Fractional excretion of magnesium as an early indicator of renal tubular damage in normotensive diabetic nephropathy

Fatih Ozcelik*, Serif Kactas, Halime Hanim Pence, Saadet Kurcenli, Erdim Sertoglu, Busra Efem Toy, Alper Kutukcu, Refik Demirtunc and Kadir Kayatas

Abstract

Objectives: The aim of the present study is to evaluate the diagnostic powers of fractional magnesium, sodium and potassium as markers of renal tubular damage in normotensive type 2 diabetes mellitus (T2DM) patients with respect to microalbuminuria and estimated glomerular filtration rate (eGFR).

Materials and methods: Forty healthy volunteers and 91 normotensive T2DM patients were included in the study. Patient group was divided into two according to albuminuria level; 49 were normoalbuminuric and 42 were microalbuminuric. In addition to albumin in urine, urine and serum Na, K, Mg and creatinine values were measured to calculate fractional electrolyte excretion rates.

Results: In normoalbuminuric and microalbuminuric groups, fractional excretion of magnesium (FEMg) values were found to be significantly higher than the control group (p < 0.05). There was a moderate correlation between FEMg and albumin to creatinine ratio (ACR) (Spearman r = 0.3215, p < 0.05). In the ROC analysis for eGFR and FEMg based on microalbuminuria, the areas under the curve were 0.625 and 0.732, respectively (diagnostic sensitivity 59.52% and 66.67%; specificity 70.79% and 77.53%, p < 0.05).

Conclusion: For renal tubular damage predicted by microalbuminuria, FEMg could be accepted as a candidate biochemical marker with diagnostic and prognostic value.

Keywords: FEMg; Microalbuminuria; Normotensive diabetic nephropathy.
**Bulgular:** Normoalbüminürik ve mikroalbüminürük gruplardaki, magnezyumun fraksiyonel atılım (FEMg) değerleri, kontrol grubuna göre anlamlı derecede yüksek olduğu saptandı (p<0.05). FEMg ve albümin kreatinin oranı arasında orta derecede bir korelasyon vardı (Spearman r=0.3215, p<0.05). Mikroalbumin baz alınarak eGFR ve FEMg için yapılan ROC analizinde, eğri altında alanlar sırasıyla 0.732 ve 0.625’tür (% 59.52 ve% 66.67 tanısal duyarlılık; özgüllük% 70.79 ve% 77.53, p<0.05).

**Sonuç:** Mikroalbuminüri ile ön görülen renal tübüler hasar için FEMg, tanısal ve prognostik değeri olan aday bir biyokimyasal belirteç olarak kabul edilebilir.

**Anahtar kelimeler:** FEMg; Mikroalbuminüri; Normotensif diyabetik nefropati.

**Introduction**

Being among the most common global health problems, diabetes mellitus (DM) is a chronic disease caused by insufficient production of insulin by pancreas or inadequate usage of it [1]. The disease is characterized by high blood glucose levels and most common complications are seen in eyes, heart, kidneys and nervous system. Diabetic nephropathy (DN) is a microvascular complication of DM and it is the most frequent cause of chronic kidney disease in developed and developing countries [2, 3]. Besides this, it is also one of the causes of acute tubular necrosis (ATN), which may occur due to various etiological factors. There is no consensus yet on choosing a reliable screening test to recognize this early renal injury.

