Urinary Albumin Excretion and Glomerular Filtration Rate across the Spectrum of Glucose Abnormalities in Essential Hypertension

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The objective of this study was to assess the relationship between urinary albumin excretion (UAE) and GFR across the spectrum of the glucose metabolism abnormalities in a large population of patients with hypertension. The Microaluminuria en Pacientes con Glucemia Basal Alterada (MAGAL) is a multicenter, cross-sectional study that was carried out by 1723 primary care physicians. A total of 6227 patients with essential hypertension (in three groups: [1] normal fasting glucose <100 mg/dl, [2] impaired fasting glucose ≥100 to 126 mg/dl, and [3] type 2 diabetes) were analyzed in this substudy. GFR was estimated by using the Modification of Diet in Renal Disease (MDRD) abbreviated equation. A single first-morning urine albumin/creatinine ratio was measured using Bayer reagent strip Microalbustix, a semiquantitative method. Abnormal UAE was defined as an albumin/creatinine ratio ≥3.4 mg/mmol (equivalent to ≥30 mg/g). The prevalence of abnormal UAE, ≥3.4 mg/mmol, increased across the spectrum of glucose abnormalities: 39.7, 46.2, 48.6, and 65.6% for normoglycemic, low-range, high-range impaired fasting glucose, and type 2 diabetes, respectively. UAE was positively related to SBP (P = 0.003) and inversely to GFR (P < 0.001). Renal insufficiency (GFR <60 ml/min per 1.73 m²) was present in 21.8% of the patients, more frequently older patients, women, and those with diabetes. The factors that were related to renal insufficiency were UAE ≥3.4 mg/mmol (odds ratio 1.86; 95% confidence interval 1.60 to 2.17) and diabetes (odds ratio 1.62; 95% confidence interval 1.29 to 2.04). There is a close relationship between abnormal UAE and renal insufficiency in essential hypertension. This is more marked in patients with diabetes and moderate in patients with high-range impaired fasting glucose.


A n increase in urinary albumin excretion (UAE) even to a small extent, microalbuminuria, has become a marker for cardiovascular and renal disease. Initially tested in diabetes, its prognostic value in hypertensive patients without diabetes and in subgroups of the general population has been well established during the past few years (1–11). In both patients with diabetes and without diabetes, elevated SBP and glucose levels are the main factors related to development of increased UAE. One of the largest epidemiologic studies, the Australian Diabetes Obesity and Lifestyle Study (AusDiab) (12), clearly showed the interaction of both factors in the prevalence of microalbuminuria. The relationship between UAE and estimated GFR, however, has received less attention even though GFR, like UAE, is a predictor of cardiovascular risk.

Widespread use of formulas to calculate GFR has enabled the influence of renal function in cardiovascular risk to be assessed. Therefore, alterations in renal function have emerged as a predictive marker for cardiovascular disease, and it has been reflected as such in the guidelines for clinical management (13,14). Several studies have shown calculated GFR to be a risk indicator for general mortality and cardiovascular death after myocardial infarction (15–20) and also for mortality associated with heart failure (21). Likewise, a large health registry has revealed a gradual relationship between estimated GFR and the risk for death, cardiovascular events, and hospitalization, independent of other risk factors (22).

Microalbuminuria and renal insufficiency frequently run in parallel (23). Both of them are influenced by BP and glucose levels. Whereas BP is the major determinant of microalbuminuria, glucose level is the major determinant of renal insufficiency (23). Despite the frequent cluster of microalbuminuria and low GFR, the potential interaction between UAE and GFR is not well understood even though it can provide useful clinical information. Therefore, the objective of the present study was to analyze the relationship between UAE and GFR across
the spectrum of the glucose metabolism abnormalities in a large population of patients with hypertension. Combining both glucose abnormalities and hypertension, we included a population that was prone to developing microalbuminuria and renal insufficiency, which enabled us to assess their potential interactions.

Materials and Methods

This study was a post hoc analysis from the Microaluminuria en Pacientes con Glucemia Basal Alterada (MAGAL) study, the design of which is described elsewhere in this journal. In brief, it is a multicenter, cross-sectional, observational study that was carried out by 1723 primary care physicians all over Spain. Each physician consecutively enrolled six patients with essential hypertension and age ≥18 and ≤80 yr divided into three categories according to carbohydrate metabolism: (1) Normal fasting glucose (NFG): fasting plasma glucose <100 mg/dl; (2) impaired fasting glucose (IFG): fasting plasma glucose ≥100 and <126 mg/dl; and (3) type 2 diabetes. Hypertension was defined as a previous diagnosis of hypertension and/or receiving antihypertensive medication. Exclusion criteria were type 1 diabetes, pregnancy or breast-feeding, urinary tract infection, pyuria, hematuria, fever, and having done strenuous physical exercise during the 24 h before UAE determination. The study was approved by the Ethics and Clinical Trials Committee of the Hospital Central de Asturias. Informed consent of the patient was obtained in all cases.

