Uremic Pruritus and Serum Phosphorus Level

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Abstract- Pruritus is a common and bothersome problem among uremic patients which negatively affects life quality and prognosis of the patient. Various factors are known to be involved in the development of pruritus. The aim of this study was to assess the frequency and the factors which may have relationship with uremic pruritus, especially bone mineral metabolism indicators. Current cross-sectional study was done on 99 hemodialysis patients. Having pruritus, its duration, severity and correlation with patient’s laboratory data was evaluated. For each patient a questionnaire was filled. The mean age of patients was 55.9±15.4 (23-87) years and 35.7% were female. They were on hemodialysis for 74.79±75.04 months. Frequency of pruritus was 58.6% (58 patients). Considering the severity, 16.2% suffered from severe pruritus, measured by visual analogue scale (VAS). Pruritus was more common in those on dialysis for more than 2 years (0.014). 82.8% of those with VAS of less than 3, in comparison with 37.5% of those with VAS of greater than 7, had no complaint of awakening due to pruritus. The frequency of pruritus and its severity was more in patients with higher serum phosphorus level (P=0.048). It seems that phosphate control which is not mainly attributed to dialysis adequacy and efficiency, needs more attention not only by medical team but also by patient. Decreasing the phosphate content of regimen may be cheap and helpful modality in pruritus management.

Keywords: Hemodialysis; Hyperphosphatemia; Kidney Failure; Phosphorous; Uremic Pruritus

Introduction

The prevalence of uremic pruritus, a considerable cause of morbidity in patients with end stage renal disease (ESRD) is still tremendously high. Approximately 50-90% of hemodialysis (HD) patients suffer from pruritus, which does not improve with dialysis and has no correlation with duration of dialysis or the cause of renal failure. The mechanism of uremic pruritus is not yet fully understood but it has prognostic value and is associated with poor survival (1-3). Pro-inflammatory state due to immune system derangement with high level of some cytokines, opioid-receptor system abnormalities, malnutrition, interface of dermal mast cells with distal ends of unmyelinated C fibers and possibly mineral bone metabolism and nutritional disturbances are among various mechanisms referred to as its cause or intensity (4-6). It usually starts half a year before dialysis and can be persistent or transient, localized or generalized. It may have great negative impact on the life quality of the patient. Moderate to severe pruritus increase mortality risk by 13% to 21%. Nevertheless, it is important to rule out other possible causes of pruritus due to gastrointestinal or hematologic diseases and allergic dermatitis (7).

Chronic kidney disease (CKD) is accompanied by profound disturbances in calcium, phosphate, vitamin D, and intact parathyroid hormone (PTH) homeostasis that may play a role in the pathophysiology of pruritus. Optimal serum levels of phosphorus (3.5-5.5 mg/dl), serum calcium (8.4-9.5 mg/dl), calcium-phosphorus product, less than 55 mg²/dl² and serum intact PTH (150-300 pg/ml) as bone mineral metabolism indicators, have been recommended by National Kidney Foundation Dialysis Outcomes Quality Initiative (K/DOQI) guidelines (8). However, achieving such targets is a serious challenge in the management of patients. Mahdavi-Mazdeh et al. in a study in 2630 hemodialysis patients showed only 2% and 35% achieved all or 3 targets, respectively (9).

The main objective of this study was to estimate the frequency of pruritus in patients on chronic maintenance
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hemodialysis and evaluate its relation to some recognized factors in pathogenesis of uremic pruritus, especially bone mineral metabolism indicators.

Patients and Methods

99 patients on maintenance thrice weekly hemodialysis at our center (Imam Khomeini Hospital, Tehran, Iran) were included in a cross-sectional study in 2010. Duration of each session was 4 hours and dialyzer was polysulfone. A questionnaire was used to assess patient’s pruritus. Those with history of dermatologic disease or chemical exposure were excluded. Patients were asked to report the severity of their pruritus on a visual analogue scale (VAS) graded from 0 to 10 with grade 0 representing no discomfort and grade 10 for unbearable severe pruritus. Duration and presence during dialysis session and/or the day after dialysis were questioned. The severity was evaluated by questions on the subject of awakening the patient from sleep, existence of excoriation due to scratching and/or scratches scars and administered drugs.

