

# Association between chronic renal disease and psoriasis risk in diabetes patients: A Korean population-based study

Seung Ah Yoo<sup>1</sup>, Marianne Isabel Abola Sayo<sup>2</sup> , Ji Hyun Lee<sup>1</sup>

<sup>1</sup>Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seocho-gu, Seoul, Republic of Korea,

<sup>2</sup>Department of Dermatology, East Avenue Medical Center, Quezon City, Metro Manila, Philippines.

## Abstract

**Background:** Several studies have reported that psoriasis has a positive correlation with type 2 diabetes mellitus (DM). Understanding the risk of psoriasis in diabetic patients is significant because it allows for early intervention and potential insights into the common pathways between the two conditions.

**Objectives:** We analysed the risk of psoriasis according to the estimated glomerular filtration rate (eGFR) and proteinuria level in DM patients using Korean population-based data.

**Methods:** This study was a retrospective cohort study using data collected from the country in the form of exploratory data analysis. A total of 927,234 participants diagnosed with DM were enrolled. Patients under the age of 20 with existing psoriasis or psoriasis developed within 1 year and missing data were excluded. The development of psoriasis was the primary outcome within a follow-up period of  $7.83 \pm 1.68$  years.

**Results:** Of the 840,395 final participants, 28,010 (3.33%) patients developed psoriasis. In multivariate-adjusted Cox proportional hazards regression models, the DM patients with eGFR < 30 had a higher risk of psoriasis after adjustment (eGFR 60–90, hazard ratio [HR] 1 (Ref.); eGFR < 30, HR 1.173, 95% CI 1.089–1.264). In addition, there was an increased psoriatic risk of patients with DM and proteinuria after adjustment (negative, HR 1 (Ref.); 2+, HR 1.164, 95% CI 1.080–1.254; 3+, HR 1.433, 95% CI 1.273–1.613; 4+, HR 1.508, 95% CI 1.177–1.931).

**Limitations:** The severity of psoriasis was not measured since the occurrence of psoriasis was the outcome. Details of oral hypoglycaemic agents such as type and dose were not investigated.

**Conclusion:** This study showed that a decrease in eGFR and aggravation of proteinuria increase the risk of psoriasis in diabetic patients. Therefore, by using eGFR and proteinuria as predictive risk factors of psoriasis in DM patients, early and proactive treatment may play a vital role in managing diabetic patients.

**Key words:** Diabetes, epidemiology, chronic, renal failure, proteinuria, psoriasis

## Introduction

Psoriasis is a chronic inflammatory disease known to have various comorbidities.<sup>1–3</sup> Two meta-analyses reported that the risk of diabetes mellitus (DM) increased in psoriatic patients with an odds ratio (OR) of 1.59 (95% CI 1.16–2.04) and 1.76 (95% CI 1.59–1.96), respectively. And one of them showed a dose effect (OR 2.10 in severe psoriasis, 95% CI

1.73–2.55).<sup>4,5</sup> A more recent meta-analysis and systematic review reported an OR of 1.69 (95% CI 1.51–1.89).<sup>6</sup>

Chronic kidney disease (CKD) is a complication of DM, diagnosed by a decrease in glomerular filtration rate (GFR) and symptomatic proteinuria.<sup>7,8</sup> CKD and proteinuria have also been reported to be associated with psoriasis.<sup>1–3,9,10</sup> A meta-analysis reported that patients with psoriasis had an

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**Corresponding author:** Dr. Ji Hyun Lee, Department of Dermatology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea. [yji1@hanmail.net](mailto:yji1@hanmail.net)

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increased CKD and end-stage renal disease (ESRD) risk with a pooled OR of 1.34 (95% CI 1.14–1.27) and 1.29 (95% CI 1.05–1.60), respectively.<sup>11</sup> Another study reported that patients with psoriasis had an increased prevalence of pathologic albuminuria compared to controls (24% vs. 2%,  $P = 0.005$ ), correlating with psoriasis severity ( $r = 0.458$ ,  $P = 0.007$ ).<sup>12</sup>

Although associations among psoriasis, DM, CKD, and proteinuria have been reported, there were no studies on the risk of psoriasis in diabetes patients with abnormal renal function. In this study, based on the fact that both psoriasis and diabetes are related to CKD and proteinuria, we investigated the risk of psoriasis according to eGFR and proteinuria level in diabetic patients using population-based data from the National Health Insurance Service (NHIS) of Korea.

