Dermatology Practical & Conceptual

Renal Implications of Psoriasis: Urinary Podocyte Markers and Disease Progression

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ABSTRACT

Introduction: Psoriasis may lead to glomerular inflammatory damage and disruption of the podocyte barrier, allowing podocyte degradation products to leak into the urine.

Objectives: We aimed to analyze the concentrations of podocyte surface glycoprotein podocalyxin (PDX) and podocyte slit protein nephrin in spot urine samples from patients with mild, moderate, or severe psoriasis vulgaris.

Methods: A total of 78 participants, including 58 patients diagnosed with mild, moderate, or severe psoriasis vulgaris and 20 healthy controls, were included in the study. Psoriasis was diagnosed based on the typical morphological characteristics of the lesions. Morning urine samples were used to evaluate urine PDX and nephrin levels. Albuminuria was evaluated by calculating the urine albumin-to-creatinine ratio (uACR).

Results: Urinary PDX and nephrin levels were significantly higher in the psoriasis group than in the control group. Urinary PDX and nephrin levels in the mild and moderate psoriasis groups were similar but higher than those in the control group and significantly higher in the severe psoriasis group than in the mild and moderate psoriasis groups. The microalbuminuria rates were similar between the psoriasis and control groups. A significant positive correlation was observed between urine PDX, nephrin, uACR, and SBP. After adjusting for age, BMI, and sex, urine PDX and nephrin levels were found to be independent risk factors for microalbuminuria.

Conclusion: This study showed that podocyte damage in patients with psoriasis begins in the early stages of the disease and significantly increases in the severe stage of the disease.

Introduction

Psoriasis vulgaris, also known as plaque psoriasis, is a chronic autoimmune inflammatory dermatosis with a worldwide prevalence of 2% [1]. Cardiometabolic comorbidities, such as chronic kidney disease (CKD) and end-stage renal disease (ESRD), are frequently observed throughout the course of the disease [2]. In particular, severe psoriasis has been reported as an independent risk factor for CKD and ESRD. The increased incidence of glomerulonephritis in psoriasis has been reported to be one of the main causes of CKD [3]. Although the incidence of kidney disease increases in proportion to the severity of the disease, an increased risk can also be detected in moderate-type psoriasis [4-6]. Activation of the toll-like receptor/nuclear factor kappa-b pathway in the glomeruli due to the chronic inflammatory nature of the disease, redox balance disturbed in favor of oxidative stress, nephrotoxic side effects of some drugs used in treatment, and the presence of osteoarthritis are some of the mechanisms that trigger chronic renal damage [6,7]. The association between psoriasis and CKD and death from ESRD has been reported to persist even after adjusting for potential confounders such as age, sex, osteoarthritis, and use of methotrexate, cyclosporine, or nonsteroidal anti-inflammatory drugs [2,4].

Podocytes, which form the outer surface of the glomerular basement membrane, are important filtration barriers in the glomeruli. Structural or functional podocyte pathologies are the main causes of albumin leakage into Bowman's space [8-11]. Podocalyxin (PDX) and nephrin are podocyte proteins that ensure the integrity of the renal filtration barrier both physically and chemically. While nephrin creates a physical barrier with its transmembrane protein feature specific to the slit diaphragm, PDX creates a chemical barrier with its glycocalyx feature [9,10]. Denaturation of these proteins causes a defect in the glomerular endothelial barrier, leading to podocyte dysfunction, glomerulosclerosis, and subsequent renal failure [10,11]. In the early diagnosis of kidney damage due to psoriasis, it is recommended to check serum creatinine and blood urea nitrogen levelsando perform routine urine analysis for microalbuminuria. Although predictive tests have a high rate of detecting renal damage in severe psoriasis cases with a body surface area of ≥3%, albumin leakage, serum creatinine, and serum nitrogen levels may be normal in mild and moderate psoriasis despite the presence of early stage glomerular damage [6,12]. Since albumin passage into the urine occurs following podocyte damage, podocyte-specific proteins PDX and nephrin can be detected in mild or moderate psoriasis cases, where no protein is detected in urine spot samples.

