PROGNOSTIC VALUE OF THE MONOCYTE/HIGH DENSITY LIPOPROTEIN CHOLESTEROL RATIO IN DIABETIC NEPHROPATHY PATIENTS

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ABSTRACT

Introduction: Diabetic nephropathy (DN), a microvascular complication associated with diabetes mellitus (DM), manifests in urinary albumin excretion (UAE) and may lead to end-stage renal failure. Recent studies have reported that the monocyte/high-density lipoprotein cholesterol ratio (MHR) serves as an inflammatory marker. The purpose of this study is to analyze the prognostic value of the MHR in DN patients.

Material and methods: The medical records of type 2 DM patients who received follow-up care at the internal medicine clinic were examined, and the data of all patients who had undergone estimation of 24-hour UAE were recorded. These patients were separated into 3 groups on the basis of the UAE levels and the biochemical data and the MHR were compared between the groups.

Results: The serum creatinine (p = 0.008), 24-hour UAE (p < 0.001), and MHR (p = 0.005) were all significantly different between the groups. The MHR was positively correlated to the 24-hour UAE (p = 0.007) and negatively correlated to the glomerular filtration rate (GFR) (p = 0.023).

Conclusion: The MHR can be an inexpensive, accessible, and useful early prognostic marker in diabetic nephropathy patients.

Keywords: Albuminuria, diabetes mellitus, diabetic nephropathy, monocyte, high density lipoprotein.

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Introduction

World has 386,667.28 people with diabetes mellitus (DM) (8.33%) having Turkey in upper extreme of prevalence of diabetes with 14.9%. In recent years DM increased 156% (from 2.7% to 6.9%) for males and 103% (from 2.9% to 5.9%) for females35. Diabetic nephropathy (DN) is a major complication associated with type 2 DM and it ranks first in end-stage renal failure etiology. DN is a microvascular complication of DM and seen by 25%-40% of diabetic patients. DN is associated with increase in urinary albumin excretion (UAE) and decrease in the glomerular filtration rate (GFR), both of which are accompanied by high blood pressure and end-stage renal failure2,3. DN has been didactically categorized into stages based on the values of urinary albumin excretion (UAE): microalbuminuria and macroalbuminuria46.

More than 80% of DM patients with microalbuminuria progress to clinical nephropathy within 10 years. Besides being the earliest sign of nephropathy, microalbuminuria is also a determinant of cardiovascular mortality and morbidity in type 1 and type 2 DM patients5,6. It has been demonstrated that DM and hyperlipidemia are associated with chronic low-grade inflammation. Inflammation also plays a major role in the devel-
Development and progression of DN\textsuperscript{7}. And we know increased UAE and increased cardiovascular risk are associated with long-term low-grade inflammation. Various studies on inflammatory cytokines support this relation\textsuperscript{8, 9}.

It has been reported that monocyte subsets could be a valuable marker for inflammatory diseases and increased cardiovascular disease risk\textsuperscript{10}. Increased monocyte counts and decreased high-density lipoprotein cholesterol (HDL-C) levels in the blood may lead to accelerated atherosclerosis\textsuperscript{11}. It has been proposed that the monocyte/HDL-C ratio (MHR) has prognostic value in cardiovascular diseases and that it could be used as a systemic inflammatory marker. In recent studies, the MHR has been shown to be associated with coronary artery disease, slow coronary blood flow, and atrial fibrillation\textsuperscript{12, 13}. In this study, the aim is to examine the relationship between albuminuria level, which is an indicator of diabetic nephropathy, and the MHR, and to determine its prognostic value in diabetic nephropathy.

**Materials and methods**

A total of 134 type 2 DM patients, who were followed between June 2014 and June 2015, were enrolled in the study. The patients 24-hour urinary albumin levels were checked and their medical files were screened retrospectively. Demographic data included age, gender, and duration of disease, and laboratory data included serum hemoglobin, white blood cell (WBC) count, platelet count, monocyte count, blood biochemistry (serum urea, serum creatinine, serum albumin, glycated hemoglobin A1c (HbA1c), serum total cholesterol, serum HDL-C, serum low-density lipoprotein cholesterol [LDL-C], and serum triglycerides [TG]), C-reactive protein (CRP), GFR, and 24-hour UAE.

The measured creatinine clearance values of the patients were used for the GFR levels. Patients were separated into 3 groups based on the severity of albuminuria: the normoalbuminuria group with UAE of 0-30 mg/day, the microalbuminuria group with UAE of 30-300 mg/day, and the macroalbuminuria group with UAE of >300 mg/day. Patients with active infection, known malignancy, nephrotic syndrome, or hematologic disease were excluded from the study.