## Methods

### Study population and data collection

This study was a retrospective cohort study using data collected from the country in the form of exploratory data analysis. The dataset was provided by the NHIS of South Korea and included information on the patient's age, sex, income status, diagnosed diseases based on the International Classification of Disease 10 Clinical Modification (ICD-10-CM), medications, procedures, and medical examination results. Of note, the study population was recommended to undergo standard health examination every 2 years under the National Health Insurance Corporation.<sup>13</sup>

In the dataset, DM individuals were identified as either 1) using the ICD-10-CM code E11-14 and taking DM medication or 2) fasting glucose  $\geq 126$  mg/dL at the time of screening. DM patients with a confirmed diagnosis of DM during health screening in 2009 were enrolled in this study. Among 927,234 participants, those who were younger than 20 years ( $n = 85$ ), diagnosed with DM and psoriasis before the study ( $n = 29,461$ ), and diagnosed with psoriasis within 1 year ( $n = 11,085$ ) were all excluded. In addition to this, 46,208

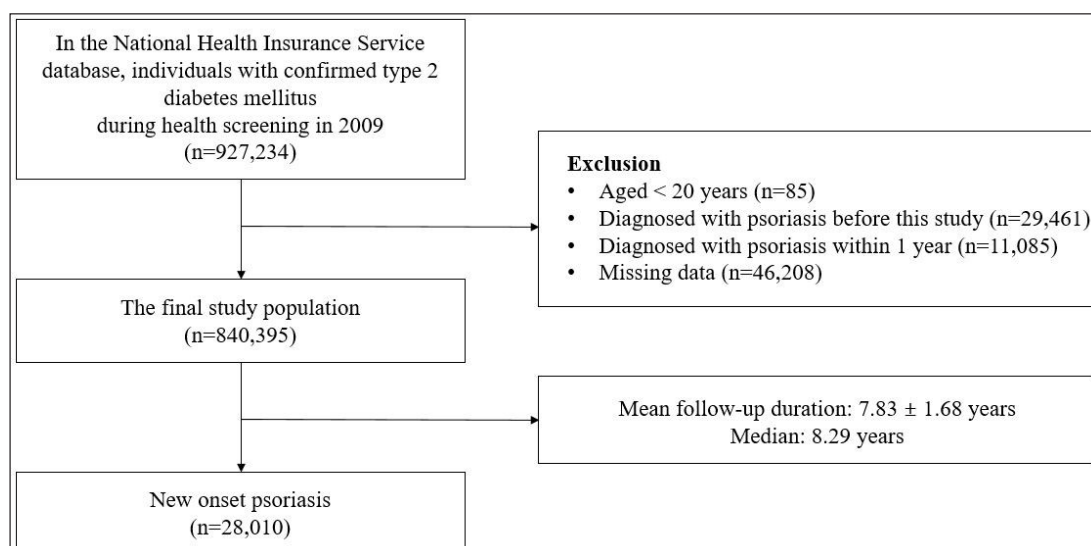
individuals with incomplete information were also excluded. Hence, the final study population was a complete data set of 840,395 participants [Figure 1]. This study was approved by the Ethics Committee of Seoul St. Mary's Hospital, the Catholic University of Korea (KC22ZISI0406). The dataset was anonymised, and de-identified, and informed consent was waived by the Institutional Review Board of the Korean National Institute for Bioethics Policy. This was carried out according to the principles of the Declaration of Helsinki.