Objectives

In systemic diseases accompanied by glomerular damage, such as psoriasis, chronic inflammation, and oxidative stress, inflammatory damage, adhesion, and scarring in the glomeruli can cause disruption of the podocyte barrier and leakage of podocyte degradation products into the urine before protein leakage [7]. However, except for a few experimental studies, data on the role of urine podocyte-specific protein analysis in the early diagnosis of renal involvement in psoriasis are limited. In this study, we analyzed the levels of the podocyte surface glycoprotein podocalyxin and podocyte slit protein nephrin in spot urine samples of patients diagnosed with mild, moderate, or severe psoriasis vulgaris to reveal the relationship between disease severity and podocyte damage.

Methods

This cross-sectional study was approved by the Ethics Committee of the Firat University Non-interventional Research (ethical approval number: 2024/01-35, date: 09.01.2024). A total of 78 participants, 58 with psoriasis vulgaris at different stages of severity (mild, moderate, or severe psoriasis vulgaris) and 20 controls were included in the study. Twenty patients who did not have chronic, inflammatory, or systemic dermatosis and who were matched with the psoriasis group in terms of age and BMI were included in the control group. Participants were selected from patients admitted to the Gozde Academy Hospital Dermatology Clinic. Some patients were previously diagnosed with psoriasis, whereas others were newly diagnosed with the disease. Considering the prevalence of the disease, the number of psoriasis patients who attending our outpatient clinic was not very high, so we invited patients diagnosed with psoriasis from other centers to participate in the study. Psoriasis was diagnosed based on the typical morphological appearance of the lesions. The diagnosis was confirmed based on the presence of a symmetrical, sharply demarcated erythematous plaque covered with silver scales. Although psoriasis is histopathologically characterized by epidermal acanthosis, hyperkeratosis, and parakeratosis, a biopsy is not required for diagnosis in any patient [13]. The distribution of plaques differed among the patients. In addition to isolated plaques, the plaques merged and occupied large skin areas. Plaques were more frequently located on the trunk, scalp, lower and upper extremities, and the buttocks. Disease severity was determined using data from the Canadian Psoriasis Guideline Committee [14]. Patients with <3% body surface area (BSA) involvement, whose quality of life was minimallyaffected,d and whose lesions were controlled with topical treatment were included in the mild disease group. Patients with 3–10% BSA

involvement that was difficult to control with routine topical use and whose quality of life was significantly affected were considered to have moderate disease. Patients who did not benefit from topical treatments, had >10% BSA covered with plaques, and showed severe deterioration in quality of life were considered to have severe disease. Patients with a history of urinary tract infection, metabolic syndrome, nephritic or nephrotic syndrome, or diabetes were excluded from the study. Patients who had used nephrotoxic drugs in the preceding six months, had diabetic nephropathy, were diagnosed with chronic kidney disease, underwent hemodialysis, or had a history of single or combined use of azathioprine, cyclosporine, or methotrexate were not included in the study. Urine samples were not collected from patients with psoriasis flares upon admission. The exclusion criteria were also applied to the control group.

