Orthostatic proteinuria revisited: new clinical impact of the “old” clinical entity?

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Orthostatic proteinuria (OP) is a clinical entity that has been encountered in daily clinical practice since approximately >35 years ago (1,2). In general, OP is defined as the appearance of significant proteinuria while in the upright or lordotic position, but not in the recumbent position, in healthy individuals without kidney diseases. Its long-term outcome is usually good (1,2). The postulated prevalence of OP is not rare in children and adolescents (for approximately >10% in asymptomatic proteinuria (3); it is occasionally encountered even in adults, particularly those with low body mass indexes (BMIs) (4,5). Although the etiology of OP remains unclear, probable renal congestion due to the left renal vein entrapment phenomenon (left renal vein entrapment syndrome or nutcracker syndrome) is attributable to the transient increase in the permeability of the glomerular filtration barrier that leads to the appearance of proteinuria (6). As low BMI that results in a narrow space between the aorta and the superior mesenteric artery is the main cause of the nutcracker syndrome in children and adolescents, low BMI is thought to modulate OP as well (3-5,7). The nutcracker syndrome usually resolves with time; a correlation between increased BMI and growth, body weight gain, and regression of urinary abnormalities is apparent (8,9). Thus, most cases of OP tend to show spontaneous remission with time and have a favorable long-term prognosis (1,2). However, no validated clinical diagnostic index for differential diagnosis of OP and glomerulonephritis (GN) has been established to date (10-12). OP is not a new clinical entity but still lacks clear definitive diagnostic criteria.

In this context, Niu et al. recently reported something new aspects of the clinical diagnostic criteria of OP in this journal (13). They examined the measurement parameters of microproteinuria such as urinary ratios of albumin to creatinine (Alb/Cr), IgG to creatinine (IgG/Cr), N-acetyl-β-D-glucosaminidase to creatinine (NAG/Cr) and α1-microglobulin to creatinine (α1Mu/Cr) with ultrasonography (USG) of the left renal vein (LRV) in 60 “strictly chosen” patients with OP (median age at onset, 10.6±2.8 years) at rest and after activity to determine whether changes in these parameters could help in preliminary screening for OP in patients with suspected OP. When compared with the 15 controls without OP (median age, 10.9±3.3 years) at rest and after activity to determine whether changes in these parameters could help in preliminary screening for OP in patients with suspected OP.
after the 15-minute upright lordotic posture; and Robinson test, sequential urine sample collection in the morning and after the hourly activity under dry food intake and fluid intake restrictions. Thus, participants were “strictly chosen” for this study. Given the remarkable patient selection, Niu et al. focused on the new impact of OP as an “old” clinical entity (13).

To date, some interesting papers that aimed to identify urinary simple biomarkers of OP to determine their diagnostic values have been published (10,12). Previously, Ohshima reported that the ratio of urinary IgG/IgA and serum IgG/IgA were significantly decreased in patients with GN than that in patients with OP (10). However, the sample size remained low (n=14) and the diagnosis of OP depended only on the upright lordotic posture test result. Thus, compared with that in the previously published articles, Niu et al.’s sample size may be sufficient enough for drawing definitive conclusion. These issues are summarized in Table 1.

OP is considered a clinical entity with benign asymptomatic proteinuria particularly in children and adolescents (1,2). Low BMI leading to a narrow space between the aorta and the superior mesenteric artery may modulate OP (3-6). On the contrary, some validated diagnostic criteria for OP remain to be studied. In this context, the measurement parameters of microproteinuria, especially urinary Alb/Cr and IgG/Cr, in combination with USG of the LRV may be useful for screening of OP in patients with asymptomatic proteinuria. However, further studies are warranted.

### Table 1: Representative published reports of urinary measurement parameters for differential diagnosis of orthostatic proteinuria from glomerulonephritis

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Number of Study participants</th>
<th>Mean age of study participants</th>
<th>Mean body mass index</th>
<th>Diagnostic rationale of OP</th>
<th>Performance of USG of the LRV</th>
<th>Significant urinary parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohshima (10)</td>
<td>Orthostatic proteinuria, 14</td>
<td>11.5±2.4 years</td>
<td>Not described</td>
<td>The upright lordotic posture test</td>
<td>Not performed</td>
<td>IgG to IgA ratio</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis, 13.0±1.4 years</td>
<td>Not described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jin et al. (11)</td>
<td>Orthostatic proteinuria, 17</td>
<td>21.8±7.3 years</td>
<td>19.7±2.1 kg/m²</td>
<td>The upright lordotic posture test</td>
<td>All the study participants</td>
<td>albumin to creatinine ratio</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis, 35</td>
<td>26.5±10.7 years</td>
<td>19.8±2.6 kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanai et al. (12)</td>
<td>Orthostatic proteinuria, 16</td>
<td>12.8 years</td>
<td>Not described</td>
<td>The upright lordotic posture test</td>
<td>Not performed</td>
<td>FDP to creatinine ratio</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis, 26</td>
<td>9.1 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niu et al. (13)</td>
<td>Orthostatic proteinuria, 60</td>
<td>10.6±2.8 years</td>
<td>17.1±2.7 kg/m²</td>
<td>The upright lordotic posture test</td>
<td>All the study participants</td>
<td>albumin to creatine ratio and IgG to creatinine ratio</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis, 15</td>
<td>10.9±3.3 years</td>
<td>19.2±4.7 kg/m²</td>
<td>Plus the West and Robinson test</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

USG, ultrasonography; LRV, left renal vein; FDP, fibrin/fibrinogen degradation products.

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**Footnote**

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