### Measurement and definition of covariates

Medical records included in this study were the past medical histories, blood pressure, weight, height, and laboratory test results for fasting glucose and estimated glomerular filtration rate. The body mass index (BMI) was calculated by weight in kilograms divided by the height in metres squared.<sup>14</sup> Information on health-related behaviours was obtained using a standardised questionnaire. Smoking status was classified as a non-smoker, ex-smoker, and current smoker. Drinkers were classified as mild or heavy drinkers who consumed  $<30$  g and  $\geq 30$  g of alcohol per day, respectively.<sup>15</sup> Physical activity was an activity or exercise that make the individual more breathless than usual. Regular physical activity was taken to be either  $\geq 30$  minutes a day, five times a week for moderate physical activity, or  $\geq 20$  minutes a day, three times a week for strenuous physical activity. We defined the low income as individuals belonging to the lowest 25% of the income quartile.

### Study design

To determine the association among psoriasis, CKD, and proteinuria in DM patients, the patients were divided into five subgroups according to eGFR levels and six subgroups according to proteinuria severity. In this study, CKD was defined as eGFR  $<60$  ml/min/1.73 m<sup>2</sup>. During a follow-up period of  $7.83 \pm 1.68$  years among the subgroups, patients newly diagnosed with psoriasis (ICD-10-CM code, L40) were identified.



**Figure 1:** Flow chart of this study.

**Statistical analysis**

The general, characteristics of DM patients are presented as means with standard deviations or numbers and percentages. The incidence possibility of psoriasis according to the presence of CKD and proteinuria in DM patients was obtained using Kaplan–Meier curves and the log-rank test was used to analyse differences between the groups. To analyse the presence and severity of CKD and proteinuria in association with psoriasis risk, multivariate-adjusted Cox proportional hazards regression models were used in two different ways: Model 1 was not adjusted for any variable. Model 2 was performed adjusting for age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidemia, fasting glucose, DM duration ≥5 years, and ≥3 oral hypoglycemic agents used. Model 3 was adjusted

additionally for urine protein or eGFR. Variables in the models were chosen according to the clinical characteristics of developing psoriasis and the statistical significance of our study. Compared to controls (DM patients without CKD and proteinuria), hazard ratios (HRs) and 95% CIs were calculated. Statistical significance was defined as a two-sided P-value less than 0.05. All statistical analyses were performed using SAS software (ver. 9.4; SAS Institute, Cary, NC, USA) and R programming (version 3.1.0; The R Foundation for Statistical Computing, Vienna, Austria).<sup>16</sup>

**Results**

**Baseline characteristics**

The baseline characteristics of the patients according to the level of eGFR are summarised in Table 1. The baseline