Measurements of Urine Podocalyxin, Nephrin, and Albumin-Creatinine Ratio

Morning urine samples were used to evaluate the urine PDX and nephrin levels. Strenuous exercise was prohibited two days before sample collection because of the possibility of increasing the risk of protein leakage from urine. Fresh urine samples were collected in sterile containers, centrifuged at 3000 rpm for 3 min, and then stored frozen until the day of analysis. Urinary podocalyxin and nephrin levels were measured using ELISA with commercially available kits. Kits for nephrin and podocalyxin measurements were purchased from Sunred Biotechnology Company (Shanghai, China). Analyses were performed in accordance with the manufacturer's instructions, as specified in the kit catalogue. An automatic washer (Biochrom Anthos Fluido 2; Biochrom Ltd., Cambridge, UK) was used for plate washing. Absorbance was measured at 450 nm using a CLARIOstar PLUS microplate reader (BMG Labtech, Germany). The test results were expressed as ng/mL. The measurement range of the PDX was 0.2-60 ng/mL and the minimum measurable level was 0.153 ng/mL. The standard curve range for nephrin was 0.2-40 ng/mL. The minimum measurable nephrin level was 0.166 ng/ml. While the intra-assay CV value for both kits was <10%, the inter-assay CV value was <12%. Albuminuria was evaluated by calculating the albumin-to-creatinine ratio (uACR) in morning urine samples. Normal albuminuria was defined as albumin/g creatinine ≤ 30 mg. Microalbuminuria was defined as uACR >30–300 mg albumin/g Cr. As psoriasis is associated with many comorbidities such as obesity, diabetes, hypertension, and cardiovascular disease, the following biochemical and demographic parameters were analyzed [15]: systolic and diastolic blood pressures of each participant were recorded, the height and weight of the participants in the psoriasis and control groups were measured, and their BMI values were calculated [weight (kg)/square of height (kg/m^2]). Following an 8–10h overnight fast, blood samples were collected from both groups and stored until analysis. Fasting blood glucose, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and creatinine levels were measured using an autoanalyzer. Fasting blood glucose and creatinine levels were measured using the hexokinase and Jaffe methods, respectively. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR): insulin (μU/mL) × glucose (mg/dL)/405 [16].

Statistical Analysis

Statistical analyses were performed using SPSSv-27 (IBM Corp., Armonk, NY, USA). Graphs were created using GraphPad Prism 8.3.0 (GraphPad Software, San Diego, California, USA). The suitability of the variables for normal distribution was examined using the Shapiro-Wilk test. Data are presented as mean ± standard deviation or median (1^{st} quartile–3^{rd} quartile) for continuous variables according to the normality of distribution and as frequencies (percentages) for categorical variables. Variables with a normal distribution were analyzed using the independent samples t-test, and those with a non-normal distribution were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square or Fisher's exact tests. A one-way ANOVA test was used to compare more than two groups with normal distribution, and parameters that did not show normal distribution within groups were compared using the Kruskal-Wallis test. The Bonferroni test was used for post hoc pairwise comparisons. Spearman's correlation test was used to determine the relationship between variables. Multivariate regression analysis was performed to identify independent risk factors for albuminuria in patients with psoriasis vulgaris after adjusting for age, body mass index (BMI), and sex. The "Metan" R package was used to generate a correlation heatmap using Spearman's method [17]. Statistical significance was set at $P<.05$.

Results

When classified according to disease severity, 22 of the 58 patients had mild psoriasis, 16 had moderate psoriasis, and 20 had severe psoriasis. Of the 58 patients, 32 were male and 26 were female (M/F ratio, 32/26). The mean age and BMI of the psoriasis and control groups were similar. In addition to SBP and DBP, serum creatinine and FBG levels were similar between the psoriasis and control groups (Table 1). HDL-C levels were significantly lower and TG levels were higher in the psoriasis group than in the control group. The mean HOMA-IR values in the psoriasis group were significantly higher than those in the control group. Mean urinary

Table 1. Demographic and Laboratory Characteristics of Psoriasis Vulgaris and Control Groups.

Parameter	Psoriasis (N=58)	Control (N=20)	*p-value*
Age (years)	35.03± 4.96	34.05± 4.95	0.447
Sex (Male/Female)	32/26 (55.2%)	10/10 (50%)	0.889
Body Mass Index (kg/m^2)	24.7 ± 1.5	23.86± 2.21	0.060
PDX (ng/mL)	42.38 ± 10.10	17.76 ±5.87	**<0.001**
Nephrin (ng/mL)	32.57 ± 8.4	13.54 ± 2.83	**<0.001**
FBG (mg/dL)	90.5 (85-97)	91.5 (88-98)	0.753
Urea (mg/dL)	30.16± 6.59	28.95± 6.64	0.482
Creatinine (mg/dL)	0.75 (0.72 - 0.89)	0.72 (0.63 - 0.83)	0.065
SBP (mm/Hg)	115.0 (110-120)	110 (110-115)	0.180
DBP (mm/Hg)	75 (70-80)	72.5 (70-80)	0.098
HDL-C (mg/dL)	34.45± 11.09	46.7± 15.85	**0.004**
TG (mg/dL)	127 (89- 170)	92.5 (75.5- 119.5)	**0.006**
HOMA-IR	2.05± 0.35	1.29± 0.15	**<0.001**
uACR	14 (8 - 21)	7 (4-8)	**<0.001**
Micro-albuminuria (uACR >30-300 mg/gCr)	10 (17.2%)	1 (5%)	0.272

Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variable. Abbreviations: DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment insulin resistance; SBP = systolic blood pressure; PDX = podocalyxin; TG = triglyceride; uACR = albumin-creatinine ratio.

