Original Article
Increased Renal Arterial Resistance Predicts the Course of Renal Function in Type 2 Diabetes With Microalbuminuria

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Type 2 diabetic patients often die because of end-stage renal failure, but no definitive reliable factor predicting long-term renal outcome has been identified. We tested whether a renal arterial resistance index (R/I) \( \geq 80 \), using Doppler ultrasound technique, was predictive of worsening renal function. The primary end points of the study were 1) the course of glomerular filtration rate (GFR) and 2) the albumin excretion rate in 157 microalbuminuric, hypertensive, type 2 diabetic patients after a 7.8-year follow-up period (range 7.1–9.2). Kaplan-Meier curves for the primary end point (decrease of GFR \( \geq -3.0 \) ml/min per 1.73 m\(^2\) per year) was two to three times more frequently observed in patients with R/I \( \geq 80 \). Four- to fivefold fewer patients showed a regression to normoalbuminuria during the follow-up period from baseline microalbuminuria in the cohort with R/I \( \geq 80 \). Overt proteinuria did develop in 24% of patients with R/I \( \geq 80 \) and in 3% of patients with R/I \( < 80 \) (\( P < 0.01 \)). In conclusion, intrarenal arterial resistance appears to play a nontrivial role in deteriorating renal function in type 2 diabetic patients. R/I is a noninvasive diagnostic procedure, which strongly predicts the outcome of renal function in type 2 diabetic patients, even when GFR patterns are still normal. Diabetes 55:234–238, 2006

Diabetic nephropathy accounts for end-stage renal disease (ESRD) in \( \sim 40\% \) of patients who need dialysis or renal transplantation in the U.S. (1) and in \( \sim 15–20\% \) of patients in Italy. ESRD is not the mandatory fate of diabetic patients with altered albumin excretion rate (AER). In fact, it has been shown that the course of renal function is ominous in some type 2 diabetic patients, who have been called “progressors,” whereas other patients show steady patterns of renal function for years or even a regression of AER from microalbuminuria to normoalbuminuria (“nonprogressors”) (2–4). Similar findings have also been reported in type 1 diabetic patients (5). Extensive evidence clearly demonstrates that prolonged hyperglycemia underlines chronic complications of diabetes (6). Moreover, it has been convincingly reported that tight blood pressure control, particularly using drugs that inhibit the renin angiotensin system, significantly delay the progression of renal damage in diabetic patients with incipient or advanced nephropathy (7–10). Nevertheless, 15–20% of the diabetic patients still relentlessly develop ESRD, despite aggressive antihypertensive and hypoglycemic therapy (4,6,10,11).

Although captopril renography was once the noninvasive diagnostic method of choice for patients with renal stenosis, it has now been relegated to use in secondary screening, because the quality of other noninvasive imaging methods is highly reliable and less cumbersome (12,13). It has recently been found that a renal arterial resistance index (R/I) of \( \geq 80 \), using Doppler ultrasound technique, predicts worsening renal function in patients with renal diseases other than renal artery stenosis (14,15). The aim of the present study was to investigate the capacity of R/I of predicting the course of renal function in hypertensive, type 2 diabetic patients with microalbuminuria and the clinical features of progressor patients.

RESEARCH DESIGN AND METHODS
The criteria we have used since 1997, 1998, and 1999 to recruit a group of type 2 diabetic patients are as follows: age between 35 and 65 years, onset of diabetes after the age of 35 years, and no insulin need in the first 3 years after diagnosis. All of the subjects were hypertensive (>130/85 mmHg), had microalbuminuria, and were randomly treated by ACE inhibitors (one with 10 mg/day ramipril, the other one with 40 mg/day lisinopril, and so on). Twelve to 5 mg/day thiazides and 100 mg/day atenolol in the last 3–4 years, previous to the entry in the study, and 1,500 mg/day metformin with insulin analog, before meals, or once daily ultralente insulin injection was given to each patient. These two ACE drugs were chosen because the National Health Agency in Italy decided between 1995 and 2000 that these two drugs (with these daily dosages) were the only ones useful to prevent the onset of overt kidney failure in diabetic patients when the study started. Thus we adopted their advice, and we provided these drugs at no cost to the patients. Patients were consecutively admitted to the study and randomized blindly to either ramipril or to lisinopril treatment. During the 15-day withdrawal from antihypertensive therapy, the patients were instructed with the help of the National Centers for the Care of Diabetes Mellitus and of the General Practitioners, strictly in touch with National Centers for the Care of Diabetes Mellitus in

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Received for publication 11 July 2005 and accepted in revised form 26 September 2005.

