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 mm^2.

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 treatment(1). 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 normal(2). 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 population(3). The prevalance 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 concentration(4). In addition, a close relationship was found between elevated plasma homocysteine and increased oxidative stress in patients with chronic kidney disease(5).

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 pyelonephritis and previous surgery until at least three months earlier, such as open surgery, shock wave lithotripsy

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Table 1. Blood Sample Results

	Preoperative (Mean ± SD)	48th hour (Mean ± SD)	3rd month (Mean ± SD)	*p* value
Hemoglobin (g/dL)	13.226 ± 2.04	12.26 ± 2.26	12.78 ± 1.95	0.019
Folic acid (ng/mL)	7.75 ± 2.86	8.05 ± 3.09	7.20 ± 2.67	0.492
Vitamin B12 (pg/ml)	146.65 ± 49.01	127.78 ± 41.62	141.58 ± 35.87	0.096
WBC (x103/uL)	8878.26 ± 3591.39	10086.96 ± 3120.79	9626.09 ± 3539.03	0.218
Platelet (x 103/µL)	278.30 ± 95.19	227.48 ± 83.71	230.53 ± 86.94	0.016
Glucose (mg/dL)	84.61 ± 13.78	94.43 ± 16.27	81.61 ± 18.50	0.012
AST (U/L)	20.65 ± 6.91	22.04 ± 6.63	21.95 ± 7.67	0.697
ALT (U/L)	14.03 ± 7.86	16.43 ± 8.39	18.52 ± 5.20	0.418
GGT (U/L)	14.65 ± 14.09	14.82 ± 14.88	13.04 ± 4.03	0.558

(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 all cases except in two patients who underwent a tubeless procedure. The ureteral and urethral catheters were removed 24 hours after the operation in the two patients who underwent a tubeless procedure. The urethral catheter was removed 24 hours after the operation in 21 patients. A kidney-ureter and bladder graphy was performed and the nephrostomy catheter was removed 48 hours after the operation if no hematuria was observed . An antegrade nephrostogram was performed 48 hours after the operation if necessary. Patients were discharged after break up of urine leakage. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analyses

Data were analyzed using SPSS software version 20 (SPSS, Inc., Chicago, IL, USA). Categorical variables are shown as number and percent, and quantitative variables are shown as the mean and standard deviation. A P-value < 0.05 was considered significant. Comparisons between groups were performed using the t test for normally distributed data. The Mann Whitney U test and Wilcoxon test were used to compare data that were not normally distributed. To evaluate the change in the measurements over the three time points, the Repeated Measurements Analysis was applied. Correlations between numerical measures were analyzed using the Pearson Correlation when assumptions were provided and, when the assumptions were not provided, Spearman Correlation was used.

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 fewer. 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.

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

Table 2. Homocysteine Levels and GFR Levels Over Time

	Preoperative (Mean ± SD)	48th hour (Mean ± SD)	3rd month (Mean ± SD)	*P* value
Homocysteine (µmol/L)	16.03 ± 5.41	18.26 ± 10.20	9.53 ± 4.60	0.001* 0.003** 0.460***
GFR(ml/min)	134.05 ± 7.9	130.87 ± 11.7	159.1 ± 13.8	0.093* 0.012** 0.123***
BUN (mg/dL)	12.09 ± 2.99	11.52 ± 4.12	12.39 ± 3.36	0.528
Creatinine (mg/dL)	0.74 ± 0.22	0.82 ± 0.31	0.66 ± 0.25	0.056

*Preoperative to 3rd month
** 48th hour to 3rd month
*** Preoperative to 48th hour

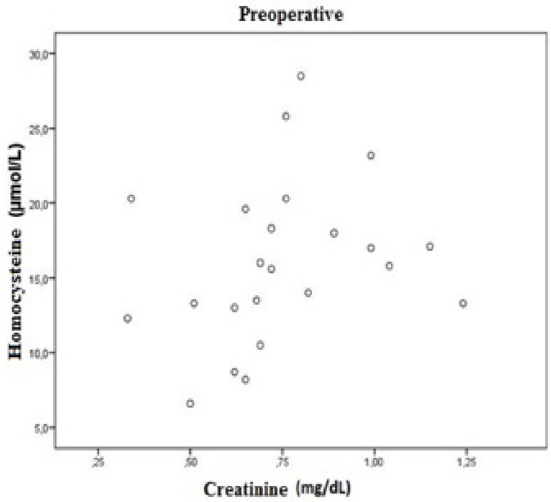

Figure 1. Distribution of the level of plasma homocysteine-creatinine preoperatively.