PDX (42.38±10.10 ng/mL vs. 17.76±5.87 ng/mL, *P*<0.001) levels of psoriasis group were significantly higher than the control group (Table 1 and Figure 1). The mean urinary PDX levels in the mild (37.20 ± 8.87 ng/mL) and moderate (38.51 ± 7.87 ng/mL) psoriasis groups were similar but higher than those in the control group (17.76±5.87 ng/mL). Mean urinary nephrin (32.57±8.4 ng/mL vs. 13.54 ± 2.83 ng/mL, *P*<0.001) levels of psoriasis group were significantly higher than the control group (Table 1 and Figure 1). The mean urinary nephrin levels in the mild (28.21 ±7.04 ng/mL) and moderate (29.59± 5.03 ng/mL) psoriasis groups were similar but higher than those in the control group (13.54 ± 2.83 ng/mL). Urinary PDX (51.17±6.73 ng/mL) and nephrin (39.74 ±7.33 ng/mL) levels of the severe psoriasis group were significantly higher than the mild and moderate psoriasis groups (Table 2 and Figure 2). Microalbuminuria was detected in 10 of the 58 patients in the psoriasis group and in one of the 20 patients in the control group. The microalbuminuria rates were similar in the psoriasis and control groups (17.2% vs. 5%, *P*=0.272). The risk of microalbuminuria did not vary with psoriasis severity. A significant positive correlation was detected between the urine PDX and nephrin levels (r=0.612, *P*<0.001). Urine PDX showed a significant positive correlation with SBP (r=0.515, *P*<0.001) and uACR (r=0.644, *P*<0.001). Urine nephrin levels were also significantly positively correlated with SBP (r=0.337, *P*=0.01) and uACR (r=0.312, *P*=0.017). No significant correlation was found between urine PDX, nephrin, and serum creatinine levels (Figure 3). In the logistic regression analysis performed after adjusting for age, BMI, and sex, urine PDX and nephrin levels were found to be independent risk factors for microalbuminuria in psoriasis. A 1-unit increase in PDX (OR, 1.831; 95% CI: 1.189–2.821; *P*=0.006) and nephrin (OR: 1.625, 95% CI: 1.129–2.339; *P*=0.009) led to a 1.83-fold and 1.62-fold increase in the risk of microalbuminuria, respectively.

Conclusions

Many studies have shown that the risk of renal disease is higher in patients with psoriasis vulgaris than in the disease-free population and that this risk increases withpsoriasis severitys [1-3]. The chronic inflammatory nature of psoriasis and its association with obesity, diabetes, and cardiovascular diseases are considered the main causes of renal damage [15]. Accompanying osteoarthritis with psoriasis and the use of methotrexate, cyclosporine, or nonsteroidal anti-inflammatory drugs for therapeutic purposes significantly increases the risk of renal damage [2,4]. In contrast, psoriasis is thought to initiate kidney damage by causing nephritis in the glomeruli, regardless of the accompanying comorbidities [3]. Therefore, early detection of subclinical renal dysfunction in psoriasis is important to prevent the progression of renal damage. Although predictive tests are more likely to detect kidney damage in severe psoriasis

