to-severe psoriasis was 1 in 8,888 and 1 in 10,562 patients, respectively.

Our results were robust to multiple sensitivity analyses (Table 2), suggesting that surveillance bias, outcome misclassification, and confounding from medications are unlikely to explain our findings. Unknown, unmeasured confounders are possible, although known risk factors for renal disease did not explain the association. The primary limitation was that IgAN and GD are statistically rare, thus our estimates have wide confidence intervals.

This work advances the literature by illustrating that the association between moderate-to-severe psoriasis and IgAN and glomerular disease is unlikely to be due to chance alone or to common confounders measured in routine clinical practice. Defects in host response to mucosal infections may predispose patients to both diseases, as streptococcal infections trigger and flare guttate psoriasis and may also incite or exacerbate pre-existing IgAN[9,10]. In contrast to the findings of Chiu et al., mild psoriasis was not associated with an increased risk for GD possibly due to inherent differences in study populations or varying outcome definitions.

In conclusion, patients with moderate-to-severe psoriasis have an increased risk of glomerular disease, particularly IgAN. Clinicians should maintain a high index of suspicion when patients present with renal dysfunction.

Acknowledgments

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Table 1

Baseline characteristics and incidence rates of outcomes in patients with and without psoriasis

BASELINE CHARACTERISTICS

	Any Psoriasis		Mild Psoriasis		Moderate-to-severe Psoriasis	
	Unexposed	Overall PsO	Unexposed	Mild PsO	Unexposed	Moderate-to-severe PsO
N	1,019,140	205,815	955,721	193,013	63,415	12,806
Age, mean (SD)	50.66 (17.82)	47.17 (17.55)	50.62 (17.83)	47.00 (17.67)	51.36 (17.68)	49.83 (15.30)
Female sex, N (%)	570,359 (55.96)	106,569 (51.78)	534,679 (55.94)	99,975 (51.80)	35,676 (56.26)	6,598 (51.52)
BMI, mean (SD)[1]	26.39 (5.47)	26.76 (5.64)	26.40 (5.47)	26.66 (5.59)	26.37 (5.38)	28.11 (6.11)
Drinking history, N (%)[2]						
None	115,738 (11.36)	21,634 (10.51)	108,415 (11.34)	20,221 (10.48)	7,321 (11.54)	1,415 (11.05)
Current	651,393 (63.92)	133,805 (65.01)	611,581 (63.99)	125,285 (64.91)	39,811 (62.78)	8,521 (66.54)
Past	43,615 (4.28)	8,257 (4.01)	41,052 (4.30)	7,398 (3.83)	2,562 (4.04)	860 (6.72)
Smoking history, N (%)[3]						
None	488,477 (47.93)	80,067 (38.90)	458,226 (47.95)	75,124 (38.92)	30,249 (47.70)	4,945 (38.61)
Current	219,759 (21.56)	58,963 (28.65)	206,406 (21.60)	55,579 (28.80)	13,351 (21.05)	3,386 (26.44)
Past	209,354 (20.54)	45,790 (22.25)	196,829 (20.59)	42,073 (21.80)	12,525 (19.75)	3,717 (29.03)
Townsend[4], median quintile (IQR)	3 (1,4)	3 (2,4)	3 (1,4)	3 (2,4)	3 (1,4)	3 (1,4)
Hypertension	210,359 (20.64)	35,801 (17.39)	196,995 (20.61)	32,939 (17.07)	13,362 (21.07)	2,864 (22.36)
Diabetes	67,635 (6.64)	12,558 (6.10)	63,499 (6.64)	11,349 (5.88)	4,136 (6.52)	1,209 (9.44)
Hyperlipidemia	95,117 (9.33)	16,734 (8.13)	89,114 (9.32)	15,346 (7.95)	6,003 (9.47)	1,388 (10.84)
Cardiovascular disease (CVD)[5]	90,411 (8.87)	15,530 (7.55)	84,404 (8.83)	14,459 (7.49)	14,459 (7.49)	6,007 (9.47)
Psoriatic arthritis	Not applicable	10,308 (5.01)	Not applicable	5,504 (2.85)	Not applicable	4,804 (37.51)