Blood samples were taken from all patients for assessment of serum levels of calcium, phosphate, PTH, KT/V (index of dialysis dose), lipid profile and other parameters on the first session of HD of the week. Then the findings were entered in software SPSS version 16 and the results were yielded after analyzing the data. The study was approved in research council, deputy of research of Tehran University of Medical Sciences.

Descriptive data are given as mean±standard deviation (range). Student’s t-t test was used to compare means between patients with and without pruritus. Pearson correlation coefficient and Chi-square test were used for relationship of quantitative and comparison of qualitative variables respectively. The level of significance was P<0.05.

Results

The mean age of 99 studied patients was 55.9±15.4 (23-87) years and 35.7% were female. Diabetes mellitus was the cause of ESRD in 28.4%. Patients were on HD for 74.79±75.04 (1-288) months. Frequency of pruritus was 58.6% (58 patients). Considering the severity of pruritus, measured by VAS, 16 patients (16.2%) suffered from severe pruritus. Duration of dialysis did not show correlation with perception or intensity of pruritus (P=0.057), but pruritus was more common in those on dialysis for more than 2 years (0.014). Demographic and laboratory data in two groups of those suffering from pruritus in comparison with those without pruritus are presented in table 1.

Table 1. Patient Demographic data according to pruritus status.

<table>
<thead>
<tr>
<th></th>
<th>Patients without pruritus</th>
<th>Patients with pruritus</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(year)</td>
<td>56.80±16.84</td>
<td>55.26±14.33</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>30/10</td>
<td>33/25</td>
<td>NS</td>
</tr>
<tr>
<td>HD duration (months)</td>
<td>≤24</td>
<td>59.25±68.30</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td></td>
<td>&gt;24</td>
<td>86.09±78.25</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.014*</td>
<td></td>
</tr>
<tr>
<td>KT/V</td>
<td>1.20±0.23</td>
<td>1.12±0.19</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.82±0.62</td>
<td>8.86±0.82</td>
<td>NS</td>
</tr>
<tr>
<td>PTH</td>
<td>337.28±396.06</td>
<td>423.09±637.82</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphate</td>
<td>6.28±1.67</td>
<td>7.09±1.86</td>
<td>0.048</td>
</tr>
<tr>
<td>Alk phosphatase</td>
<td>347.94±238.18</td>
<td>392.07±374.76</td>
<td>NS</td>
</tr>
<tr>
<td>Uric acid</td>
<td>9.92±15.60</td>
<td>7.41±1.35</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>146.88±38.42</td>
<td>150.08±38.09</td>
<td>NS</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>142.53±72.69</td>
<td>161.55±92.11</td>
<td>NS</td>
</tr>
<tr>
<td>AST</td>
<td>15.29±5.89</td>
<td>16.90±13.06</td>
<td>NS</td>
</tr>
<tr>
<td>ALT</td>
<td>11.88±10.07</td>
<td>15.71±27.06</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2. Univariate comparison and pruritus severity.