**Table 1: Baseline characteristics of diabetes mellitus patients**

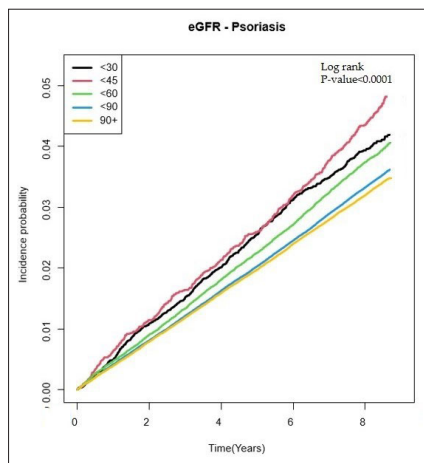
	eGFR					p-value
	≥90	60–90	45–60	30–45	<30	
	<b>278,622</b>	<b>455,490</b>	<b>73,548</b>	<b>13,236</b>	<b>19,499</b>	
Age, years	53.4 ± 11.3	58.0 ± 11.8	66.2 ± 9.7	68.2 ± 9.7	55.6 ± 12.3	<.0001
<40, n (%)	31,814 (11.4)	28,941 (6.4)	644 (0.9)	71 (0.5)	1,928 (9.9)	
40–64, n (%)	206,250 (74.0)	274,303 (60.2)	27,280 (37.1)	4,197 (31.7)	12,652 (64.9)	
≥65, n (%)	40,558 (14.6)	152,246 (33.4)	45,624 (62.0)	8,968 (67.8)	4,919 (25.2)	
Male, n (%)	182,394 (65.5)	282,266 (62.0)	32,251 (43.9)	5,834 (44.1)	13,472 (69.1)	<.0001
Low income, n (%)	59,106 (21.2)	93,976 (20.6)	15,091 (20.5)	2,605 (19.7)	2,545 (13.1)	<.0001
Smoker, n (%)						<.0001
Non-smoker	142,450 (51.1)	254,752 (55.9)	52,079 (70.8)	9,513 (71.9)	9,659 (49.5)	
Ex smoker	48,598 (17.4)	86,645 (19.0)	11,219 (15.3)	2,112 (16.0)	4,701 (24.1)	
Current	87,574 (31.4)	114,093 (25.1)	10,250 (13.9)	1,611 (12.2)	5,139 (26.4)	
Drinker, n (%)						<.0001
Non drinker	140,437 (50.4)	261,485 (57.4)	55,053 (74.9)	10,766 (81.3)	10,621 (54.5)	
Mild drinker	102,477 (36.8)	150,863 (33.1)	15,182 (20.6)	2,059 (15.6)	7,260 (37.2)	
Heavy drinker	35,708 (12.8)	43,142 (9.5)	3,313 (4.5)	411 (3.1)	1,618 (8.3)	
Regular physical activity, n (%)	59,615 (21.4)	100,674 (22.1)	15,022 (20.4)	2,419 (18.3)	4,616 (23.7)	<.0001
BMI, kg/m <sup>2</sup>	24.9 ± 3.4	25.1 ± 3.2	25.2 ± 3.3	25.0 ± 3.4	24.7 ± 3.2	<.0001
<18.5	4,776 (1.7)	5,870 (1.3)	1,057 (1.4)	220 (1.7)	295 (1.5)	
<23	74,579 (26.8)	109,387 (24.0)	17,108 (23.3)	3,310 (25.0)	5,438 (27.9)	
<25	69,590 (25.0)	116,988 (25.7)	18,386 (25.0)	3,296 (25.0)	5,114 (26.2)	
<30	109,161 (39.2)	191,785 (42.1)	31,554 (42.9)	5,397 (40.8)	7,486 (38.4)	
≥30	20,516 (7.4)	31,460 (6.9)	5,443 (7.4)	1,013 (7.7)	1,166 (6.0)	
Waist circumference, cm	85.0 ± 8.6	85.6 ± 8.3	86.1 ± 8.6	86.6 ± 8.8	85.2 ± 8.2	<.0001
Hypertension, n (%)	140,229 (50.3)	261,649 (57.4)	55,399 (75.3)	11,364 (85.9)	11,494 (59.0)	<.0001
Dyslipidaemia	102,814 (36.9)	186,125 (40.9)	36,877 (50.1)	7,562 (57.1)	8,112 (41.6)	<.0001
Cardiovascular disease, n (%)	11,079 (4.0)	26,932 (5.9)	8,332 (11.3)	2,107 (15.9)	1,452 (7.5)	<.0001
Fasting glucose, mg/dL	150.6 ± 50.4	145.5 ± 48.4	141.4 ± 51.5	141.6 ± 60.0	143.2 ± 48.5	<.0001
eGFR (mL/min/1.73 m <sup>2</sup> )	110.2 ± 48.9	76.0 ± 8.0	54.6 ± 4.2	39.4 ± 4.0	8.9 ± 6.9	<.0001
DM duration ≥5 years, n (%)	81,266 (29.2)	148,105 (32.5)	34,060 (46.3)	8,083 (61.1)	7,412 (38.0)	<.0001
Insulin user, n (%)	21,547 (7.7)	37,359 (8.2)	10,419 (14.2)	3,606 (27.2)	3,312 (17.0)	<.0001
≥3 Oral hypoglycaemic agent user, n (%)	44,858 (16.1)	74,371 (16.3)	15,858 (21.6)	3,402 (25.7)	2,754 (14.1)	<.0001
CKD, n (%)	-	-	73,548 (100)	13,236 (100)	19,499 (100)	<.0001
Urine protein positive, n (%)	17,484 (6.3)	31,733 (7.0)	9,142 (12.4)	3,483 (26.3)	3,552 (18.2)	<.0001

Data are presented as means ± standard deviations or numbers and percentages. BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

characteristics represented information from the 2009 medical examination. During the follow-up period with a mean of  $7.83 \pm 1.69$  years, psoriasis was evident in 28,010 (3.33%) of the 840,395 DM patients.