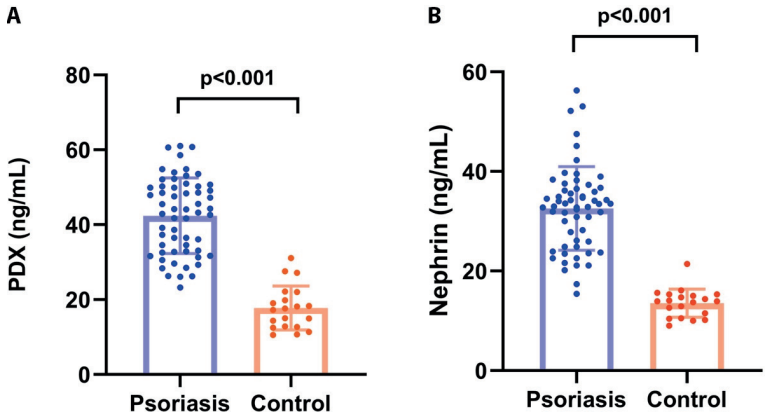

Figure 1. Graphical representation of podocalyxin (PDX) and nephrin levels of psoriasis and control groups. Note that both markers were higher in the psoriasis group compared to controls.

Table 2. Comparison of Demographic and Laboratory Parameters of The Groups According to Psoriasis Severity.

	Mild Psoriasis (n=22)	Moderate Psoriasis (N=16)	Severe Psoriasis (N=20)	Control(N=20)
Age (year)	34.59 ± 3.9	33.56±5.49	36.70±5.32	34.05 ± 4.95
BMI (kg/m^2)	24.53±1.51	24.49±1.64	25.06±1.38	23.86±2.21
BSA (%)	<3%	3% to 10%	>10%	-
Male/female	12/10 (54.5%)	10/6 (62.5%)	10/10 (50%)	10/10 (50%)
PDX (ng/mL)	37.20 ± 8.87***,###	38.51 ±7.87***,###	51.17 ± 6.73***	17.76±5.87
Nephrin (ng/mL)	28.21 ± 7.04***,###	29.59 ± 5.03***,###	39.74 ± 7.33***	13.54±2.83
FBG (mg/dL)	86.5 (80-95)	91.5 (87-98.5)	92.5 (87.5-97)	91.5 (88-98)
Urea (mg/dL)	30.68 ±8.35	29.39 ±3.95	30.21 ±6.35	28.95 ±6.64
Creatinine (mg/dL)	0.70 (0.64-0.78)##	0.79 (0.74-0.89)	0.88 (0.75-0.98)*	0.72 (0.63 - 0.83)
SBP (mm/Hg)	112.5 (105-120)	110 (110-115)	120 (110-122.5)	110 (110-115)
DBP (mm/Hg)	75.0 (70.0-80.0)	75.0 (70.0-80.0)	80.0 (75.0-85.0)	72.5 (70.0-80.0)
HDL-C (mg/dL)	35.55 ±12.03	33.06 ± 13.90*	34.35 ± 7.31*	46.70 ± 15.85
TG (mg/dL)	106.5 (89- 154)	107.5 (81 -165)	156.5 (133.5-198)**	92.5 (75.5- 119.5)
HOMA-IR	1.95 ± 0.29*	2.08 ± 0.35*	2.15 ± 0.38*	1.29 ± 0.15
Normo-albuminuria (uACR≤30 mg/gCr)	20 (90.9%)	14 (87.5%)	14 (70%)	19 (95%)
Micro-albuminuria (uACR>30-300 mg/gCr)	2 (9.1%)	2 (%12.5)	6 (30%)	1 (5%)

Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variable. Bonferroni adjusted p values were used. *P <0.05, **P <0.01, ***P <0.001 Vs. Control; ##P <0.01, ###P <0.001 vs. severe psoriasis group. Abbreviations: BMI = body mass index; BSA = body surface area; DBP =diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostasis model assessment insulin resistance; SBP = systolic blood pressure; PDX = podocalyxin; TG = triglyceride; uACR = albumin-creatinine ratio.

cases, albumin leakage, serum creatinine, and serum nitrogen levels may be normal in mild and moderate psoriasis cases [6,12]. This study provides new data showing that the urinary levels of the podocyte degradation proteins PDX and nephrin are significantly increased in patients with psoriasis compared to those in healthy controls. The positive correlation between uACR, PDX, and nephrin indicates that the urinary excretion of podocyte degradation proteins and albumin are interrelated. Although microalbuminuria is observed in 17.2% of patients with psoriasis, an increase in urinary PDX and nephrin levels is detected in the majority of patients with psoriasis, suggesting that the passage of podocyte destruction proteins into the urine begins before albumin. Even if renal dysfunction and podocyte damage