<table>
<thead>
<tr>
<th></th>
<th>1&gt;VAS≤3</th>
<th>4&gt;VAS≤6</th>
<th>7&gt;VAS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of patients</td>
<td>29</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age(year)</td>
<td>57.08±14.07</td>
<td>5.62±14.58</td>
<td>55.40±14.94</td>
<td>0.546</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>15/14</td>
<td>7/6</td>
<td>11/5</td>
<td>0.527</td>
</tr>
<tr>
<td>Pruritus During HD (yes/no)</td>
<td>6/23 (20.7)</td>
<td>8/5 (61.5)</td>
<td>9/7 (56.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Having pruritus on the day after dialysis (yes/no)</td>
<td>27/2 (93.1)</td>
<td>13/0 (100)</td>
<td>16/0 (100)</td>
<td>0.36</td>
</tr>
<tr>
<td>Scar (yes/no)</td>
<td>3/26 (10.3)</td>
<td>3/10 (23.1)</td>
<td>8/8 (50)</td>
<td>0.012</td>
</tr>
<tr>
<td>Awakening no</td>
<td>24 (82.8)</td>
<td>7 (53.8)</td>
<td>6 (37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1dy/wk</td>
<td>3 (10.3)</td>
<td>1 (7.7)</td>
<td>1 (6.2)</td>
<td></td>
</tr>
<tr>
<td>2dys/wk</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3dys/wk</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4dys/wk</td>
<td>0</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>HD duration (month)</td>
<td>93.97±87.21</td>
<td>75.08±66.61</td>
<td>79.54±11.02</td>
<td>0.73</td>
</tr>
<tr>
<td>≤24</td>
<td>24.1%</td>
<td>23.1%</td>
<td>23.1%</td>
<td>0.99</td>
</tr>
<tr>
<td>&gt;24</td>
<td>75.9%</td>
<td>76.9%</td>
<td>76.9%</td>
<td></td>
</tr>
<tr>
<td>KT/V</td>
<td>1.12±0.18</td>
<td>1.15±0.21</td>
<td>1.09±0.20</td>
<td>0.74</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.97±0.82</td>
<td>8.59±0.93</td>
<td>8.85±0.73</td>
<td>0.41</td>
</tr>
<tr>
<td>&lt;8.5</td>
<td>17.9%</td>
<td>33.3%</td>
<td>13.3%</td>
<td>0.40</td>
</tr>
<tr>
<td>8.5-10.2</td>
<td>82.1%</td>
<td>66.7%</td>
<td>86.7%</td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>385.56±566.22</td>
<td>476.17±807.50</td>
<td>452.79±659.04</td>
<td>0.90</td>
</tr>
<tr>
<td>&lt;150</td>
<td>50%</td>
<td>58.3%</td>
<td>35.7%</td>
<td></td>
</tr>
<tr>
<td>150-300</td>
<td>17.9%</td>
<td>16.7%</td>
<td>21.4%</td>
<td></td>
</tr>
<tr>
<td>&gt;300</td>
<td>32.1%</td>
<td>25%</td>
<td>42.9%</td>
<td></td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>7.07±1.91</td>
<td>7.29±1.93</td>
<td>6.98±1.82</td>
<td>0.91</td>
</tr>
<tr>
<td>3.5-5.5</td>
<td>21.4%</td>
<td>25%</td>
<td>26.7%</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;5.5</td>
<td>78.6%</td>
<td>75%</td>
<td>73.3%</td>
<td></td>
</tr>
<tr>
<td>Calcium-phosphorus product (mg2/dl2)</td>
<td>62.57±14.88</td>
<td>62.49±15.83</td>
<td>61.39±14.53</td>
<td>0.968</td>
</tr>
<tr>
<td>&lt;55</td>
<td>52.9%</td>
<td>44.4%</td>
<td>50%</td>
<td>0.919</td>
</tr>
<tr>
<td>&gt;72</td>
<td>47.1%</td>
<td>55.6%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Alk phoshatase</td>
<td>354.68±259.03</td>
<td>419.83±206.18</td>
<td>439.67±610.77</td>
<td>0.44</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.49±1.50</td>
<td>7.33±1.48</td>
<td>7.35±0.97</td>
<td>0.92</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>155.08±39.05</td>
<td>152.25±45.35</td>
<td>139.67±29.76</td>
<td>0.46</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>175.21±105.82</td>
<td>168.75±90.80</td>
<td>130.27±62.45</td>
<td>0.31</td>
</tr>
<tr>
<td>AST</td>
<td>15.92±8.30</td>
<td>13.56±7.57</td>
<td>22.25±21.78</td>
<td>0.38</td>
</tr>
<tr>
<td>ALT</td>
<td>16.00±24.62</td>
<td>7.11±5.01</td>
<td>8.00±24.88</td>
<td>0.42</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.09±0.57</td>
<td>3.79±0.52</td>
<td>3.99±0.45</td>
<td>0.30</td>
</tr>
</tbody>
</table>

