THE RELATIONSHIP BETWEEN THE SERUM URIC ACID LEVEL, NEUTROPHIL-LYMPHOCYTE RATIO, AND CAROTID INTIMA MEDIA THICKNESS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Aims: The aim of the present study was to investigate the relationship between carotid intima media thickness, and the neutrophil-lymphocyte ratio (NLR) and uric acid level in patients with chronic kidney disease (CKD).

Methods: The study included 75 patients (mean age 56.0 ± 15.5 years) with stage 2-5 CKD (non-dialysis). NLR was calculated as the ratio of the neutrophil and lymphocyte counts obtained from the same automated blood sample. Serum uric acid levels were measured and carotid intima thickness (CIMT) was determined using ultrasonography in each patient. Statistical analysis was performed using the Kolmogorov-Smirnov test, Pearson's and Spearman’s correlation analyses and multivariate linear regression analyses.

Results: Data show that there was a positive significant correlation between CIMT, and NLR and the serum uric acid level. (r = 0.243, p = 0.035; r = 0.265, p = 0.022, respectively).

Conclusion: Based on the present findings, we think that assessment of NLR and the uric acid level could improve the evaluation of the inflammatory process leading to coronary artery disease in patients with CKD.

Key words: Carotid intima media thickness, Chronic kidney disease, Neutrophil-lymphocyte ratio, Uric acid.

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Introduction

Cardiovascular diseases are the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD). In CKD all types of cardiovascular diseases, including coronary artery disease (CAD), arrhythmia, heart valve diseases, and heart failure increase. In addition to traditional cardiovascular risk factors, such as diabetes mellitus, hypertension, and hyperlipidaemia, factors associated with uraemia, including anemia, hyperparathyroidism, hyperphosphatemia, hyperhomocysteinemia, and chronic systemic inflammation, are associated with an increase in CAD in patients with CKD1,3).

The serum uric acid level increases in CKD, which might be due to a decrease in the glomerular filtration rate (GFR). In addition, hyperuricaemia can lead to chronic renal failure, resulting in the progression of disease6). The relationship between the serum uric acid level and cardiovascular diseases is well known6). Many studies have reported that there is a close relationship between an elevated serum uric acid level, and hypertension, CAD, metabolic syndrome, cerebrovascular dementia, and vascular dementia. It has also been suggested that uric acid might cause vascular injury via a pathophysiological role in oxidative stress and via triggering inflammation6-9).

C-reactive protein (CRP) is an acute phase reactant indicative of inflammation, and an association between a high CRP level and CAD has been reported10). Although such inflammatory markers as CRP, interleukin-6, and tumor necrosis factor alpha
are used to assess inflammation and predict cardiovascular prognosis, these markers have not been routinely used to monitor CKD patients\textsuperscript{(11,12)}.

The neutrophil-lymphocyte ratio (NLR), which is measured via a routine complete blood count (CBC) examination, is a reproducible, inexpensive, and widely available inflammation marker. A systemic inflammatory response can be assessed via NLR. Numerous studies reported that NLR is indicative of disease activity, inflammatory load, and/or systemic inflammation in such diseases as diabetes mellitus, myocardial infarction, cerebrovascular disease, and cancer\textsuperscript{(13,16)}. In patients with CKD, including patients on dialysis and those that are not, a relationship between NLR and inflammation was reported.

An increase in carotid intima media thickness (CIMT) is considered the first step of the atherosclerotic process. Many studies reported that CIMT, measured non-invasively, is associated directly with CAD and can be used as a prognostic factor for CAD\textsuperscript{(17)}. Increasing evidence supports involvement of systemic inflammation in the development and progression of CAD. It was recently reported that a high NLR is associated with CAD\textsuperscript{(15,16,18)}. The aim of the present study was to determine the relationship between CIMT, and NLR and the uric acid level in patients with CKD.

Materials

The study protocol was reviewed and app

Study population

The study included 75 patients (mean age 56.0 ± 15.5 years) with stage 2-5 CKD (non-dialysis). Those with diabetes mellitus, CAD, heart failure, peripheral artery disease, a positive cerebrovascular event history, acute-chronic infection, malignancy, systemic inflammatory disease, leukaemia, leucocytosis, immune-suppressive drug use, haematological disorder, and gout, and cigarette smokers were excluded from the study. The study protocol was approved by the Local Ethics Research Committee, and was implemented in accordance with the Declaration of Helsinki. All the patients provided written informed consent to participate in the study.