**Statistical analysis**

All statistical analyzes were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 21 (IBM Corp., Armonk, NY, USA). All data were tested for normality using the Kolmogorov-Smirnov test. Data were expressed as means ± standard deviation. Comparisons between the groups were performed using the one-way ANOVA post hoc LSD test, and the relationships between variables were assessed via the nonparametric Spearman correlation test. Differences were considered statistically significant at p ≤ 0.05.

**Results**

Of the 134 patients enrolled in the study, 84 were male (62.5%) and 50 were female (37.5%). There was no statistically significant difference between the groups in the female/male ratio (p = 0.147). The demographic characteristics of the patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normoalbuminuria (n = 43)</th>
<th>Microalbuminuria (n = 50)</th>
<th>Macroalbuminuria (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1 ± 7.8</td>
<td>62.9 ± 9.8</td>
<td>57.8 ± 10.6</td>
<td>0.039</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>62.7</td>
<td>59.8</td>
<td>64.9</td>
<td>0.147</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5.1 ± 3.3</td>
<td>5.8 ± 3.9</td>
<td>5.3 ± 2.9</td>
<td>0.509</td>
</tr>
</tbody>
</table>

**Table 1**: Descriptive statistics of population.

No statistically significant differences were detected between the groups in mean values of serum urea, creatinine clearance, serum total cholesterol, serum TG, serum HDL-C, serum LDL-C, hemoglobin level, WBC count, monocyte count, platelet count, serum albumin, CRP, and HbA1c level (Table 2). However, statistically significant differences were seen in the mean values of serum creatinine (p = 0.008), 24-hour UAE (p < 0.001), and the MHR (p = 0.005) (Figure 1).

Spearman correlation analysis indicated that the MHR was correlated with 24-hour UAE (r = 0.244, p = 0.007), creatinine clearance (r = -0.201, p = 0.023), WBC count (r = 0.315, p < 0.001), serum urea (r = -0.265, p = 0.005), and duration of diabetes (r = 0.259, p = 0.003). The relationship between MHR and 24-hour UAE is shown in Figure 2.

There was statistically significant difference in the monocyte count between the normoalbuminuria and macroalbuminuria groups (p = 0.047).
There was no statistically significant difference in the MHR between the normoalbuminuria and microalbuminuria groups (p = 0.910), but there was a significant difference between the microalbuminuria and macroalbuminuria (p = 0.004) and between the normoalbuminuria and macroalbuminuria groups (p = 0.004).

Table 2: Laboratory results of the three groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normoalbuminuria</th>
<th>Microalbuminuria</th>
<th>Macroalbuminuria</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea (mg/dL)</td>
<td>37.3 ± 15.2</td>
<td>42.4 ± 25.7</td>
<td>41.8 ± 16.1</td>
<td>0.467</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 ± 0.3</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.5</td>
<td>0.008</td>
</tr>
<tr>
<td>CC</td>
<td>108.7 ± 90.3</td>
<td>115.5 ± 85.4</td>
<td>90.8 ± 69.7</td>
<td>0.366</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>197.8 ± 52.9</td>
<td>201.4 ± 51.3</td>
<td>179.2 ± 48.5</td>
<td>0.104</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>196.7 ± 156.4</td>
<td>194.3 ± 122.8</td>
<td>172.5 ± 101.1</td>
<td>0.644</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>46.5 ± 10.9</td>
<td>47.3 ± 14.3</td>
<td>42.5 ± 14.9</td>
<td>0.215</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>116.2 ± 41.7</td>
<td>122.5 ± 41.7</td>
<td>103.3 ± 38.3</td>
<td>0.089</td>
</tr>
<tr>
<td>WBC</td>
<td>7.8 ± 2.9</td>
<td>7.4 ± 1.7</td>
<td>8.3 ± 2.3</td>
<td>0.242</td>
</tr>
<tr>
<td>Hemoglobin level, g/dL</td>
<td>13.2 ± 1.8</td>
<td>12.8 ± 1.7</td>
<td>13.2 ± 2.0</td>
<td>0.452</td>
</tr>
<tr>
<td>Monocyte count (10⁹/l)</td>
<td>0.52 ± 0.19</td>
<td>0.55 ± 0.18</td>
<td>0.62 ± 0.33</td>
<td>0.124</td>
</tr>
<tr>
<td>Platelet count (10³/mm³)</td>
<td>259.3 ± 92.9</td>
<td>253.2 ± 90.7</td>
<td>246.5 ± 65.8</td>
<td>0.791</td>
</tr>
<tr>
<td>MHR</td>
<td>0.114 ± 0.004</td>
<td>0.119 ± 0.005</td>
<td>0.252 ± 0.038</td>
<td>0.005</td>
</tr>
<tr>
<td>24-h UAE</td>
<td>15.2 ± 7.6</td>
<td>109.2 ± 69.9</td>
<td>503.0 ± 291.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albümin</td>
<td>4.0 ± 0.6</td>
<td>4.0 ± 0.7</td>
<td>3.8 ± 0.7</td>
<td>0.389</td>
</tr>
<tr>
<td>CRP</td>
<td>1.1 ± 1.3</td>
<td>2.1 ± 2.6</td>
<td>1.9 ± 2.9</td>
<td>0.305</td>
</tr>
<tr>
<td>HbA1c</td>
<td>9.9 ± 2.4</td>
<td>8.6 ± 2.5</td>
<td>8.4 ± 2.5</td>
<td>0.121</td>
</tr>
</tbody>
</table>