In clinical practice, early detection and staging of diabetic nephropathy is attempted by measurement of urinary albumin excretion rate (U-albE) and glomerular filtration rate (GFR). Although U-albE is accepted as a marker for DN and progressive kidney failure, the results are not consistent and it has a low predictive value for underlying renal pathology [4, 5]. GFR can be calculated <60 mL/min/1.73 m² without any increase in U-albE (microalbuminuria) [6]. Also normal kidney structure in some patients with microalbuminuria and lesions of diabetic nephropathy in some diabetic patients with normoalbuminuria were observed [7]. In summary, glomerular pathology and renal tubular pathology are not always co-exist. Besides this, approved study equations including age, gender, race, serum creatinine (Cr) and cystatin-C are considered successful in determination of glomerular function. Lately, molecules like kidney injury molecule-1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), N-acetyl-b-D-glucosaminidase (NAG) and heart fatty acid-binding protein (H-FABP) are added to tubular damage markers [8, 9]. However, the usage of these markers are still controversial and not practical. On the contrary, the use of serum and urine electrolyte levels as indicators of renal tubular function in clinical routine seems to be more practical, as the renal tubules are responsible from the secretion and re-absorption of electrolytes and many other substances. In addition, there are some studies in the literature that mention the usage of fractional excretion (FE) of electrolytes for evaluation of renal damage [10, 11].

In patients with early stage DN with normoalbuminuria, tubular function markers are of critical importance for clinical evaluation and prognostic follow-up and also crucial for treatment management in early stage. Under the light of data mentioned above, FE of electrolytes were calculated among with albuminuria to detect patients under risk of developing chronic kidney disease and to interpret tubular function in these patients. In addition, the relation between eGFR, albuminuria and FE of electrolytes was evaluated.

**Materials and methods**

The study was designed as an analytical cross-sectional study and conducted in University of Health Sciences, Haydarpasa Numune Training Hospital, Department of Medical Biochemistry between 01.09.2017 and 01.04.2018. Ethical approval was given by Haydarpasa Numune Training Hospital (protocol no: HNEAH-KAEK 2017/KK/107).

**Study participants and exclusion criteria**

Ninety-one normotensive type 2 DM (T2DM) patients and 40 control group subjects were included in the study. In spot urine, albumin-to-creatinine ratio (ACR) was used as an indicator of albuminuria. Patients were divided into two groups according to ACR. Among the 91 patients, 49 of them were normoalbuminuria (<30 mg/day Cr) group and 42 were microalbuminuria (30–300 mg/g Cr = 30–300 mg/day) group. Besides, as ACR is accepted as an indicator of renal pathological conditions, microalbuminuric group was classified as renal pathology positive while the other group was renal pathology negative.

Exclusion criteria were; <25 and >70 years of age, pregnancy/lactation, usage of aminoglycosides, diuretics, cathartics containing sodium and magnesium, hypertension (systolic blood pressure >140, diastolic blood pressure >90 mmHg), having diseases that might cause nephrotic syndrome such as amiloidosis, sarcoidosis and Sjogren disease; infections, neoplasies, heredofamilial diseases; burns and gastrointestinal disorders that may cause
electrolyte loss. Patients who took diuretics 24 h prior to tests were not included in the study. In addition, macroalbuminuric patients (≥300 mg/gr Cr) was not included in the study because enough patient number could not be reached. Exclusion criteria for the control group were; fasting blood glucose (FBG) ≥100 mg/dL and, HbA1c ≥ 5.9, pregnancy/lactation and presence of any chronic disease.

Study design

Blood pressure (BP) measurements of the participants were made after 15 min rest in sitting position. Participants with <140/90 BP were accepted as normotensive.

American Diabetes Association criteria were used in evaluation of T2DM in patient group [12]. Blood samples were drawn from participants after 12 h fasting into one yellow-capped and one EDTA containing tubes. To prevent orthostatic proteinuria, all participants were requested to collect the first urine in the morning. Serum levels of Cr, magnesium (Mg), sodium (Na), potassium (K) and urinary levels of Cr, Mg, Na, K and albumin were measured in patient and control group subjects. Prior to analysis, serum samples were centrifuged for 10 min at 4000 rpm and urine samples were centrifuged for 5 min at 3000 rpm.

