The spectrum of renal abnormalities in patients with psoriasis

Erkan Dervisoglu · Aysun Sikar Akturk · Kursat Yildiz · Rebiay Kiran · Ahmet Yilmaz

Abstract
Objective Kidney involvement secondary to psoriasis is a controversial issue. In this study, we evaluated the prevalence of urinary abnormalities in patients with psoriasis.

Materials and methods Forty-five psoriasis patients (28 women, 17 men, mean age 44 ± 14 years) and 45 age- and gender-matched control subjects without hypertension or diabetes were enrolled in the study. Psoriasis area and severity index (PASI) was used to assess the severity of psoriasis. Urinalysis by dipstick and microscopic evaluation and 24-h proteinuria and albuminuria were measured in all patients and controls. Pathologic albuminuria was defined as albumin excretion of more than 30 mg/24 h. Renal biopsy was performed in psoriasis patients with urinary abnormalities.

Results Patients with psoriasis and controls were not significantly different with respect to the prevalence of abnormal urinalysis (17.7% vs. 13.3%, P = 0.56), mean 24-h proteinuria (145 ± 66 mg/24 h vs. 141 ± 71 mg/24 h, P = 0.54), and albuminuria (21 ± 34 mg/24 h vs. 8 ± 9 mg/24 h, P = 0.31). However, patients with psoriasis had an increased prevalence of pathologic albuminuria compared with controls (24% vs. 2%, P = 0.005). PASI scores in psoriasis patients correlated significantly with 24-h albuminuria (r = 0.458, P = 0.007). Of the eight patients with psoriasis who had urinary abnormalities, four underwent renal biopsy. Two of them had biopsy-proven glomerulonephritis: mesangial proliferative glomerulonephritis in one and IgA nephropathy in the other.

Conclusion The presence of abnormal urinalysis was not more common in patients with psoriasis than in controls. However, the increased prevalence of pathologic albuminuria and its positive correlation with psoriasis severity may suggest subclinical glomerular dysfunction in these patients.

Keywords Albuminuria · Hematuria · IgA nephropathy · Kidney involvement · Proteinuria · Psoriasis

Introduction
Psoriasis is a chronic inflammatory skin disease characterized by keratinocyte hyperproliferation, vascular hyperplasia, and mononuclear infiltration
of the dermis and epidermis [1–3]. The pathophysiology of psoriasis is not completely understood, but the trigger of the keratinocyte response is thought to be the activation of the cellular immune system including T cells, dendritic cells, and various cytokines and chemokines. The disease affects about 25 million people in North America and Europe and is probably the most prevalent immune-mediated skin disease in adults [1].

The prevalence of renal disease in psoriatic patients is unknown; recently, the number of references describing an association between psoriasis and glomerulopathies has increased [4]. Whether the renal involvement in psoriasis is coincidental or causative is debated [4, 5]. Certain glomerular diseases, including IgA nephropathy, secondary renal amyloidosis, membranoproliferative glomerulonephritis, and membranous glomerulopathy have been reported to be more common in psoriatic patients than in the general population [6–9].

In the systemic treatment of severe psoriasis, agents with nephrotoxic side effects are frequently used. Cyclosporine-induced nephrotoxicity results from interstitial fibrosis, arteriolar hyalinosis, and glomerular sclerosis [10]. Methotrexate may also play a role in nephrotoxicity via a direct toxic effect on the renal tubules or via precipitation in the renal tubules [11]. However, several reports describe abnormalities in renal function (mainly microalbuminuria) in psoriasis patients who had never been exposed to nephrotoxic drugs [12–14].

In this observational study, we evaluated the prevalence and type of urinary abnormalities in patients with psoriasis and controls, with the aim of determining whether renal disease was more prevalent in psoriasis patients than in controls.

**Materials and methods**

The study was conducted at the Kocaeli University Hospital, Kocaeli, Turkey, and was approved by the Ethics Committee of our university. Between June 2007 and April 2008, both incident and prevalent psoriasis patients (diagnosed by clinical and histopathologic criteria) over 18 years of age from our university hospital outpatient dermatology clinic were approached for participation in the study. Exclusion criteria were: any other dermatologic disorder, prior systemic treatment (including cyclosporine and methotrexate) other than acitretin, systemic treatment (including acitretin) in the prior 4 weeks, and any systemic disease such as diabetes mellitus or hypertension.

Forty-five patients gave informed consent and participated in the study. The psoriasis area and severity index (PASI) was used to assess the severity and extent of psoriasis. The PASI score is based on the extent of psoriatic involvement of body surface area on the head, trunk, arms, and legs, as well as the severity of scale formation, erythema, and plaque induration in each region of the body [15]. Forty-five age- and gender-matched control subjects over the age of 18 were recruited on a volunteer basis from our ‘check-up clinic’. All controls gave written informed consent before entering the study.