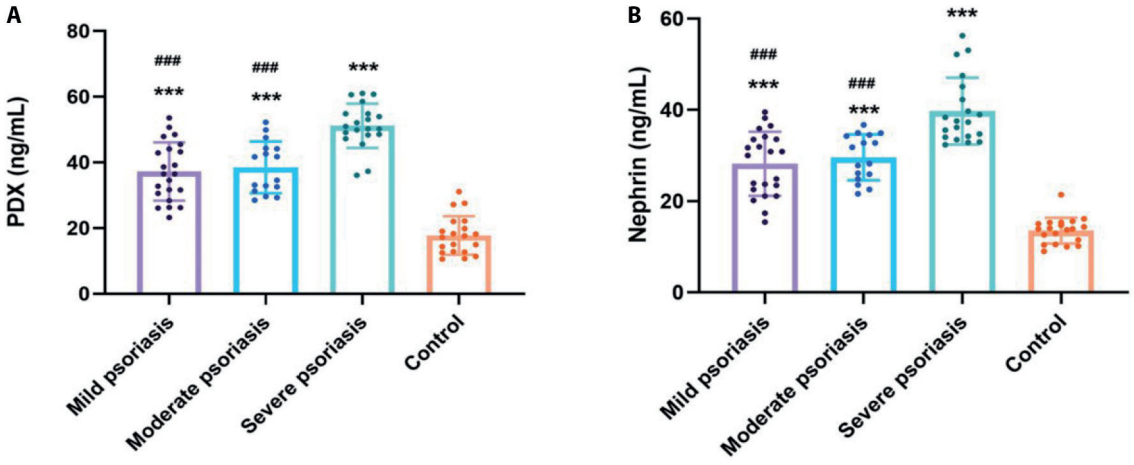

Figure 2. Graphical representation of changes in podocalyxin (PDX) and nephrin levels according to psoriasis severity. $^{***}P<0.001$ vs. control; $^{###}P<0.001$ vs. severe psoriasis group.