Laboratory procedures

Blood sampling was performed between 8 and 10 a.m. after an overnight fast. Laboratory parameters included CBC, kidney function tests, calcium, uric acid, fasting glucose, lipid profile, and CRP. NLR was calculated as the ratio of the neutrophil and lymphocyte counts obtained from the same automated blood sample. The GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: 

\[ GFR = \frac{141 \times \min (\text{Scr/κ,1})^{\alpha} \times \max (\text{Scr/κ,1})^{1.209} \times 0.993 \times \text{Age} \times 1.018 \times 1.159 \times 1.018 \times 1.018}{1.018} \]

For CBC, including the white cell count, blood was collected from patients and transferred to EDTA tubes. CBC was measured with using a Symex XT-1800i automated device. The serum CRP level was measured using a nephelometer (Roche Hitachi Modular P, Germany) (normal value: <5 mg/dL).

Carotid intima-media thickness measurement

For the measurement of CIMT patients were placed in the supine position with their hands bent backwards. Measurements were made using a high-resolution B-mode ultrasound device (Lociq 7, GE Yokogawa Medical systems, Japan) and a linear probe on the right and left common carotid artery by 1 radiologist that was blinded to the characteristics of the patients. CIMT measurements were made at 3 different points, including the right and left common carotid artery, bifurcation, and the first 2 cm of the internal carotid artery. Longitudinal measurements were made from the distances defined as the vessel wall echogenicity and media-adventitia echogenity. The mean CIMT was calculated as the mean of measurements made in triplicate from each carotid artery\textsuperscript{(20)}.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences v.20.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to determine if data were distributed normally. Numerical variables with normal distribution are shown as mean ± SD and those not normally distributed are shown as median (range). The relationship between parameters was analysed using Pearson and Spearman’s correlation analyses. Multivariate linear regression analysis was used to determine which factors were associated with an increase in CIMT.

Results

In total, 75 CKD patients (35 females and 40 males) that fulfilled the inclusion criteria were recruited into the study. Mean age of the patients was 55.11 ± 15.9 years. Among the patients, 60
(80.0%) had hypertension and 34 (52.3%) had hyperlipidaemia. Mean duration of CKD was 3.9 ± 1.4 years, mean GFR was 43.2 ± 12.8 mL/min/1.73 m2, and the mean creatinine level was 1.89 ± 0.85 mg/dL. The mean NLR was 2.66 ± 0.95 and the mean serum uric level was 7.68 ± 1.72 mg/L. Mean CIMT was 0.57 ± 0.38 mm. Laboratory parameters are shown in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
<th>Median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.89±0.85</td>
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</tr>
<tr>
<td>GFR (mL/min/1.73 m2)</td>
<td>43.2±12.8</td>
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<tr>
<td>Albumin (g/L)</td>
<td>*44 (38-52)</td>
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</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>78.2±6.4</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.68±1.72</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.2±38.21</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>*144 (49-364)</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>6.11±7.53</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>13.3±1.79</td>
<td></td>
</tr>
<tr>
<td>Neutrophil (µL)</td>
<td>4877.73±1170.43</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte (µL)</td>
<td>1978.27±582.03</td>
<td></td>
</tr>
<tr>
<td>NLR</td>
<td>2.66±0.95</td>
<td></td>
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<tr>
<td>CIMT (mm)</td>
<td>0.57±0.38</td>
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</tbody>
</table>

Table 1: Laboratory parameters of patients with chronic kidney disease.

Data are given as mean±standard deviation or *median (min-max).

Abbreviations: CIMT; Carotid intima media thickness, CRP; C-Reactive protein, GFR; Glomerular filtration rate, NLR; neutrophil-lymphocyte ratio

There was a positive correlation between the uric acid, and CRP (r = 0.497, P = 0.001) and NLR (r = 0.615, P = 0.001). In addition, there was a positive correlation between CRP and NLR (r = 0.431, P = 0.001). Moreover, there was positive significant correlation between CIMT, and the serum uric acid level (r = 0.265, P = 0.022) and NLR (r = 0.243, P = 0.035) (Figure 1 and 2). There wasn’t a statistically significant correlation between CIMT and the other laboratory parameters, except for a positive correlation between CIMT and fasting serum glucose (r = 0.253, P = 0.033) (P > 0.05).

NLR, and the uric acid and fasting blood sugar levels were associated with CIMT in the CKD patients, and were subjected to multivariate linear regression analysis. It was noted that among the factors that affected CIMT, a 1-unit increase in NLR caused a 0.146-fold increase in CIMT (B + SE = 0.146 ± 0.057, P = 0.013) and change in the uric acid caused a 0.074-fold increase in NLR (B + SE = 0.074 ± 0.033, P = 0.29). Fasting serum glucose had no effect on CIMT (P > 0.05). Among the risk factors examined in this study, the parameter with the strongest effect on CIMT was NLR.

Discussion

In the present study there was a positive correlation between CIMT, both the serum acid level and NLR in CKD patients that were not on dialysis.
Atherosclerosis is a disease that develops in response to atherogenic lipoproteins of plasma origin lodging on the intima layer of vessel walls, and as a consequence of inflammatory and fibroproliferative events. Many factors play a role in its pathogenesis\(^{21}\). An increase in CIMT is an early sign of atherosclerosis. CIMT is regarded as an accurate indication of the presence and degree of CAD\(^{22,23}\). In CKD patients, including those on dialysis, there is a relationship between the degree of increase in CIMT, and the presence of cardiovascular disease and cardiovascular mortality\(^{22,23}\).