**Association between eGFR and psoriasis in DM patients**

As seen in Figure 2a, DM patients with  $eGFR < 60$  showed a higher incidence probability of psoriasis than those with  $eGFR \geq 60$  (log-rank  $p < 0.0001$ ). Psoriasis HR according to eGFR levels were assessed as seen in Table 2. Before adjustment, DM patients with CKD exhibited a higher risk of psoriasis than those without CKD [Table 2]. These results showed similar trends after adjustment for age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidemia, fasting glucose, DM duration  $\geq 5$  years, and  $\geq 3$  oral hypoglycemic agents used in Model 2. The lower the eGFR, the higher the HR of psoriasis in CKD patients [Table 2]. This tendency persisted after additionally adjusting the urine protein in Model 3 [Table 2]. In addition, the incidence rates of psoriasis showed similar tendencies with HRs [Figure 2b].



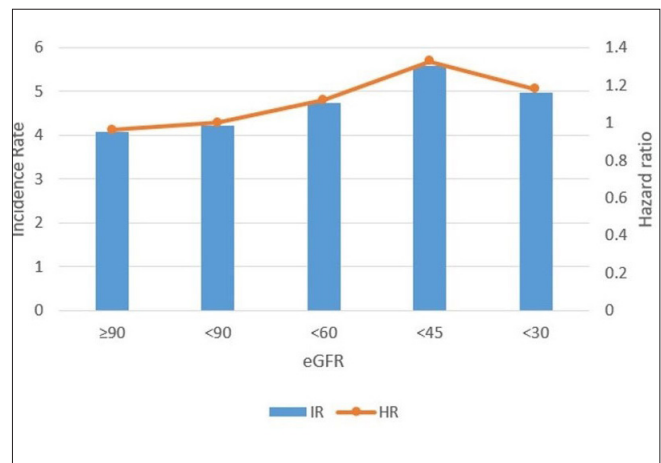
**Figure 2a:** Incidence probability of psoriasis according to the eGFR level in patients with diabetes mellitus.

**Relationship between urine protein and psoriasis in DM patients**

DM patients with proteinuria showed a higher incidence of psoriasis than those without proteinuria (log-rank  $p < 0.0001$ , [Figure 3a]). Psoriasis HR according to proteinuria levels were assessed and are presented in Table 3. Before adjustment, DM patients with proteinuria had a higher risk of psoriasis than those without proteinuria and the HR of psoriatic patients showed a positive correlation to the severity of proteinuria [Table 3]. This persisted after adjustment for age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidemia, fasting glucose, DM duration  $\geq 5$  years and  $\geq 3$  oral hypoglycemic agent use in Model 2 and even after additionally adjusting for eGFR in Model 3 [Table 3]. Further, the incidence rate of psoriasis also significantly increased as the proteinuria level increased [Figure 3b].

**Discussion**

Psoriasis is a chronic systemic inflammatory disease with a decreased quality of life and increased mortality rate for a variety of reasons.<sup>1,17-19</sup> So far, the only study on the risk of psoriasis in diabetic patients was by Jacob *et al.* (2017).<sup>20</sup>



**Figure 2b:** Incidence rates and hazard ratios of psoriasis according to the eGFR level in patients with diabetes. (HR: Hazard ratios, IR: Incidence rates.)

**Table 2: Unadjusted and adjusted HR and 95% CI of psoriasis according to eGFR level**

eGFR	n	Psoriasis, n (%)	Incidence rate (per 1000 person-years)	HR (95% C.I.)		
				Model 1	Model 2	Model 3
$\geq 90$	278,622	9,015	4.0	0.9 (0.9, 0.9)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
60-90	455,490	15,153	4.2	1 (Ref.)	1 (Ref.)	1 (Ref.)
45-60	73,548	2,608	4.7	1.1 (1.0, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
30-45	13,236	501	5.5	1.3 (1.2, 1.4)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)
$< 30$	19,499	733	4.9	1.1 (1.0, 1.2)	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)
p-value				$< 0.0001$	$< 0.0001$	$< 0.0001$