Figure 1: The MHR values in diabetic nephropathy.

Figure 2: Relationship between MHR and 24-hour UAE.

Discussion

In DM, microalbuminuria creates an advanced renal disease and is an important predictor of cardiovascular mortality and morbidity. The cardiovascular mortality rate associated with microalbuminuria was found to be 2.4 times higher\(^{14}\). In fact, microalbuminuria in type 2 DM is a precursor of cardiovascular deaths rather than end-stage renal failure\(^{15}\). It is not completely clear how microalbuminuria increases cardiovascular risk, but traditional risk factors, inflammatory indicators, and endothelial dysfunction appear to be responsible for the increase in risk in individuals with microalbuminuria\(^{16}\).

Numerous epidemiological studies have shown that dyslipidemia may be an important risk factor in the progression of chronic renal failure\(^{17,18}\). While high TG and low HDL-C levels have been reported to be associated with renal dysfunction, the relationship of LDL-C levels with renal dysfunction has not been established\(^{19}\).

Numerous studies have found low HDL-C levels to be associated with increased UAE and low GFR in patients with chronic renal failure\(^{20,21}\). In the study by Ravid et al., 574 recently diagnosed type 2 DM patients without complications were followed for approximately 8 years. Microalbuminuria developed in 20.6% of patients with high total cholesterol vs. 7.8% of patients with low HDL-C. The authors concluded that high serum total cholesterol and low serum HDL-C were risk factors for the progression of diabetic nephropathy\(^{22}\).

In our study, no significant differences were observed between the groups in total cholesterol, TG, and LDL-C levels. However, the HDL-C level was significantly lower in the macroalbuminuria group as compared to the normoalbuminuria group.
Recent experimental findings have shown that impaired cholesterol efflux pathways and decreased HDL-C levels stimulate growth in hematopoietic stem cells, especially in the monocyte cell lines, and thereby promote atherosclerotic plaque formation in mice(25,26). Many studies have shown that the monocyte count is increased, with abnormal distribution of monocyte subgroups, in chronic renal failure patients(25,26).

In our study, the monocyte count was higher in the macroalbuminuria group than in the normoalbuminuria group.

Kanbay et al. determined the ratio between monocyte count and HDL cholesterol levels in the circulation and designated it as “MHR”. They determined this ratio to be an independent risk factor for chronic renal patients in major cardiovascular events in terms of poor prognosis(27). Furthermore, the MHR was found to have a negative correlation with estimated GFR (eGFR). Our study analyzed the relationship between the MHR and albuminuria levels in diabetic nephropathy patients who did not develop chronic renal disease. In the group classified according to albuminuria levels and whose GFR levels did not show any significant difference, there was a significant difference in the MHR. The MHR showed positive correlation with 24-hour UAE levels and negative correlation with GFR levels. This supports the thesis that the positive correlation of the MHR with WBC count could serve as an inflammatory marker.

The results of our study suggest that the MHR can be used as an inexpensive and accessible prognostic marker in diabetic nephropathy patients. Additionally, the correlation between the MHR and the albuminuria levels in patients who did not develop chronic renal failure showed that the MHR had an early prognostic value. Further, comprehensive, prospective studies are needed to confirm our findings.

References


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