Is the Homocysteine Level a Good Predictive Marker for Evaluating Kidney Function in Patients After Percutaneous Nephrolithotomy?

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Purpose: The purpose of this study is to evaluate the preoperative, early and late postoperative homocysteine levels and its relationship with kidney function in patients after undergoing percutaneous nephrolithotomy (PNL).

Materials and Methods: Twenty-three patients with kidney stones underwent PNL and blood samples were taken preoperatively as well as at 48 hours and three months after the operation. The homocysteine level was determined by high pressure liquid chromatography and the fluorometric method in blood samples with ethylenediaminetetraacetic acid. The Cockcroft – Gault formula was used to calculate the glomerular filtration rate (GFR). Non-contrast computed tomography was performed for all patients before surgery. Stone burden was calculated as the sum of the area of each stone in mm².

Results: Fourteen male (60.9%) and nine female (39.1%) patients were recruited for this study, and the median age was 44.3 ± 15.17 (20 – 71) years. There were no statistically significant differences between the preoperative homocysteine level and the level at 48 hours post-operation (P = .460). However, the homocysteine level three months after the operation was significantly lower than the preoperative and 48 hour levels (P = .001 and P = .003, respectively).

Conclusion: Renal function, which deteriorated after the PNL procedure, was preserved or improved over time. Homocysteine may be a sensitive indicator to assess the change in renal function pre-and post-PNL.

KeyWords: homocysteine; oxidative stress; percutaneous nephrolithotomy; kidney function.

INTRODUCTION
Currently, percutaneous nephrolithotomy (PNL), a minimal invasive technique, is a standard method of kidney stone treatment1. Although this operation can cause minimal renal parenchymal damage, reflected in a decrease in the glomerular filtration rate (GFR) after the operation, the GFR later returns to normal2. Homocysteine is a natural amino acid that is contained in mammalian tissues. Methionine is an amino acid that contains essential sulfur. Homocysteine is produced by methionine transmethylation. Kidney function is a significant determinate of the homocysteine level in plasma, and there is a close relationship between the homocysteine level and kidney function. The homocysteine level in patients with renal failure is two to four times higher than healthy population3. The prevalence of hyperhomocysteinemia is 5-10% in a healthy population and 70-100% in patients with renal failure. There is a cross correlation between GFR and the homocysteine concentration3. In addition, a close relationship was found between elevated plasma homocysteine and increased oxidative stress in patients with chronic kidney disease3.

In the present study, we evaluated the relationship between preoperative, early and late postoperative homocysteine levels and kidney function in patients after the PNL procedure. According to our knowledge, this is the first study regarding the varying homocysteine levels in patient after the PNL procedure.

PATIENTS AND METHODS

Study population and Study design
Twenty-three patients with kidney stones underwent the PNL procedure and blood samples were taken preoperatively as well as 48 hours and three months after operation. The blood cell count, homocysteine, folic acid, vitamin B12, blood urea nitrogen, creatinine, glucose, alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (GGT), sodium and potassium levels were assessed. The homocysteine level was determined by high pressure liquid chromatography and fluorometric methods in blood samples with ethylenediaminetetraacetic acid. The plasma homocysteine reference distance was 3.3 to 7.2 µmol/L. The Cockcroft – Gault formula was used to calculate the GFR (GFR ml/min = [ (140 – age) x weight (kg) / serum creatinine (mg/dl) x 72]. The study was approved by the Ethics Committee of Çukurova University, and all patients signed an informed consent form. Patient with a solitary kidney, chronic renal failure, diabetes mellitus and/or hypertension for more than five years, renovascular hypertension, previous history of pylonephritis and previous surgery until at least three months earlier, such as open surgery, shock wave lithotripsy

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Received March 2017 & Accepted July 2017

Vol 15 No 04 ‖ July-August 2018 ‖ 153
(SWL) or percutaneous nephrostomy were excluded from this study. Non-contrast computed tomography was performed for all patients before surgery. Stone burden was calculated as the sum of the area of each stone in mm\(^2\).

**Surgical technique and Outcome assessment**

Under general anesthesia, a 6 French (Fr) open ended ureteral catheter was placed into the ureter and then fixed to a 14 Fr urethral catheter in the lithotomy position. The patient was then turned to the prone position. Contrast medium was injected from the ureteral catheter to visualize the collecting system under fluoroscopy. The most appropriate posterior calix was selected and punctured with an 18 gauge percutaneous entry needle to enter the collecting system. A J type guide wire was inserted through the needle and dilation was performed with Amplatz dilators (Amplatz Sheath Boston Scientific, USA) up to 24 Fr. A 24 Fr access sheath was placed, and a rigid nephroscope (Karl Storz, Tuttlingen, Germany) was used for all patients. Stones were cracked with a pneumatic lithotripter (Elmed Vibrolith, Elmed Lithotripsy System, Ankara, Turkey) and extracted with forceps (Karl Storz, Tuttlingen, Germany). A 14 Fr re-entry malecot was placed at the end of the procedure in only one patient. The stone free rate was 91% (21 patients), and the clinicaly insignificant residue fragment (< 4 mm) rate was 9% (2 patients). The mean hospitalization time was 2.65 ± 0.71 (1 – 4) days.