Model 1: Non-adjusted

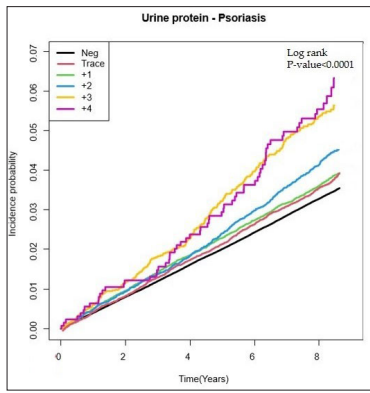
Model 2: Age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidaemia, fasting glucose, DM duration  $\geq 5$  years, Insulin use, and oral hypoglycaemic agent  $\geq 3$  agents adjusted.

Model 3: Age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidaemia, fasting glucose, DM duration  $\geq 5$  years, Insulin use, oral hypoglycaemic agent  $\geq 3$  agents, and urine protein (positive vs. negative) adjusted.

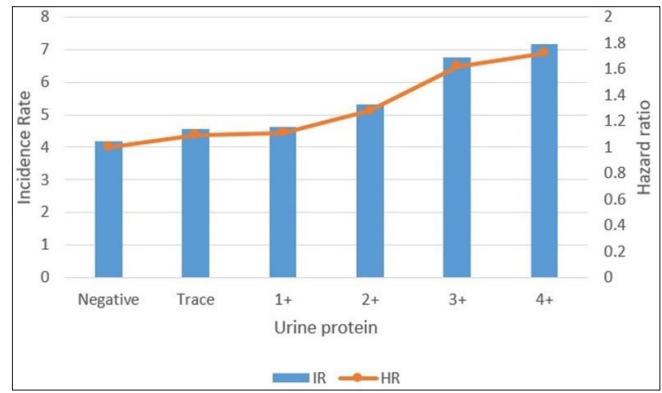
eGFR estimated glomerular filtration rate; HR hazard ratio

CI: Confidence interval





**Figure 3a:** Incidence probability of psoriasis according to the proteinuria level in patients with diabetes mellitus.



**Figure 3b:** Incidence rates and hazard ratios of psoriasis according to the proteinuria level in patients with diabetes. (IR: Incidence rates, HR: Hazard ratios.)

**Table 3: Unadjusted and adjusted HR and 95% CI of psoriasis according to urine protein**

Urine protein	Number	Psoriasis, n (%)	Incidence rate (per 1000 person-years)	HR (95% C.I.)		
				Model 1	Model 2	Model 3
Negative	743,503	24,428	4.1			
Trace	31,498	1,115	4.5	1.0 (1.0, 1.1)	1.060 (0.998, 1.125)	1.060 (0.998, 1.125)
1+	35,195	1,238	4.6	1.1 (1.0, 1.1)	1.043 (0.985, 1.105)	1.043 (0.985, 1.105)
2+	18,189	714	5.3	1.2 (1.1, 1.3)	1.164 (1.080, 1.254)	1.164 (1.080, 1.254)
3+	5,902	281	6.7	1.6 (1.4, 1.8)	1.433 (1.273, 1.613)	1.433 (1.273, 1.613)
4+	1,267	63	7.1	1.7 (1.3, 2.2)	1.508 (1.177, 1.931)	1.508 (1.177, 1.931)
p-value				<.0001	<.0001	

Model 1: Non-adjusted

Model 2: Age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidaemia, fasting glucose, DM duration ≥5 years, Insulin use, and oral hypoglycaemic agent ≥3 agents adjusted.

Model 3: Age, sex, low income, smoking, drinking, regular physical activity, BMI, hypertension, dyslipidaemia, fasting glucose, DM duration ≥5 years, Insulin use, oral hypoglycaemic agent ≥3 agents, eGFR adjusted.

(HR: hazard ratio, CI: Confidence interval)

Comparing 72,148 diabetic patients with non-diabetic controls, they found that diabetic patients developed psoriasis more than controls (3.4% vs 2.8%). They hypothesised that psoriasis and diabetes share obesity and overweight as risk factors, that anxiety increases the risk of developing psoriasis in diabetic patients, and that skin infections may mediate the relationship between psoriasis and diabetes. On the other hand, we investigated the association between the two diseases from the new perspective of renal dysfunction, and found an association between renal dysfunction in diabetes and the development of psoriasis.