Serum/urine glucose, Cr, Mg and Na/K levels and urine albumin levels were determined by an autoanalyzer (Abbott Architect CI 4100 autoanalyser, California, USA) using hexokinase/glucose-6-P dehydrogenase, kinetic alkaline picrate, isocitrate dehydrogenase, ion selective electrode (indirect) and immunoturbidimetric methods (Architect, Abbott Laboratories, IL, USA), respectively. Urine electrolytes were measured using spot urine. Urine samples taken for electrolyte were diluted according to electrolyte concentration using automatic dilution protocol by the autoanalyzer system. The measurement range of the method used for urine Mg was 1.8–26.4 mg/dL, sensitivity was 0.45 mg/dL and imprecision was ≤6% total CV. HbA1c levels were determined via HPLC reverse phase ion exchange chromatography method (Akray Adams HA-8180V analyzer, Minneapolis, MN, USA).

eGFR was calculated with MDRD (Modification of Diet in Renal Diseases Study) formula [13]:

\[ \text{eGFR} = 186 \times ((\text{Serum Cr}) - 1.154) \times (\text{age} - 0.203) \times (0.742 \text{ if female}) \]

FE of Na, K, Mg and urea were calculated as shown by the formula [14]:

\[ \text{FE}(\alpha) \% = \frac{[\text{Urine}(\alpha) \times \text{Serum Cr level} \times 100]}{[\text{Serum}(\alpha) \times \text{Urine Cr level}]} \]

\[ \alpha: \text{Electrolyte calculated by FE.} \]

Power analysis

With the priori power analysis (by using PS-Power and Sample Size Calculation software) based on the data of the study conducted by Gheissari et al., in which they found FE of Na (FENa) and FE of Mg (FEMg) levels of patient group (n: 20) with acute tubular necrosis significantly higher than those of control group (n: 25) (FENa = 1.035 ± 0.65 vs. 0.56 ± 0.28, p < 0.005 and FEMg = 9.49 ± 7.76 vs. 2.28 ± 1.54, p < 0.001, respectively) [15], minimum of 30 patients and 30 control subjects for FENa and a minimum of 19 patients and 19 controls for FEMg were calculated.

Statistical analysis

SPSS statistics 25 software (IBM Corp, Chicago, IL, USA) and MedCalc version 15.8 software were used for statistical analysis. In comparison of data for more than two independent groups, one-way ANOVA was used for parametric variables, while Kruskal-Wallis test was used for nonparametric ones. For correlation analysis between urine albumin levels, ACR, FE of electrolytes and eGFR, Pearson correlation analysis was used in parametric data and Spearman correlation analysis was used for nonparametric data. Multiple regression analysis was carried out to detect the degree of effect of independent variables (FEMg, FENa, FE of K (FEK) and eGFR) on ACR (dependent variable), which is accepted as an important marker in renal pathogenesis. Chi-Square test was used in evaluation of categoric variables. To evaluate the diagnostic power of FEMg and eGFR in microalbuminuric patients, which is considered as an important indicator of renal injury, receiver operating characteristic (ROC) analysis was carried out. Fischer’s Exact Test was used in odds ratio calculation to test the risk of FEMg and eGFR in development of renal damage in microalbuminuric patients.

Results

Subject characteristics

The cases of 40 healthy subjects (control group) and 91 normotensive (49 normoalbuminuric and 42 microalbuminuric) T2DM patients were confirmed by HbA1c and fasting plasma glucose results. There was no difference between the age of healthy group, normoalbuminuric group and microalbuminuric group (respectively, 51 ± 9, 53 ± 8 and 52 ± 9 years, p = 0.4390). Fifty-three percent
(n=70) were female and 47% (n=61) were male of the patients included in the study (Table 1).

**Comparison of groups and correlational studies**

FE of electrolytes and eGFR values of the groups are shown in Table 2. When the groups were compared according to the FEMg values, the values of control group were lower than the normoalbuminuric and microalbuminuric groups (respectively, p<0.05 and p<0.001). In addition, the FEMg values of the normoalbuminuric group were lower than the microalbuminuric group (p<0.01) (Figure 1A). There were no differences between groups according to FENa, FEK and eGFR values (p>0.05) (Table 2 and Figure 1B).