## RESULTS

Fourteen male (60.9%) and nine female (39.1%) patients were recruited for this study and the median age was 44.3 ± 15.17 (20 – 71) years. Mean stone burden was calculated as 319.57 ± 313.24 (100 – 1500) mm\(^2\). Single access was performed in 22 patients and double access in only one patient. The mean operation time was 67.61 ± 31.65 (40 – 180) minutes. One patient received a single unite of red blood cell transfusion during the operation, and one patient received intravenous antibiotics (imipenem/cilastatin) for a high post-operative fever. The stone free rate was 91% (21 patients), and the clinically insignificant residue fragment (< 4 mm) rate was 9% (2 patients). The mean hospitalization time was 2.65 ± 0.71 (1 – 4) days.

The homocysteine, hemoglobin, white blood cells, platelet, creatinine, blood urea nitrogen, sodium, potassium, ALT, AST, GGT, glucose, folic acid and vitamin B12 levels were shown in Tables 1 and 2.

### Table 1. Blood Sample Results

<table>
<thead>
<tr>
<th></th>
<th>Preoperative (Mean ± SD)</th>
<th>48th hour (Mean ± SD)</th>
<th>3rd month (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.22 ± 2.04</td>
<td>12.26 ± 2.26</td>
<td>12.78 ± 1.95</td>
<td>0.019</td>
</tr>
<tr>
<td>Folic acid (µg/mL)</td>
<td>7.75 ± 2.86</td>
<td>8.05 ± 3.09</td>
<td>7.26 ± 2.67</td>
<td>0.492</td>
</tr>
<tr>
<td>Vitamin B12 (µg/dL)</td>
<td>146.65 ± 49.01</td>
<td>127.78 ± 41.62</td>
<td>141.58 ± 35.87</td>
<td>0.006</td>
</tr>
<tr>
<td>WBC (103/µL)</td>
<td>8878.6 ± 3391.39</td>
<td>10086.96 ± 3120.79</td>
<td>9626.09 ± 3539.03</td>
<td>0.218</td>
</tr>
<tr>
<td>Platelet (103/µL)</td>
<td>278.30 ± 95.19</td>
<td>227.48 ± 83.71</td>
<td>230.53 ± 86.94</td>
<td>0.016</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>84.61 ± 13.78</td>
<td>94.83 ± 16.27</td>
<td>81.61 ± 18.50</td>
<td>0.012</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>20.65 ± 6.91</td>
<td>22.04 ± 6.63</td>
<td>21.95 ± 7.67</td>
<td>0.697</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>14.03 ± 7.86</td>
<td>16.43 ± 8.39</td>
<td>18.52 ± 5.20</td>
<td>0.418</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td>14.65 ± 14.09</td>
<td>14.82 ± 14.88</td>
<td>13.04 ± 4.03</td>
<td>0.558</td>
</tr>
</tbody>
</table>

### Table 2. Homocysteine Levels and GFR Levels Over Time

<table>
<thead>
<tr>
<th></th>
<th>Preoperative (Mean ± SD)</th>
<th>48th hour (Mean ± SD)</th>
<th>3rd month (Mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine (µmol/L)</td>
<td>16.03 ± 5.41</td>
<td>18.26 ± 10.20</td>
<td>9.53 ± 4.60</td>
<td>0.001*</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>134.05 ± 7.9</td>
<td>130.87 ± 11.7</td>
<td>159.1 ± 13.8</td>
<td>0.009*</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>12.09 ± 2.99</td>
<td>11.52 ± 4.12</td>
<td>12.39 ± 3.36</td>
<td>0.024</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.74 ± 0.22</td>
<td>0.82 ± 0.31</td>
<td>0.66 ± 0.25</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*Preoperative to 3rd month
** 48th hour to 3rd month
*** Preoperative to 48th hour
There was no statistically significant difference between the preoperative homocysteine level and the level 48 hours after the operation ($P = .460$). However, the homocysteine level three months after the operation was lower than the preoperative and 48 hour levels, and this difference was statistically significant ($P = .001$ and $P = .003$, respectively) (Table 2). The GFR level was calculated as $134.05 \pm 7.9$ mL/min preoperatively and $130.87 \pm 11.7$ mL/min 48 hours postoperatively. The decrease in the GFR level was not statistically significant ($P = .123$). The three month GFR level was $159.1\pm13.8$ mL/min. There was no statistically significant difference between the preoperative GFR and the GFR at three months ($P = .093$). However, the three month GFR was higher than the 48 hour GFR, and this difference was statistically significant ($P = .012$) (Table 2). The correlation between plasma homocysteine levels and creatinine levels was shown in Table 3. Distribution of the level of plasma homocysteine-creatinine on preoperative, postoperative 48th hour and 3rd month are shown in Figures 1, 2 and 3.