All patients and controls had blood drawn for blood urea nitrogen (BUN) and serum creatinine determination. All participants had a 24-h urine collected (from 8 a.m. to 8 a.m. according to a standard protocol) to measure creatinine clearance and to quantify total proteinuria and albuminuria. Creatinine clearance was calculated according to the formula: creatinine clearance = \( \frac{U_{Cr} \times V}{S_{Cr}} \), where urine creatinine (\( U_{Cr} \)) and serum creatinine (\( S_{Cr} \)) were expressed in mg/dL, and \( V \) corresponded to the urinary flow rate, in mL/min. Normal renal function was defined as a creatinine clearance of more than 75 mL/min in women and 95 mL/min in men [16, 17]. Urine samples were not collected during or just after menstruation.

In all patients and controls, urine samples were also collected on admission for urinalysis (not necessarily from the first morning void). Samples were tested by dipstick (UriScan, YD Diagnostics, Seoul, Korea) and microscopy for the presence of blood, protein, and other abnormalities. All abnormal urinalyses were performed twice. Microscopic hematuria was defined as the presence of at least 2+ occult blood by dipstick analysis and/or more than 5 red blood cells per high power field. Pathologic proteinuria was defined as at least 1+ protein by dipstick analysis and/or total protein excretion of more than 250 mg/24 h, measured by turbidimetric assay. Pathologic albuminuria was defined as albumin excretion of more than 30 mg/24 h, measured by turbidimetric immunoassay [18].

Psoriasis patients with urinary abnormalities underwent additional laboratory tests, including serum lipids and uric acid, viral hepatitis and HIV serology,
serum levels of total IgG, IgA, IgM, complement C3 and C4, screening for antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibody (ANCA), and anti-dsDNA antibodies. Patients with urinary abnormalities underwent abdominal ultrasonography and/or intravenous urography, as needed.

A percutaneous renal biopsy was performed in psoriasis patients presenting with urinary abnormalities and who had normal abdominal ultrasonography and/or intravenous urography. Biopsies were performed using a 14-gauge tru-cut biopsy needle under ultrasound guidance. No complications related to the renal biopsy occurred. Two specimens were taken, one for light microscopy and one for immunofluorescence examination. Specimens for light microscopy were formalin-fixed and paraffin-embedded; 5-micron sections were mounted and stained with hematoxylin and eosin, periodic acid Schiff, Masson trichrome, Congo red, and silver methenamine dyes. Frozen sections for immunofluorescence examination were incubated with antisera against IgA, IgG, IgM, and C3 (Dako, Polyclonal Rabbit Anti-Human, Glostrup, Denmark). Both psoriasis patients and controls with abnormal urinary findings were followed up in the nephrology outpatient clinic.

Statistical analysis

Data were analyzed using SPSS version 13.0 for Windows® (SPSS Inc., Chicago, USA). Data are expressed as mean ± standard deviation (SD), unless otherwise stated. Comparisons between groups were made using Student-t test for normally distributed variables and the Mann–Whitney U test for parametric variables with non-normal distributions. Chi-square testing was used to analyze categorical data. Spearman’s correlations were used to evaluate the relationship between 24-h albuminuria, proteinuria, and PASI scores. A P value of <0.05 was considered statistically significant.

Results

Forty-five patients (28 women and 17 men, mean age 44 ± 14 years) and 45 control subjects (28 women and 17 men, mean age 43 ± 14 years) participated in the study. The mean duration of psoriasis was 8.2 ± 8.6 years, and the mean PASI was 6.4 ± 5.2. The general characteristics of the patient and control groups are given in Table 1. Age, gender, mean arterial blood pressure, blood urea nitrogen, serum creatinine, creatinine clearance, and urinary protein and albumin excretion were not significantly different between patients and controls. Pathologic albuminuria was more common in psoriasis patients than in healthy controls (24.4% vs. 2.2%, P = 0.005, Table 2). In patients with psoriasis, the extent of psoriatic lesions, as measured by PASI scores, correlated significantly with the amount of 24-h albuminuria (r = 0.458, P = 0.007) but not with 24-h proteinuria (r = 0.163, P = 0.364).