A moderate positive correlation between FEMg values and ACR and FENa values were found (Spearman r=0.371; p<0.0001, respectively). There was a significant positive correlation between eGFR and age (Spearman r=0.357; p<0.001). However, there was a very weak negative correlation between FEMg and eGFR (Spearman r=-0.193; p<0.0269). The correlation between ACR and FENa, FEK and eGFR values was statistically insignificant (Spearman r=-0.023; p=0.795, Spearman r=0.032; p=0.717 and Spearman r=-0.173; p=0.0478, respectively). While the correlation between eGFR and FENa was insignificant, there was a significant positive correlation between eGFR and FEK (Spearman r=-0.078; p=0.378 and Pearson r=-0.379; p=0.011, respectively). There was also no significant correlation between FEMg and age (Spearman r=0.1271, p=0.1480).

According to the results multiple regression, FEK values were found to be insufficient (p=0.1873), although the four independent variable model in the table seemed to be appropriate (p=0.002). New model was found to be stronger by subtracting the FEK variable to predict FEMg values (p<0.001) (Table 3).

**ROC analysis studies for diagnostic values of tests**

ROC analysis and comparison of ROC curves were performed to evaluate the diagnostic power of FEMg and eGFR values in renal pathologies based on microalbuminuria. The area under curve (AUC) for FEMg values was determined as 0.732. In addition, the best cut-off value for FEMg to determine renal pathology was 3.67% with diagnostic sensitivity and specificity of 66.67% and 77.53%, respectively (p<0.0001). Similarly, the AUC for eGFR was 0.625. The best cut-off point for eGFR values was 5.5 (0.5–23).

---

**Table 1: Demographic distribution of control group and diabetic patients.**

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>NAG</th>
<th>&gt;MAG</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>49</td>
<td>42</td>
<td>–</td>
</tr>
<tr>
<td>Female (%)</td>
<td>22 (55)</td>
<td>25 (51)</td>
<td>23 (55)</td>
<td>0.9128</td>
</tr>
<tr>
<td>Male (%)</td>
<td>18 (45)</td>
<td>24 (49)</td>
<td>19 (45)</td>
<td></td>
</tr>
</tbody>
</table>

*p-Value was obtained with Chi-Square Tests. CG, Control group; NG, normoalbuminuric group; MAG, microalbuminuric group.

**Table 2: Fractional excretion of Na, K and Mg and statistical comparison of albumin-creatinine ratio according to groups.**

<table>
<thead>
<tr>
<th></th>
<th>CG (I)</th>
<th>NAG (II)</th>
<th>MAG (III)</th>
<th>p-Value</th>
<th>Comparison of groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>49</td>
<td>42</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>u-ACR (mg/g Cr)</strong></td>
<td>6.3 ± 3.5</td>
<td>11.3 ± 6.5</td>
<td>74.6 ± 50.5</td>
<td>&lt;0.0001</td>
<td>&lt;0.05, &lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td><strong>FEMg (%)</strong></td>
<td>2.5 ± 0.7</td>
<td>3.5 ± 1.6</td>
<td>4.8 ± 2.7</td>
<td>0.0001</td>
<td>&lt;0.05, &lt;0.001, &lt;0.01</td>
</tr>
<tr>
<td><strong>FENa (%)</strong></td>
<td>0.60 ± 0.24</td>
<td>0.59 ± 0.37</td>
<td>0.60 ± 0.28</td>
<td>0.4189</td>
<td>–</td>
</tr>
<tr>
<td><strong>FEK (%)</strong></td>
<td>9.2 ± 3.3</td>
<td>11.3 ± 4.8</td>
<td>10.6 ± 4.5</td>
<td>0.0710</td>
<td>–</td>
</tr>
<tr>
<td><strong>eGFR (ml/min)</strong></td>
<td>96 ± 13</td>
<td>93 ± 17</td>
<td>89 ± 15</td>
<td>&lt;0.0105</td>
<td>–</td>
</tr>
</tbody>
</table>

*Mean±SD, Median (Minimum-Maximum), p-Value from One-way ANOVA and Post-hoc test (Tukey-Kramer Multible Comparison Test).