Study Protocol

Demographic and clinical data were obtained for each patient. Physical examination that included weight, height, body mass index (BMI), and SBP and diastolic BP (DBP) measurements was carried out on the visit day. Sitting SBP and DBP were measured according to the Spanish Hypertension Society guidelines (24), after 5 min of rest and with the cuff fitted to the perimeter of the arm. Three readings were taken, and the mean value of the last two was accepted as valid.

Serum glucose levels, creatinine levels, and the lipid profile were determined in blood samples that were obtained after at least 8 h of fasting. Glucose status was stratified as NFG, IFG, and diabetes, as described previously. In addition, patients with IFG were subdivided into two groups, those with fasting glucose of between 100 and 109.9 mg/dl (low-range IFG) and the remainder between 110 and 125.9 mg/dl (high-range IFG), based on the current and the former criteria for IFG. GFR was estimated as ml/min per 1.73 m² according to the Kidney Disease Outcomes Quality Initiative guidelines (25).

A single first-morning urine albumin/creatinine ratio was measured using the Bayer reagent strip Microalbuminustix (Leverkusen, Germany), a semiquantitative method. Abnormal UAE was defined as an albumin/creatinine ratio ≥3.4 mg/mmol (equivalent to ≥30 mg/g). According to the manufacturer, the Bayer Microalbuminustix test has a sensitivity of 90% and a specificity of 88% for the albumin/creatinine ratio. As defined in the protocol, urine samples with creatinine concentrations of ≥10 mg/dl were ruled out because they were considered too diluted.

Statistical Analyses

The variables are presented as frequency (95% confidence interval [CI]), mean (SD), or median (25th to 75th percentiles) according to the distribution of the variable. ANOVA was used for comparisons among groups. The association between qualitative variables was evaluated using the χ² or Fisher exact test, depending on the application conditions. All hypothesis contrasts rejected the null hypothesis with an α error <0.05.

The relationship between GFR and UAE was assessed by Pearson correlation coefficients and multiple regression analysis. Factors that were related to abnormal GFR were assessed by using a multiple logistic regression model. The odds ratio (OR) of these variables, together with their CI and level of significance, were reported. The analysis was carried out using SAS for Windows (version 9.1; SAS Institute, Cary, NC).

Results

General Characteristics of the Study Population

This post hoc analysis was performed in 6227 patients: 1138 (18%) in the NFG group, 2491 (40%) in the IFG group (591 [9%] in the low-range IFG, 1900 [31%] in the high-range IFG), and 2598 (41%) in the diabetes group. The characteristics of the patients as grouped by the glucose categories are shown in Table 1. Age increased progressively from NFG to diabetes and gender was equally distributed among the four groups. SBP increased significantly from the normal carbohydrate metabolism group to the diabetes group. A BP <140/90 mmHg was observed in 41.4% of the patients with NFG and in 36.9% of those with IFG. In the patients with diabetes, BP was controlled (<130/80 mmHg) in 11.5% of cases. BMI was higher in patients with abnormalities in glucose values as compared with normoglycemic patients. A progressive increment in fasting plasma glucose, by definition, and in triglycerides was observed from the NFG to the diabetes groups. HDL cholesterol, however, followed an inverse association.

UAE

The prevalence of abnormal UAE (≥3.4 mg/mmol) was 54.5%, which increased across the spectrum of glucose abnormalities (39.7, 46.2, 48.6, and 65.6% for normoglycemic, low-range IFG, high-range IFG, and diabetes, respectively). In a multiple regression analysis, UAE was positively related to the SBP (P = 0.003) and inversely to the GFR (P < 0.001). In normoalbuminuric patients, GFR values did not differ among the glucose categories: 76.7, 76.8, 75.9, and 74.6 ml/min per 1.73 m² for NFG, low-range and high-range IFG, and diabetes, respectively. In contrast, in those with abnormal UAE, GFR was significantly lower in the diabetes group (67.9 ml/min per 1.73 m²) as compared with the other two groups (74.7, 74.4, and 74.3 ml/min per 1.73 m²; P < 0.01 for each comparison).