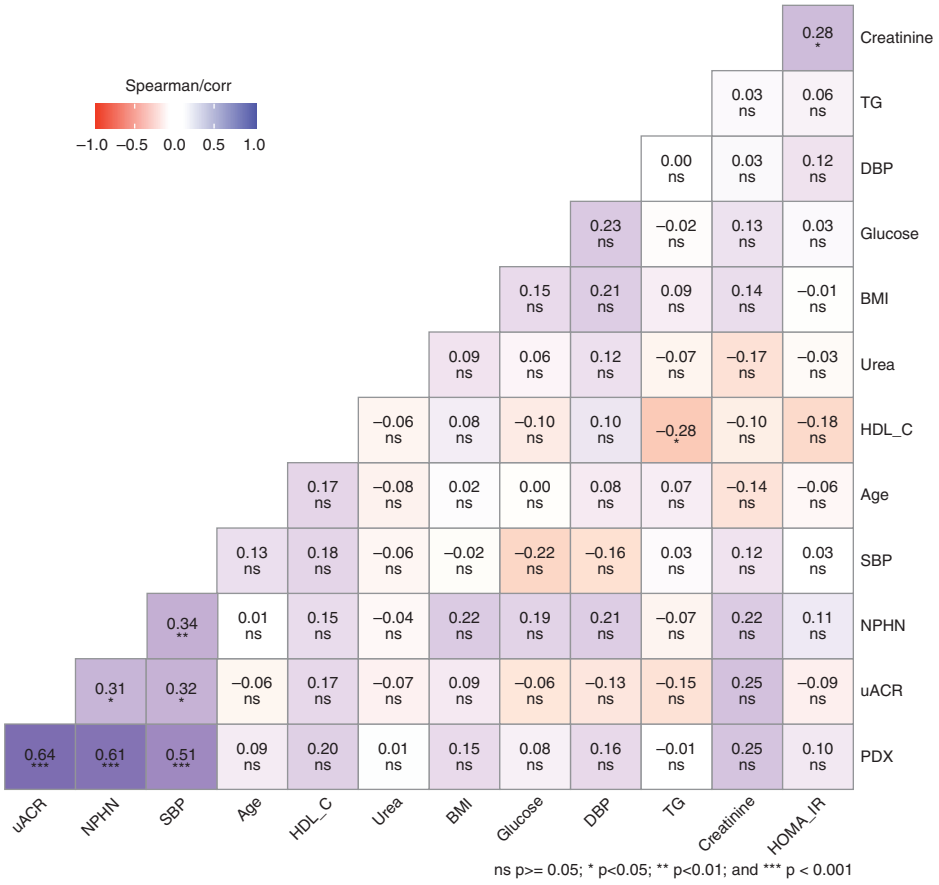

Figure 3. Correlation matrix showing the correlation coefficients between podocalyxin (PDX), nephrin, and laboratory and demographic variables as a heat map. A correlation coefficient of 0 indicates no correlation between variables, +1 indicates a positive correlation, and -1 indicates a negative correlation. Color intensity (red, negative correlation; blue, positive correlation).

begin in mild and moderate psoriasis cases, it is obvious that a certain amount of time is needed for podocyte destruction proteins to become detectable in the urine. As disease severity affects the incidence of long-term renal damage, we evaluated the changes in urine PDX and nephrin levels in the mild, moderate, and severe groups. Urinary PDX and nephrin levels were significantly higher in all groups than in healthy controls. The similarity in urinary podocyte degradation product levels in the mild and moderate groups suggests that an increase in disease severity does not cause a gradual increase in glomerular damage. The PDX and nephrin levels in both groups may be similar because the

transition from the mild to moderate group occurred, or the process of being in the moderate group was at an early stage. The significantly higher albuminuria, urine PDX, and nephrin levels in patients with severe psoriasis than in those with mild and moderate psoriasis suggest exponential renal damage. The rapid increase in podocyte damage in the mild and moderate groups after switching to the severe group may be due to an increase in inflammatory reactions owing to BSA expansion. The chronic inflammatory features of psoriasis may lead to an increase in podocyte damage due to the activation of nuclear factor kappa-b, which is the main inflammatory pathway in the glomeruli, in cases of severe psoriasis [6,7]. Clinically evident nephrotoxic treatments and osteoarthritis may also be responsible for the exponential increase in urine PDX and nephrin levels in patients with severe psoriasis. After adjusting for possible confounding factors, such as age, BMI, and sex, PDX and nephrin were independent risk factors for microalbuminuria occurring in psoriasis, indicating that disease severity is an important determinant of podocyte damage, independent of other confounders. The cumulative effect of multiple etiological factors that determine the occurrence and progression of psoriasis may cause glomerular damage in patients with psoriasis. The high triglyceride levels, increased insulin resistance, and high glucose levels observed in the psoriasis group may have contributed to podocyte damage. Similarly, the positive correlation between systolic blood pressure, PDX, and nephrin levels supports the hypothesis that systemic comorbidities associated with the disease also contribute to podocyte damage. The reported increase in podocyte damage in patients with preeclampsia is evidence that blood pressure and podocyte damage are related [18]. Similarly, in the psoriasis group, hyperinsulinemia may mediate glomerular hypertrophy and podocyte damage by increasing blood pressure [19, 20]. In the psoriasis group, high triglyceride levels may cause podocyte damage by stimulating oxidative stress and fibrinogenic activity [20-22].

Although the relatively small number of participants is a significant limitation, this study shows that podocyte damage in patients with psoriasis begins in the early stage of the disease and increases significantly in the severe disease stage. Urinary PDX and nephrin levels were positively correlated with uACR and could be detected in urine before or simultaneously with microalbuminuria. Although renal damage is common in severe psoriasis, renal dysfunction in mild and moderate cases may not be detected using classical blood and urine analysis. For this reason, analyzing urine PDX and nephrin levels of patients with psoriasis in addition to conventional analyses such as microalbuminuria, serum creatinine, and blood urea nitrogen can provide an early diagnosis of renal dysfunction, making it possible to take the necessary precautions.

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