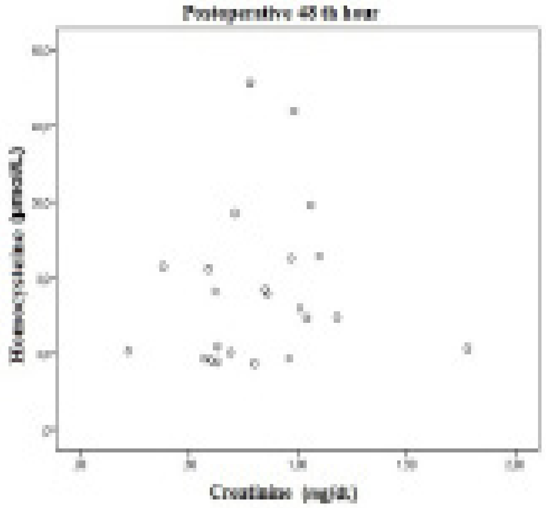

Figure 2. Distribution of the level of plasma homocysteine-creatinine on postoperative 48th hour.

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 ± 7.9 mL/min preoperatively and 130.87 ± 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±13.8 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 48 th hours 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 humoral 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 demolishes 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 ± 5.41 µmol/L and 18.26 ± 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 ± 4.60 µmol/L three months after the operation. This

Table 3. Correlation of Plasma Homocysteine-Creatinine

		Creatinine a	Creatinine b	Creatinine c
Homocysteine a	Pearson Correlation	0,003	-	-
	Sig. (2-tailed)	0,988	-	-
Homocysteine b	PearsonCorrelation	-	0,036	-
	Sig. (2-tailed)	-	0,871	-
Homocysteine c	PearsonCorrelation	-	-	-0,008
	Sig. (2-tailed)	-	-	0,973

[a] preoperative
[b] 48 hour postoperative
[c] 3rd month after operation

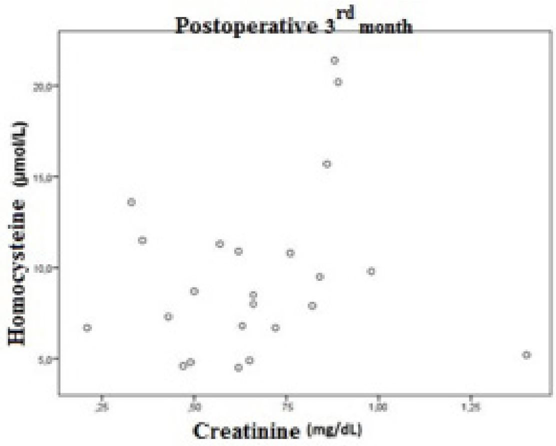

Figure 3. Distribution of the level of plasma homocysteine-creatinine on postoperative 3rd month

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 [5,10-13]. 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 and brutal manipulation by the nephroscope. The other factor is 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[2,14,15]. Authors have reported that there is a close relationship between decreased kidney function and the homocysteine level[3]. The homocysteine level increase, while kidney function progressively deteriorates over time[16]. In the present study, the GFR levels decreases initially, but the decrease was not statistically significant. Similarly, homocysteine levels increases initially and it was not statistically significant. According to this result, there is an inverse correlation between GFR and the homocysteine level initially. The GFR level then increase over time. Also homocysteine levels decreases in late postoperative period rather than the early postoperative period, and this difference was statistically significant. We found a cross correlation between the GFR and homocysteine concentration over time, in the late postoperative period. It seems likely that this situation is dependent on the close correlation between the homocysteine level and kidney function. The limitations of the present study were as follows: the study included a limited number of patients, and featured a short follow-up duration and absence of a control group of healthy volunteers.

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.

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AUTHOR DISCLOSURE STATEMENT

The authors report no conflict on interests.

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