GFR

Most of the patients had a GFR between 60 and 90 ml/min per 1.73 m² (3625 [58.2%]). Renal insufficiency (GFR <60 ml/min per 1.73 m²) was present in 1361 (21.8%) of the patients, but only 298 (4.8%) patients had a GFR ≤45 ml/min. The main characteristics of the patients in the various GFR categories are shown in Table 2. Patients with the lowest GFR more frequently were older and women and had diabetes. Although the selection criteria established a misbalanced number of study patients (more patients selected by inclusion criteria in the IFG group), the trend association between the glucose category and the GFR spectrum can be observed. The proportion of normoglycemic patients decreases
from those with GFR >90 ml/min per 1.73 m² to those with ≤45 ml/min per 1.73 m²; a similar trend is found for patients with IFG. In contrast, the proportion of diabetes increases as the GFR declines. For each GFR category, UAE values increase as well as the percentage of patients with abnormal UAE, although the increment is steeper for the diabetes group as compared with the other glucose categories (Table 3).

The factors that were related to GFR ≤60 ml/min per 1.73 m² were analyzed in a multiple logistic regression analysis. Abnormal UAE, presence of glucose abnormalities, and uncontrolled BP were related independently to the low GFR. UAE ≥3.4 mg/mmol increased the risk by 87% (OR 1.87; 95% CI 1.61 to 2.17), IFG and diabetes by 30% (OR 1.30; 95% CI 1.05 to 1.62), and BP ≥140/90 mmHg or ≥130/80 if diabetes by 23% (OR 1.23; 95% CI 1.04 to 1.45). When each of the glucose status categories was included separately in the model, abnormal UAE and diabetes were the only significant determinants of renal insufficiency. An elevated UAE (≥3.4 mg/mmol) increased the risk by 86% (OR 1.86; 95% CI 1.60 to 2.17) and diabetes by 62% (OR 1.62; 95% CI 1.29 to 2.04).

**Discussion**

In this large cohort of hypertensive patients from primary care, the proportion of patients with abnormal UAE was 54.5%, and 21.8% had renal insufficiency. This study shows a clear association between UAE and frequency of renal insufficiency with a higher prevalence among those with higher UAE. Urinary albumin excretion was inversely related to GFR, and an abnormal UAE increases the risk for renal insufficiency (GFR ≤60 ml/min per 1.73 m²) by 89%. This association between abnormal UAE and renal insufficiency was more evident in patients with diabetes as compared with those with NFG and IFG. Likewise, for each GFR category, UAE values increased as well as the percentage of patients with abnormal UAE, although the values were higher for the diabetes group as compared with patients with NFG and those with IFG. Figures for patients with IFG, both low range and high range, were between those of NFG and diabetes.

In this study, the prevalence of abnormal UAE was greater than that observed in other cross-sectional surveys (26). This probably is due to the method used for measuring UAE and the characteristics of the study population. It has been reported that a single UAE assessment may increase by at least one fifth the prevalence of abnormal UAE (27). Selecting patients with both hypertension and glucose disorders also increases the prevalence, because high BP and glucose values are among the most important causes of UAE elevation (28). In addition, mean age and BMI in our study population was higher than in other surveys, two factors that also have been associated with abnormal UAE.

The prevalence of renal insufficiency was 21.8%, although it might be slightly overestimated as a result of the use of the
The MDRD equation to calculate GFR (29). Several studies have examined the difference between this method and the corresponding gold standard: derived GFR calculated by isotopic techniques (30–32). In the range of normal values, with true GFR >60 ml/min, the GFR may be underestimated by up to 28% when the formula is applied. As true glomerular filtration decreases, the differences become smaller, reaching an underestimation of 6% when the true GFR is <30 ml/min (31).

The factors that were associated with a worsening in renal function behaved as expected. The mean age was greater among patients with lower GFR values, and the prevalence of diabetes was higher as compared with the other groups. Not only diabetes but also a previous stage, such as the IFG, increased the risk for renal insufficiency. Likewise, uncontrolled hypertension was associated with low GFR. There were no differences, however, in the degree of obesity, with mean values >29 kg/m² in all of the groups.