*p-Value from Kruskal-Wallis test (nonparametric ANOVA) and Post-hoc test (Dunn’s Multible Comparison test). If the p-value obtained by ANOVA test was found to be <0.05, multiple comparison tests were performed to determine the p-value between the groups (I, II ve III). SD, Standard deviation; u-ACR, Albumin-creatinine ratio (ACR) in spot urine; Cr, Creatinin; FEMg, Fractional excretions of magnesium; FENa, Fractional excretions of sodium; FEK, Fractional excretions of potassium; eGFR, Estimated glomerular filtration rate; CG, Control group; NAG, Normoalbuminuric group with diabetes; MAG, Microalbuminuric group with diabetes; min, Minute.
89.83 mL/min with diagnostic sensitivity and specificity of 59.52 and 70.79%, respectively (p < 0.0172) (Figure 3). When the ROC curves of FEMg and eGFR were compared, the area under the ROC curve of FEMg values was greater than the eGFR area. However, this difference (AUC = 0.107) was not statistically significant (p = 1374).

The results of odds ratio

In the odds ratio calculation based on the cut-off value obtained from the ROC analysis, the odds ratio of FEMg and eGFR associated with microalbuminuric renal injury was determined as 6.9 (95% CI: 3.063 to 15.545, p < 0.0001) and 3.56 (95% CI: 1.654 to 7.675, p = 0.0011), respectively. In other words, the risk of microalbuminuria was found to be 6.9 times higher in patients with a higher FEMg value than eGFR's. The risk of microalbuminuria was found to be 3.56 times higher in patients with eGFR less than 89.83 mL/min compared to larger ones.
Discussion

In many cases of glomerulonephritis that cause chronic renal failure, as in DN, one of the most common pathologies of the kidney, atrophy in the tubules and interstitial fibrosis may develop rather than glomerular damage [16]. Obviously, tubular damage also plays an important role in the pathogenesis of DN [17, 18]. Therefore, there is still a need for new biomarkers to be used in evaluate the level or prognosis of renal damage.

No test alone is sufficient to define glomerular filtration, tubular secretion and reabsorption functions of kidney [2]. Currently, serum Cr levels and GFR are used in the evaluation of structural and functional disorders in DN. However, serum Cr values do not directly indicate tubular injury because the tubular damage may occur directly or may develop secondary to various glomerular damages or interstitial damage [19, 20]. In addition, even if there is serious interstitial injury, there would be no significant evidence of urine and/or only slight elevation in serum Cr levels can be observed. It is also reported that glomerular damage and tubulointerstitial damage may develop independently until severe renal failure occurs [20].

Depending on hyperglycemia in DN, hyperplasia/hypertrophy in various tubular and glomerular cells, thinning in glomerular and tubular basement membrane and expansion in tubulointerstitial mesangial areas can be observed [21]. Due to these effects in functions of renal tubules, serious changes can also be observed in substances regulated by tubules. As is well known, tubules are the main regulator of many electrolytes, including Mg [22]. Mg levels are being maintained throughout the functions of the kidneys. In some studies, it has been reported that in patients with Mg deficiency, FEMg may be lower than 0.5% (12 mg/day) and also FEMg may be increased due to excessive filtered amount due to increased intake [23, 24]. In renal insufficiency, it was found that FEMg increased gradually since reabsorption would be impaired. This increase was also found to be related to the degree of histological damage of the interstitium in tubulointerstitial nephritis (TIN). Various disorders associated with the function of the tubular epithelium can affect Mg reabsorption and cause more loss in urine. Therefore, elevation in FEMg levels may indicate the presence of a tubular damage or a disorder affecting the tubule function, such as TIN. In previous researches, the mechanism underlying TIN-related dysfunction has been reported to be directly related to tubules [25–28]. In our study conducted in the light of this information, high levels of FEMg in the normoalbuminuric group compared to the control group suggested that it thought to be a precursor of a tubular damage in the early stage of renal injury without increasing albuminuria levels. In addition, significant increase in the FEMg values of microalbuminuric group compared to normoalbuminuric group may be finding related to progression of renal pathology. In a biomarker study aiming to determine early TIN that supports our study, it is reported that various tubular damages may prevent reabsorption of Mg and cause an increase in urinary Mg excretion [27]. The same researchers also stated that FEMg values could be used as a non-invasive parameter in predicting the severity of TIN.