Of the patients with psoriasis, eight (17.7%) had abnormal findings on dipstick and microscopic examination of the urine. Six had microscopic hematuria, one had proteinuria, and one had both hematuria and proteinuria. Subsequent quantitative assay showed that four patients (8.8%) had proteinuria of over 250 mg/24 h. In the controls, 6 subjects

<table>
<thead>
<tr>
<th>Table 1 Demographics and general characteristics (mean ± SD) of psoriasis patients (n = 45) and controls (n = 45)</th>
<th>Psoriasis patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years*</td>
<td>44 ± 14</td>
<td>43 ± 14</td>
<td>0.69</td>
</tr>
<tr>
<td>Percent female**</td>
<td>62</td>
<td>62</td>
<td>1.00</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>8.2 ± 8.6</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PASI score</td>
<td>6.4 ± 5.2</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg***</td>
<td>90 ± 11</td>
<td>88 ± 10</td>
<td>0.67</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL***</td>
<td>28.3 ± 8.8</td>
<td>25.4 ± 7.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine, mg/dL***</td>
<td>0.79 ± 0.19</td>
<td>0.73 ± 0.16</td>
<td>0.09</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min***</td>
<td>105.4 ± 23.5</td>
<td>99.0 ± 17.1</td>
<td>0.22</td>
</tr>
<tr>
<td>24-h proteinuria, mg/24 h***</td>
<td>144.8 ± 66.2</td>
<td>141.4 ± 70.5</td>
<td>0.54</td>
</tr>
<tr>
<td>24-h albuminuria, mg/24 h***</td>
<td>21.3 ± 34.3</td>
<td>8.2 ± 8.8</td>
<td>0.31</td>
</tr>
</tbody>
</table>
had abnormal urinalyses: five with microscopic hematuria and one with both hematuria and proteinuria. Three control subjects (6.6%) had total proteinuria over 250 mg/24 h. Patients and controls were not significantly different with respect to the presence of an abnormal urinalysis (17.7% vs. 13.3%, \( P = 0.561 \)) or presence of quantitative pathologic proteinuria (8.8% vs. 6.6%, \( P = 0.694 \)).

Among patients with psoriasis, the eight patients with urine abnormalities were subjected to further testing to identify urinary tract or kidney pathology (Table 3). Nephrolithiasis was the cause of hematuria in one patient. In another, recurrent urinary infection was diagnosed, without anatomic abnormality of the urinary tract. Two patients (patients 3 and 4) who had normal renal imaging studies refused kidney biopsy. ANA and elevated serum IgA levels were detected in the serum of one of these patients (patient 4).

Kidney biopsy was done in only four patients with psoriasis (patients 5–8). Kidney biopsy of one patient with proteinuria (patient 5) revealed mesangial proliferative glomerulonephritis without positive immunofluorescence staining for IgA, IgG, IgM, or C3. In one patient (patient 6), biopsy revealed IgA nephropathy (grade IIB), as shown by immune deposits and glomerular and tubulointerstitial changes. Two other patients (patients 7 and 8) had normal light microscopy and immunofluorescence findings. Based on the histopathologic findings, biopsy-proven glomerulonephritis occurred in 4.4% of our psoriasis patients.

### Discussion

The present study was designed to evaluate the prevalence of renal abnormalities in a group of patients with psoriasis. When urine was analyzed by dipstick and microscopic evaluation as a screening test for kidney disease, the prevalences of abnormal findings in psoriasis patients and controls were similar. Urinary albumin excretion (UAE) was not significantly different between psoriasis patients and controls. However, our study found an increased prevalence of pathologic albuminuria in psoriatic patients compared with control subjects. Two patients with psoriasis had biopsy-proven glomerulonephritis.

Microalbuminuria is considered to be a marker of glomerular damage and can be used to predict diabetic or hypertensive nephropathy [19, 20]. Early detection of glomerular damage, when it is minimal and/or at a reversible stage, is extremely important. Studies performed in patients with psoriasis have found increased UAE in psoriatics compared with healthy controls [12–14]. In only one of these studies were patients with hypertension and diabetes mellitus included [12]. Contrary to these studies, Kaftan et al. [21] were unable to find a significant difference in UAE between psoriasis patients and healthy subjects.

### Table 2

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Psoriasis patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 30 \text{ mg/24 h} )</td>
<td>34 (75.6)</td>
<td>44 (97.8)</td>
</tr>
<tr>
<td>( &gt;30 \text{ mg/24 h} )</td>
<td>11 (24.4)</td>
<td>1 (2.2)*</td>
</tr>
</tbody>
</table>

Values are expressed as number and percentage in parenthesis: \( n (%) \)

* Chi-square \( (P = 0.005) \)

(13.3%) had abnormal urinalyses: five with microscopic hematuria and one with both hematuria and proteinuria. Three control subjects (6.6%) had total proteinuria over 250 mg/24 h. Patients and controls were not significantly different with respect to the presence of an abnormal urinalysis (17.7% vs. 13.3%, \( P = 0.561 \)) or presence of quantitative pathologic proteinuria (8.8% vs. 6.6%, \( P = 0.694 \)).