We identified that the risk and incidence rate of psoriasis increased as CKD and/or proteinuria progressed in diabetic patients. Although both CKD and proteinuria have been reported to be associated with psoriasis, whether they play a role in triggering psoriasis in diabetic patients is not yet known.<sup>9</sup> The pathogenic mechanism shared between them is also not clearly established; however, several possible explanations are discussed below.

First, Th17 lymphocytes can induce inflammation in both psoriasis and kidney disease. Especially IL-17, one of the major pro-inflammatory factors in psoriasis, is known to play a crucial role in the development and progression of renal diseases such as glomerulonephritis, nephrotic syndrome, and diabetic nephropathy.<sup>11,21</sup>

Second, both proteinuria and psoriasis reflect vascular damage. Proteinuria is the leakage of albumin from glomerular capillaries, resulting from damaged vascular endothelium. The incidence of peripheral vascular disease is higher in patients with psoriasis than those without.<sup>9</sup> In addition to this, Creamer *et al.* (2002) observed systemic vascular hyperpermeability in patients with moderate to severe psoriasis, owing to elevated plasma VEGF concentration which could also induce hyperpermeability in the renal microvasculature.<sup>22</sup>

Third, oxidative stress contributes to the pathogenesis of both kidney disease and psoriasis. Duni *et al.* (2019) found that oxidative stress promotes inflammation through proinflammatory oxidised lipids or advanced oxidation protein products in diabetic nephropathy, IgA nephropathy, and polycystic kidney disease.<sup>23</sup> Plenkowska *et al.* (2020) found that the total oxidative stress level increased in psoriasis, leading to the activation of signalling pathways and consequently to the activation of Th1 and Th17 cells.<sup>24</sup>

It is noteworthy that the group with eGFR ≥ 90 had a higher risk of psoriasis compared to the reference group (eGFR 60–90) after adjustment. The precise reason behind increased psoriasis risk in the eGFR ≥ 90 remains unclear; however, GFR exhibits favourable values during a ‘honeymoon period’ in the clinical course of DM due to glomerular hyperfiltration.<sup>25</sup> It is possible

that some individuals in the eGFR  $\geq 90$  group were classified as such due to glomerular hyperfiltration. Further, there is an ongoing debate on CKD staging, with some experts proposing the combination of stage 1 (GFR  $\geq 90$ ) and 2 (GFR 60–90).<sup>26</sup> It is also worth noting that GFR can be influenced by a variety of factors including dehydration, protein intake, medications and others which may contribute to the consistently high risk of psoriasis in the GFR  $\geq 90$  groups.

### Limitations

One limitation of this study is that the national database did not include information on the severity of psoriasis. Further research is needed to investigate the correlation between the progression of CKD/ESRD and psoriasis severity in diabetic patients. It is worth noting that psoriasis is typically diagnosed by a dermatologist and recorded in the data of NHIS of South Korea, but misclassification is possible. Additionally, this study did not investigate details of oral hypoglycemic agents such as type and dose. However, this is the first study to determine the relationship between the development of psoriasis, the progression of CKD, and the presence of proteinuria in diabetic patients based on the data obtained from a national population.

### Conclusion

If psoriasis develops in patients with abnormal kidney function, treatment may be more difficult because of the limitations to the use of oral systemic immunosuppressants in them, and CKD itself increases the mortality in psoriasis patients.<sup>1,16</sup> Therefore, according to the results of this study, proactive treatment to reduce the risk of psoriasis in diabetic patients by monitoring and early management of abnormal renal function is suggested; the eGFR as well as proteinuria may be important predictive factors therein.

**Ethical approval:** This study was approved by the Ethics Committee of Seoul St. Mary's Hospital, the Catholic University of Korea (KC22ZISI0406).

**Declaration of patient consent:** Since this study used anonymised publicly available data, it was exempted from the IRB approval process.

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**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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