DN is widely categorized according to the amount of albuminuria with diagnostic sensitivity and specificity over 80% [29]. However, it should be noted that renal damage may be present in many normoalbuminuric patients. ADA recommended threshold for diagnosis of microalbuminuria in urine as 30–300 mg/day (or in spot urine UACR 30–300 mg/g Cr) [30]. We accepted patients with microalbuminuria as positive renal pathology while the others (<30 mg/g Cr) as normoalbuminuric group with undetectable renal pathology, in our study. Afterwards, when the ROC curves were compared in order to evaluate the use of FEMg and eGFR values in renal pathology, the area under the ROC curve for FEMg was found to be as high as 0.107 compared to eGFR. In addition, FEMg values at the 3.67% cut-off point were found to have higher diagnostic sensitivity and specificity than eGFR (cutoff ≤ 89.83 mL/min). In the odds ratio calculation according to the predictive values obtained from the ROC analysis, there was a higher risk of FEMg elevation (6.9) than decrease in eGFR (3.56%) in microalbuminuric patients compared to without albuminuria. These three findings suggest that FEMg may have a stronger diagnostic and prognostic value in the determination of renal tubular pathology than GFR. However, it should be kept in mind that the reason for the lower diagnostic value in eGFR than in FEMg may be due to the MDRD formulation. Besides, the cut-off for the eGFR was higher than we expected. This situation may be the result of hyperfiltration (early hyperfunction and hypertrophy) and silent phase characterized by increased GFR [31], which are probably present in our patient population.

Mogensen et al. performed five clinical staging for diabetes which are hyperfiltration stage, silent stage, microalbuminuria stage, overt diabetic nephropathy stage and end stage renal failure. Microalbuminuria (stage 3) arises after about 6–15 years after the onset of diabetes. In this period, GFR can be estimated in high or normal limits and the amount of albumin in urine is between 30 and 300 mg/day. Blood pressure can also be determined as normal or increased [31]. As well understood by this
information, GFR can provide useful information only in advanced stages. Albuminuric, which is used as an important marker in the evaluation of renal pathology, has been reported to reflect both glomerular and tubulointerstitial damage independent of eGFR [32]. According to this staging, the use of urine ACR may be useful only in the period when microalbuminuria starts. Determining diagnostic value of FEMg higher compared to eGFR values and observing higher FEMg values in normoalbuminuric group than control group were considered as evidence that FEMg could be used for early detection of renal pathology, in our study.

An important feature of tubular reabsorption is that it can regulate the reabsorption of certain substances independently, especially through hormonal control mechanisms. As in Mg, the regulation of Na and K levels are performed by kidney. However, unlike Mg, Na and K are under the influence of strong hormonal regulation. Osmoreceptors in hypothalamus try to balance serum Na concentration and water with antiuretic hormone (ADH) secretion, as opposed to the renal mechanism [33]. In addition, aldosterone plays an important role in regulating Na reabsorption from renal tubules. As is known, in diabetes, there is an increase in local renin angiotensin-aldosterone (RAS) activation in both glomerulus and interstitium [34]. Thus, local RAS stimulation will result in more Na retention and decreased Na levels in urine [35]. Moreover, in contrast to the effect of aldosterone, increase in renal H+ ion concentration (acidosis), reduces K secretion and leads to less K output in urine [35]. All these strong regulatory mechanisms leads FENa and FEK values to be less reliable in renal tubular damage. In accordance with this information, there was no significant difference between the groups in terms of FENa and FEK levels, in our study. The probable cause was attributed to the tubular function as well as the strong hormonal or osmotic processes affecting the Na and K levels, and the condition of the tubular acidosis. However, more extensive studies are needed.