**DISCUSSION**

Management of urinary system stones should be less harmful for the kidney. PNL has some advantages over open surgery, such as a short hospitalization, minimal skin incision, less postoperative pain and better cosmetic results\(^6\). The long and short term effects of PNL on renal function has been assessed in some studies\(^2,7,8\). GFR decreases immediately following the PNL procedure\(^2\). There have been a few studies assessing the decrease in GFR after PNL. Some studies have shown that both the treated kidney and the contralateral kidney are affected that the GFR immediately decreases after PNL. The mechanism by which the GFR decrease may be related to activation of the neuronal and/or humoral systems that may occurs during the operation. One way to activate the neuronal and humorals systems is via tissue injury related factors, such as oxidative stress\(^9\). Soylemez et al. evaluated the oxidative stress effects of PNL and revealed that oxidative stress is elevated during the PNL procedure\(^6\). According to Hoffman, oxidative stress can cause inadequate methionine metabolism leading to increased homocysteine. Additionally, some studies revealed that homocysteine demoliishes cells, raises lipid peroxidation, causes apoptosis and affects antioxidant defense systems\(^10\). It seems likely that PNL can cause hyperhomocysteinemia by elevating oxidative stress. In the present study, the mean plasma homocysteine level was $16.03 \pm 5.41$ µmol/L and $18.26 \pm 10.20$ µmol/L preoperatively and at 48 hours postoperatively, respectively. Although an increase in homocysteine was detected in 56% of patients, it was not statistically significant. Although not statistically significant, homocysteine level elevation may result from increased oxidative stress during the operation. In addition, the mean plasma homocysteine level was $9.53 \pm 4.60$ µmol/L three months after the operation. This increase in homocysteine was detected in 56% of patients, it was not statistically significant. Although not statistically significant, homocysteine level elevation may result from increased oxidative stress during the operation.

**Table 3. Correlation of Plasma Homocysteine-Creatinine**

<table>
<thead>
<tr>
<th>Homocysteine</th>
<th>Creatinine a</th>
<th>Pearson Correlation</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a preoperative</td>
<td>Creatinine a</td>
<td>0.003</td>
<td>-</td>
</tr>
<tr>
<td>Creatinine b</td>
<td>0.988</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Creatinine c</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Homocysteine b</td>
<td>Pearson Correlation</td>
<td>-</td>
<td>0.036</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>-</td>
<td>0.871</td>
<td></td>
</tr>
<tr>
<td>Homocysteine c</td>
<td>Pearson Correlation</td>
<td>-</td>
<td>-0.008</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>-</td>
<td>0.973</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) preoperative  
\(^b\) 48 hour postoperative  
\(^c\) 3rd month after operation
value was lower than the homocysteine levels preoperatively and 48 hours postoperatively, and the decrease was statistically significant. We believe that the elevated homocysteine levels return to normal, while oxidative stress is reduced by defense mechanisms over time. Some studies revealed that there is a relation between the homocysteine level with folic acid and vitamin B12 (9,10-12). PCNL can cause hyperhomocysteinemia by elevating oxidative stress.

In this situation PCNL is the main reason of the hyperhomocysteinemia. On the other hand folic acid or vitamin B depletion may cause some defect in homocysteine metabolism and eventually hyperhomocysteinemia is occurred. In the latter situation, the level of homocysteine may be decreased by folic acid or vitamin B supplementation. However, oxidative stress caused by any situation such as PCNL, folic acid or vitamin B supplementation is not expected to any effect on homocysteine levels. In the present study, preoperative and postoperative level of folic acid and vitamin B12 was not changed significantly. We believe that PCNL is the main reason of the oxidative stress and changing of the homocysteine levels is directly related with PCNL rather than level of folic acid and vitamin B12.

The GFR initially decreases after PNL; however, studies have suggested that this procedure has no harmful effect on renal function in the long term. One of the factors that affect renal function in the long time is parenchymal injury caused by multiple accesses and00 tal manipulation by the nephroscope. The other factor is renal infarcts caused by angioembolization to prevent excessive bleeding. If these factors do not occur renal infarcts caused by angioembolization to prevent excessive bleeding. If these factors do not occur renal function will be preserved or improved over time after PNL (13). PCNL can cause hyperhomocysteinemia by elevating oxidative stress.

Renal function which deteriorates after the PNL procedure is preserved or improved over time. Homocysteine may be a sensitive indicator to assess changes in renal function immediately after PNL and in the long-term. Increased oxidative stress after PNL may affect homocysteine levels. However, we believe that a study with more participants would be useful for statistical analyses.

**CONCLUSIONS**

Renal function which deteriorates after the PNL procedure is preserved or improved over time. Homocysteine may be a sensitive indicator to assess changes in renal function immediately after PNL and in the long-term. Increased oxidative stress after PNL may affect homocysteine levels. However, we believe that a study with more participants would be useful for statistical analyses.

**ACKNOWLEDGEMENT**

Ethical Committee Approval: Ethics committee approval was received from the local committee of Çukurova University

**AUTHOR DISCLOSURE STATEMENT**

The authors report no conflict on interests.

**REFERENCES**