Patients with the lowest GFR more frequently were older and

Table 2. General characteristics of the study population grouped by eGFR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;90 (n = 1243)</td>
<td>[90 to 60 (n = 3623)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.2 ± 8.8</td>
<td>64.3 ± 9.7</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>81.3</td>
<td>47.9</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>29.6 ± 4.4</td>
<td>29.8 ± 4.6</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>129.7 ± 30.7</td>
<td>132.2 ± 31.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210.8 ± 36.4</td>
<td>210.8 ± 35.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>52.4 ± 12.6</td>
<td>52.9 ± 12.9</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>130.6 ± 31.3</td>
<td>130.7 ± 31.2</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>150.2 ± 63.8</td>
<td>148.1 ± 62.5</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.80 ± 0.1</td>
<td>0.95 ± 0.2</td>
</tr>
<tr>
<td>UAE (mg/mmol creatinine)</td>
<td>9.8 ± 21.5</td>
<td>9.7 ± 20.4</td>
</tr>
<tr>
<td>UAE (mg/mmol creatinine)</td>
<td>&lt;3.4 (%)</td>
<td>49.6</td>
</tr>
<tr>
<td></td>
<td>≥3.4 (%)</td>
<td>50.4</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>140.8 ± 12.9</td>
<td>140.7 ± 13.8</td>
</tr>
<tr>
<td>DBP</td>
<td>83.5 ± 8.2</td>
<td>81.9 ± 8.5</td>
</tr>
</tbody>
</table>

Table 3. UAE and prevalence of abnormal UAE (>3.4 mg/mmol) grouped by glucose status and eGFR

<table>
<thead>
<tr>
<th>Glucose Status</th>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;90 (n = 1243)</td>
<td>[90 to 60 (n = 3623)</td>
</tr>
<tr>
<td>UAE (mg/mmol creatinine)</td>
<td>normal</td>
<td>2.3 (1.1 to 5.6)</td>
</tr>
<tr>
<td></td>
<td>low-range IFG (%)</td>
<td>2.3 (1.7 to 6.8)</td>
</tr>
<tr>
<td></td>
<td>high-range IFG (%)</td>
<td>3.2 (1.7 to 6.8)</td>
</tr>
<tr>
<td></td>
<td>diabetes (%)</td>
<td>3.4 (1.7 to 6.8)</td>
</tr>
<tr>
<td>UAE (mg/mmol creatinine)</td>
<td>≥3.4</td>
<td>37.4</td>
</tr>
<tr>
<td></td>
<td>low-range IFG (%)</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td>high-range IFG (%)</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>diabetes (%)</td>
<td>58.4</td>
</tr>
</tbody>
</table>

aData are median (25th to 75th percentiles).
women and had diabetes. Although increased age and the presence of diabetes have been widely accepted as conditions that are associated with renal insufficiency, the high rate in women is less recognized, but it is in agreement with previous surveys of renal insufficiency using the MDRD equation. Differences between genders in the prevalence of GFR <60 ml/min are noteworthy, with a higher prevalence in women as compared with men. This also has been observed in other large-scale studies (32–34). The differences in the prevalence of GFR <60 ml/min between genders increases across the age range: The older the higher (33). This contradicts that more men than women receive treatment for ESRD, and it seems that the higher prevalence of renal failure in women results from the excessive dominance of age and gender in the equation.

The relationship between GFR and UAE was analyzed. Lower GFR was observed in patients with abnormal UAE, mainly in patients with diabetes. Likewise, as the GFR declined, the UAE values, as well as the prevalence of abnormal UAE, increased, and both shared common causative factors: High BP and abnormal glucose. Despite that this is a cross-sectional study, it seems that the presence of UAE increases the risk for renal function worsening, as has been demonstrated in a follow-up study (35). In patients who are prone to developing an increment in UAE, the impact over time of both BP values and abnormal glucose lead to a faster GFR decline than in those who maintain normal values of UAE. Another factor that may contribute to the association between abnormal UAE and low GFR is that during antihypertensive treatment and for a given BP, UAE values in patients with renal insufficiency resist reduction.

The main strengths of the present study lies in the large number of patients analyzed in the cross-sectional survey and a large representation of the glucose metabolism status categories. However, its limitations are that the sample size is not population based and that selection bias by the participating physicians cannot be completely ruled out. This, however, does not invalidate the main goal of the study, which was to examine the relationship between UAE and GFR in various glucose conditions. Another limitation of the study was that creatinine measurement was not calibrated with reference standards by all of the participating physicians. Finally, an unresolved question is whether the poorer prognosis for cardiovascular outcomes that are associated with UAE and GFR overlaps or is additive. Only prospective studies can help us to resolve this key issue.

Conclusion

There is a close relationship between abnormal UAE and renal insufficiency in patients with essential hypertension. This was more marked in patients with diabetes and was moderate in patients in the highest IGF range. The clinical relevance of this relationship needs to be established in terms of temporal trend, treatment changes, and impact on risk.

Acknowledgments

References


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