Low-level inflammation plays an important role in the development of CAD. It was reported that there is a strong relationship between the serum uric acid level, and various inflammatory markers and oxidative stress\(^{24}\). It was suggested that uric acid increases growth factor of platelet origin via activation of vascular smooth muscle cells, induces the release of inflammatory mediators, and contributes to infiltration of inflammatory cells via the monocyte chemoreactive protein level\(^{25}\). Although the mechanism of the association between the uric acid level and the development of atherosclerosis remains unknown, uric acid might cause endothelial dysfunction and development of atherosclerosis via triggering endothelial inflammation\(^{25,26}\).

Several studies reported that an increase in the uric acid level is a potential risk factor for such conditions as carotid atherosclerosis, CAD, acute myocardial infarction, congestive heart failure, peripheral vascular disease, and stroke. Moreover, studies on patients with hypertension, diabetes mellitus, and metabolic syndrome have shown that the uric acid level is an independent predictor of mortality due to cardiovascular disease\(^{27-30}\). Many researchers have reported the relationship between the uric acid level and an increase in CIMT. An epidemiological study that included 28,613 elderly females that were followed-up for 21 years reported that there was a relationship between an increased uric acid level and cardiovascular diseases\(^{27}\).

In a study that included 1578 Japanese elderly patients there was a correlation observed between the serum uric acid level and CIMT in patients without metabolic syndrome\(^{28}\). Kumral et al. studied patients with ischemic stroke and normal kidney functions, and reported that there was an association between CIMT and the serum uric acid level\(^{29}\). Another study based on the Brisighella Heart Study data corroborated that there is a relationship between CIMT and the uric acid level. In the CARDIA study that included 2498 young adult, coronary artery calcium scores were evaluated and hyperuricaemia was observed to be an independent risk factor for subclinical atherosclerosis. In studies that included hypertensive and diabetic patients without renal failure there was a positive correlation noted between an increase in the serum uric acid level and CIMT. It was reported that this relationship was valid for healthy young adults and the elderly, in addition to various patient groups\(^{29}\).

Patients with CKD have a high risk of accelerated development of atherosclerosis, which is closely associated with inflammation related to uraemia. Many studies reported that there is a relationship between hyperuricaemia and cardiovascular mortality in patients with CKD\(^{30,31}\). The NHANES 1 study reported that each 60-μmol L–1 increase in the serum uric acid level in adult females increases the risk of ischemic heart disease by 48% \(^{30}\). Numerous studies reported that an increase in the uric acid level is associated with such cardiovascular risk factors as hypertension, insulin resistance, diabetes, obesity, and metabolic syndrome, as well as CAD\(^{32,35}\). Another study reported that chronic inflammation was correlated with CIMT in end-stage renal disease\(^{31}\). Similarly, in the present study there was a positive correlation between CIMT and the serum uric acid level in patients with CKD.

Many markers have been suggested to indicate the severity of the inflammatory process that leads to the development and progression of atherosclerosis. NLR has also been suggested to be an indicator of subclinical inflammation, and its relationship with prognosis and mortality in CAD was reported. Williams et al. studied 683 patients with known or suspected CAD, and reported that there was a strong correlation between an increased NLR and a decrease in myocardial perfusion\(^{16}\). A study on dialysis and predialysis patients reported that NLR was positively correlated with IL-6 and hs-CRP, both of which are markers of inflammatory events\(^{34}\). Likewise, in the present study there was a positive correlation between the serum CRP level (an inflammatory marker), and NLR and the uric acid level.

Numerous studies have investigated the relationship between NLR, and inflammation and cardiovascular disease in patients with CKD. A study that included 225 patients with stage 3-5 CKD reported that an increase in NLR is associated with endothelial dysfunction and that in this patient group composite cardiovascular events could be
predicted, independent of traditional cardiovascular risk factors. In a study on patients that recently began peritoneal dialysis treatment it was suggested that there is a relationship between an increase in NLR and cardiovascular mortality.\(^{38}\) In the present study there was a correlation between NLR and CIMT, which was indicative of subclinical atherosclerosis.

**Study limitations**

Our study has several limitations. These include that the number of subjects enrolled was small, and the study was cross-sectional, and thus, we cannot draw any causal conclusion from the relationship between serum uric acid level, neutrophil-lymphocyte ratio, and carotid intima media thickness.

**Conclusion**

In conclusion, we think that assessment of NLR and the uric acid level could improve the evaluation of the inflammatory process that leads to CAD in CKD patients, and facilitate treatment that could decrease modifiable cardiovascular risk factors.

**References**