GFR is considered as a sensitive and specific measure of the functional capacity of the kidney. Therefore, change in GFR has been suggested as early laboratory indicator of kidney disease [36]. However, the expected correlation between Cr clearance and GFR is sometimes not observed due to changes in the tubulointerstitial structure. Because the presence of a tubulointerstitial disorder may not always be associated with a change in glomerular function [37]. In addition, Cr may also be discharged from the tubules as well as being filtered from the glomerulus. This may lead to unexpected errors in the GFR results calculated from serum and urine Cr levels [38]. In the current study, positive correlation between FEMg values and urine ACR was thought to indicate that FEMg may correlate with the severity of renal damage that can be staged with ACR. In addition, the inverse proportional correlation between FEMg and eGFR confirms this finding.

High urine level of N-acetyl-β-D glucosaminidase, which is found in lysosomes in proximal tubule cells and with very low in glomerular filtration due to high molecular weight, is considered good indicator of proximal tubular damage [39]. In contrast to FENa and FEK values, N-acetyl-β-D glucosaminidase has been reported to be highly correlated with FEMg values. This difference may be due to abundant tubular reabsorption of Na or K. In addition, the function of the remaining nephrons can also affect FENa and FEK, independent of severity of TIN [27]. All these findings may explain why we could not find any difference in terms of FENa and FEK values in contrast to FEMg values between normal and diabetic groups in our study. This information also supports the relationship between FEMg and urine ACR, an important finding of tubular injury.

In a study conducted in patients with various kidney pathologies by Noiri et al., a significant correlation between eGFR and FEMg in patients with eGFR ≤30 mL/min was found while there was no correlation between eGFR and FEMg in patients with eGFR >30 mL/min. They also found a moderate correlation between eGFR and FEMg in the entire patient population (r = −0.51, p < 0.01) [40]. However, we found this correlation lower (r = −0.3603, p < 0.01). The probable cause of this finding was that the patients with eGFR <30 mL/min were not included in our study. Noiri and the results of our study both indicate that there is a higher correlation between eGFR and FEMg as renal tubular pathology increases. The results also show that the expected correlation between eGFR and FEMg cannot be found in individuals with mild renal pathology, as there has not yet been a decrease in eGFR.

In a study by Gheissari et al., 20 children with ischemic acute tubular necrosis and a control group of 20 patients were compared in terms of FEMg, FENa and eGFR. There was a significant difference in terms of FEMg and eGFR values while there was no difference in terms of FENa values between patients and the control group (15). These findings are consistent with our findings. In our study, statistically significant results in multiple regression analysis showed that the value of FEMg was correlated with urine ACR and eGFR. In addition, observing no difference in terms of FENa and FEK between the groups and the fact that FENa and FEK values did not correlate with eGFR and urine ACR also coincides with the findings of these researchers. However, we believe that there is still
a need for more extensive and comprehensive studies on FEMg in order to reach data that are more precise.

In conclusion, we think that FEMg may have a diagnostic and prognostic value as another biomarker, in renal tubular damage attempted by microalbuminuria. It is also predicted that FEMg values may be used in the determination of renal tubular pathology before microalbuminuria in normotensive patients with T2DM.

Acknowledgment: I would like to thank Nursel Akbay, assistant in internal medicine, and Haydarpasa Numune Training Hospital Biochemistry Laboratory staff who contributed to this study.

References