However, more intense itching correlated with higher rate of pruritus during dialysis session (P=0.012) and interference with patient sleep (P<0.001). 82.8% of those with VAS of less than 3, in comparison with 37.5% of those with VAS of greater than 7, had no complaint of awakening due to pruritus. Regarding laboratory tests of bone metabolism (calcium, phosphorus, calcium-phosphorus product and PTH) it has been shown that only, phosphorus level correlated with pruritus duration (P=0.007), pruritus during hemodialysis session (P=0.010) and pruritus on the day after dialysis (0.016).

There was no significant finding with K/DOQI target ranges in three stages of pruritus intensity (Table 2). However, the patients with serum phosphorus level of <7 mg/dl experienced less frequent intradialysis pruritus than those with serum phosphorus level of >7 mg/dl (15.6% versus 34.1%) (P=0.039). The ratio of the patients suffering from pruritus for 6 months and more, in those with a serum phosphorus level of <7mg/dl was 21% in comparison with 48% in those with higher level (P=0.007). We also found that 54% of patients with serum phosphorus level of 7 mg/dl or less, suffered from pruritus the day after dialysis compared with 76% among patients with serum phosphorus level of more than 7 mg/dl (P=0.04).

**Discussion**

Our study as many others showed that pruritus is very common (58.6%) in HD patients. We also found that there is no correlation of its intensity with duration of
dialysis (10,11) but it was more common in those on dialysis for more than 2 years. In another study of this center 10 years ago the frequency of pruritus was 51% and similarly, it was more common in those who were on dialysis for more than 2 years (12).

Regarding mineral bone metabolism indices and pruritus the results are conflicting. We found phosphate level but not PTH correlated with the complaint of pruritus in hemodialysis patients. It is in sharp contrast with Stahle-Backdahl et al. as well as Jamal and Subramanian studies who found higher PTH level in those with pruritus (11,13). However, they did not find correlation with calcium (11,13). Yazdanpanah et al. also found correlation of high PTH level with pruritus, but again they showed that there was no effect of calcium or phosphorus level on pruritus frequency (14). Welter et al. and Melo et al. did not find any impact from calcium, PTH and phosphate on this symptom (7,10). Afshar et al. found significant correlation of uremic pruritus with intact PTH and calcium phosphate product (15).

In DOPPS study with large sample size of 17,034 patients from seven countries, independent and strong relationships were seen between higher serum calcium (>10.2 mg/dl), higher serum phosphorus (>5.5 mg/dl), and higher serum calcium phosphorus product levels (>80 mg2/dl2) with uremic pruritus. It has also been emphasized that serum phosphorus less than 3.5 mg/dl and within 5.5-6.7 mg/dl range accompanied the occurrence of pruritus with odds ratio of 1 (P=0.97), and 1.2 (P<0.0001) respectively. The odds ratio increased to 1.37 in those with serum phosphorus level higher than 6.7 mg/dl (P<0.0001) (16).

In our study, the role of phosphorus was similar, but we could not find the effect of calcium and PTH. It may be due to the fact that we did not have any patient with calcium level higher than 10.2 mg/dl, which can also explain the lower mean of calcium phosphorus product and non-existence of statistically significant finding. The next limitation of current study was the method of PTH measurement which did not measure intact PTH. In conclusion, it seems that phosphate control which is not mainly attributed to dialysis adequacy and efficiency, needs more attention not only by medical team but also by patients. The nutritional guidelines to decrease phosphate content of regimen may be cheap and helpful. Further to other advantages of decreasing serum phosphorus level which is beyond the scope of this paper it may help uremic pruritus control.

Acknowledgment

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References