INCIDENCE RATES OF IgA NEPHROPATHY AND GLOMERULAR DISEASE IN PATIENTS WITH AND WITHOUT PSORIASIS

NSAID use	Any Psoriasis		Mild Psoriasis		Moderate-to-severe Psoriasis	
	537,227 (52.71)	93,476 (45.42)	504,529 (52.79)	84,373 (43.71)	32,698 (51.56)	9,106 (71.11)
	Unexposed	Overall PsO	Unexposed	Mild PsO	Unexposed	Moderate-to-severe PsO
IgAN						
Median (IQR) duration of follow-up years	5.57 (2.37,9.92)	5.19 (2.15,9.60)	5.53 (2.35,9.87)	5.26 (2.17,9.71)	6.30 (2.89,10.75)	4.39 (1.92,7.85)
Number (%) of new IgAN cases	113 (0.01)	29 (0.01)	100 (0.01)	24 (0.01)	13 (0.02)	5 (0.04)
Incidence of IgAN per 100,000 person years (95% CI)	1.71 (1.42–2.06)	2.28 (1.58–3.28)	1.63 (1.34–1.98)	1.99 (1.34–2.97)	2.92 (1.70–5.03)	7.33 (3.05–17.62)
Glomerular disease						
Median (IQR) duration of follow-up, years	5.57 (2.37,9.92)	5.19 (2.15,9.60)	5.52 (2.35,9.86)	5.26 (2.17,9.71)	6.29 (2.89,10.75)	4.39 (1.93,7.85)
Number (%) of new glomerular disease cases	467 (0.05)	93 (0.05)	427 (0.04)	83 (0.04)	40 (0.06)	10 (0.08)
Incidence of glomerular disease per 100,000 person years (95% CI)	7.08 (6.47–7.75)	7.31 (5.96–8.95)	6.94 (6.31–7.63)	6.89 (5.56–8.54)	8.98 (6.59–12.25)	14.67 (7.89–27.26)

p<0.001 for all

[1] 19.78% and 20.37% of BMI data were missing in patients without and with psoriasis, respectively

[2] 20.45% and 20.46% of drinking data were missing in patients without and with psoriasis, respectively

[3] 9.96% and 10.20% of data on smoking habits were missing in patients without and with psoriasis, respectively

[4] Townsend score is a proxy of socioeconomic status based on employment status, car/home ownership, and household overcrowding. A higher Townsend index score correlates with greater socioeconomic deprivation (lower socioeconomic status). 4.12% and 4.87% of data on Townsend score were missing in patient without and with psoriasis, respectively.

[5] Congestive heart failure, coronary artery disease, myocardial infarction, or peripheral artery disease

Table 2

Hazard Ratios for IgAN and glomerular disease in unadjusted models, adjusted models, and various sensitivity analyses

	N		Any psoriasis HR (95% CI)	Mild psoriasis HR (95% CI)	Moderate to severe psoriasis HR (95% CI)
	Unexposed	Psoriasis			
Primary unadjusted models					
IgAN	1,019,140	205,815	1.33 (0.88–2.00)	1.16 (0.75–1.80)	4.24 (1.73–10.38)
Glomerular disease			1.03 (0.83–1.29)	0.97 (0.77–1.23)	2.08 (1.11–3.88)
Primary fully adjusted models					
IgAN [1]	1,019,140	205,815	1.37 (0.87–2.18)	1.16 (0.70–1.92)	4.75 (1.92–11.76)
Glomerular disease [2]			1.04 (0.83–1.30)	0.98 (0.78–1.24)	2.05 (1.10–3.84)
Excluding patients with PsA					
IgAN	1,019,140	195,507	1.34 (0.83–2.15)	1.20 (0.73–1.99)	4.81 (1.52–15.26)
Glomerular disease			1.06 (0.84–1.33)	0.99 (0.79–1.26)	2.69 (1.33–5.40)
Restricting to patients with at least annual GP visits					
IgAN	970,990	192,912	1.38 (0.87–2.17)	1.16 (0.70–1.92)	4.59 (1.86–11.36)
Glomerular disease			1.03 (0.83–1.29)	0.98 (0.77–1.23)	1.97 (1.06–3.70)
Redefining outcome to also require a code for renal biopsy					
IgAN	1,019,140	205,815	2.00 (0.69–5.79)	1.29 (0.36–4.63)	11.84 (2.61–53.81)
Glomerular disease			0.87 (0.46–1.65)	0.67 (0.32–1.39)	4.34 (1.36–13.83)
Excluding patients with history of methotrexate use					
IgAN	1,018,292	197,182	1.32 (0.82–2.12)	1.17 (0.71–1.92)	7.92 (2.49–25.15)
Glomerular disease			1.04 (0.83–1.30)	0.99 (0.78–1.25)	3.68 (1.64–8.24)
Excluding patients with history of cyclosporine use					
IgAN	1,018,510	204,803	1.33 (0.83–2.12)	1.10 (0.66–1.84)	5.16 (2.09–12.78)
Glomerular disease			1.01 (0.81–1.27)	0.99 (0.78–1.24)	1.56 (0.74–3.28)
Excluding patients with a history of CKD					
IgAN	993,669	201,957	1.61 (1.00–2.59)	1.34 (0.79–2.25)	5.97 (2.40–14.85)
Glomerular disease			1.03 (0.82–1.30)	0.96 (0.76–1.23)	2.22 (1.18–4.15)

[1] Our age/sex/BMI adjusted model was the fully adjusted model. Initial multivariable models included other demographic variables (smoking/drinking habits and Townsend score) as well as risk factors for glomerular disease including hypertension, diabetes, hyperlipidemia, cardiovascular disease, arthritis, and NSAID use. None of these potential confounders altered point estimates significantly (a minimum of 10%), reducing our model back to the age/sex/BMI adjusted model.

[2] Our age/sex adjusted model was the fully adjusted model. Initial multivariable models included demographic variables (BMI, smoking/drinking habits, and Townsend score) as well as risk factors for glomerular disease including hypertension, diabetes, hyperlipidemia, cardiovascular disease, arthritis, and NSAID use. None of these potential confounders altered point estimates significantly (a minimum of 10%), reducing our model back to the age/sex adjusted model.