### Table 3

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Hematuria</th>
<th>Proteinuria</th>
<th>Albuminuria (mg/24 h)</th>
<th>Proteinuria (mg/24 h)</th>
<th>Renal biopsy</th>
<th>Renal or urinary pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>42</td>
<td>+</td>
<td>–</td>
<td>3</td>
<td>122</td>
<td>ND</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>50</td>
<td>+</td>
<td>–</td>
<td>3</td>
<td>100</td>
<td>ND</td>
<td>Recurrent urinary infection</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>45</td>
<td>+</td>
<td>–</td>
<td>9</td>
<td>142</td>
<td>ND</td>
<td>Undiagnosed</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>51</td>
<td>+</td>
<td>+</td>
<td>101</td>
<td>356</td>
<td>ND</td>
<td>Undiagnosed</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>46</td>
<td>–</td>
<td>+</td>
<td>31</td>
<td>322</td>
<td>+</td>
<td>Mesangial proliferative GN</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>50</td>
<td>+</td>
<td>–</td>
<td>188</td>
<td>297</td>
<td>+</td>
<td>IgA Nephropathy, grade IIB</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>55</td>
<td>+</td>
<td>–</td>
<td>34</td>
<td>267</td>
<td>+</td>
<td>Normal renal biopsy</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>18</td>
<td>+</td>
<td>–</td>
<td>14</td>
<td>169</td>
<td>+</td>
<td>Normal renal biopsy</td>
</tr>
</tbody>
</table>

* ND Not done, GN glomerulonephritis

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However, they did find a significant correlation between UAE and skin lesion severity. In the present study, although mean 24-h albuminuria was greater in the psoriasis group, the difference did not reach statistical significance. This was probably affected by the distribution of 24-h albuminuria levels being highly skewed. When individuals were categorized according to the abnormal level of albuminuria (>30 mg/24 h), a significant difference in the number of patients with pathologic albuminuria between psoriatics and controls was demonstrated. Moreover, our results revealed a significant correlation between UAE and PASI scores, as also demonstrated in some previous studies [13, 21].

We suggest a link between UAE and the severity of psoriasis. It is difficult to compare our results with the results of previous studies because of differences in the methods of measuring UAE, in cutoff values of defining pathologic albuminuria, and in patient profiles. However, our study clearly found a higher prevalence of pathologic albuminuria in patients with psoriasis than in healthy controls. Based on this finding, we hypothesize that subclinical glomerular damage might exist in these patients [5].

Considering the increasing numbers of studies reporting microalbuminuria and abnormal urinalyses in psoriasis patients, researchers have suggested performing more detailed studies in these patients, including renal biopsies [5]. We planned our study in light of these recommendations. Although we were able to perform a biopsy in only four of six psoriasis patients having abnormal urinary findings without an obvious cause (nephrolithiasis, urinary infection, etc.), we found biopsy-proven glomerulonephritis in 4.4% of our psoriasis patients overall. However, the prevalence might have been even higher if the two patients in the study group with unknown cause of abnormal urinalysis had given their consent for biopsy. We were unable to assess the prevalence of biopsy-proven glomerulonephritis in our control cohort, because renal biopsies were not performed in the control subjects with urinary abnormalities.

In our study, we found one patient who had mesangial proliferative glomerulonephritis without immune deposition and another patient with IgA nephropathy. Based on the published case reports, IgA nephropathy is the most frequent type of glomerular disease in patients with psoriasis presenting with hematuria. These patients may also have a variable amount of proteinuria and decreased glomerular filtration rate [8, 22]. Jiao et al. [23] retrospectively studied the renal biopsy specimens of 11 psoriasis patients and found slight-to-moderate mesangial proliferative glomerulonephritis in all cases, with eight (73%) having mesangial deposits of IgA. They concluded that mesangial proliferative glomerulonephritis with or without IgA deposits was the major morphological pattern associated with psoriasis.

Various authors have sought to clarify the pathogenetic mechanisms of glomerular diseases associated with psoriasis [8, 24]. They commonly emphasized the role of underlying immunologic mechanisms; increased serum levels of IgG, IgA, and IgM immune complexes have been found, and a defect in suppressor T cell function has been defined [8, 24]. Only one of our psoriasis patients with urinary abnormalities had elevated serum IgA levels.

Methods for monitoring albuminuria include measurement of protein excretion in 24-h or timed collections and determination of the albumin/creatinine ratio in an untimed “spot” urine specimen. Twenty-four hour and timed urine collections may be associated with collection errors including improper timing, missed samples, and incomplete bladder emptying [25]. Our results might have also been affected by urine collection errors. We should have taken body surface area into account when calculating creatinine clearance. In addition, the urine samples we examined should have been taken from first-morning void urine in all subjects. Furthermore, renal biopsy was done only in psoriasis patients with abnormal urinary findings and not in controls with such findings.

In conclusion, the presence of abnormal urinalysis is not more common in patients with psoriasis than in healthy individuals. However, the increased prevalence of pathologic albuminuria and its positive association with psoriasis severity may suggest subclinical glomerular dysfunction in these patients.

Conflict of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


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