AER, albumin excretion rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; R/I, renal arterial resistance index; UKPDS, U.K. Prospective Diabetes Study.

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each center to monitor blood pressure levels. Whenever blood pressure levels rose to >165/105 mmHg, the patients received calcium channel blockers sublingually to reduce the blood pressure levels to <140/90 mmHg. Calcium blockers were chosen because these drugs were able to better control blood pressure levels without substantially modifying AER, at least according to available literature. The ethical committee approved this approach and the therapy of the patients as the only one capable to measure AER reliably, without exposing the patient to vascular risks. The administration of calcium channel blockers was used only on 12 occasions during the 8-year follow-up period in 157 patients. No adverse reaction was observed. The criterion for the administration of statins was the presence of plasma LDL cholesterol level >110 mg/dl and triglycerides >200 mg/dl. This criterion was adopted to avoid an excessive drop-out of the patients because of low compliance to drug therapy during such a long period of follow-up in a relatively large population who had already accepted a rather compelling and cumbersome series of examinations. However, the number of patients in each group was too small to draw any conclusion in this study from the hypolipidemic point of view, and nevertheless, the number of patients was not significantly different in the groups with different R/I values. Twenty-five percent of the patients were treated with 40 mg/dim simvastatin and 23% with 30 g/day cholestatyamine without differences between groups with R/I ≥ 80 or < 80. The patients were randomly allotted to each of the two treatments. All of the patients received 75 mg/day aspirin. No gastrointestinal bleeding or muscular rabdomyolysis or acute circulating increase of transaminases was observed during the follow-up period. The definition of microalbuminuria was a median between 30 and 300 μg/mg creatinine, and of macroalbuminuria, at least 300 μg/mg creatinine. Samples collected on the spot in the outpatient diabetes clinic, in the absence of hematuria. Albumin was measured by an immuno turbidimetric technique as previously described after a 15-day withdrawal from antihypertensive therapy (4); urine creatinine was measured by a modified reaction rate kinetic technique, which overcomes the drawback of the measurement of isoprostane-creatinine beside creatinine (16). With regard to coronary artery disease, we used three parameters: clinical history accompanied by electrocardiographic and ultrasound imaging changes of heart wall contraction movements. Patients had serum creatinine concentrations <1.5 mg/dl. When available in the clinical history, circulating levels of troponin were used to ascertain previous episodes of myocardial infarction. Peripheral and carotid artery disease was mainly assessed by clinical evaluation (evidence or reports of claudicatio intermittents, stroke, or transitory ischemic attacks) and ultrasound sounds to ascertain the presence of atherosclerotic plaques. A major effort was put into the study to educate the patients to stop smoking, to increase exercise, and to achieve body weight reduction, using the guidelines treatments of the U.K. Prospective Diabetes Study (UKPDS) (17) and Steno Hospital (15). The values reported in the present study, with regard to body weight, smoking habits, exercise, and HbA1c, (AICl) levels, indicate that we, at least partially, succeeded in achieving our goal in 70–75% of our patients and between the two kidneys not.

**End points.** J) The primary end point of the study was the evaluation of the number of patients with a decrease of GFR >3 ml/min per 1.73 m2 per year during a follow-up period of 7.8 years (range 7.1–9.2). Fifty-nine patients had an ultrasound Doppler R/I between the two kidneys on average index in the two kidneys.

**GFR.** GFR was measured evaluating the clearance rate of 125I-labeled EDTA. More particularly, we evaluated GFR from the clearance rate of 125I-EDTA technique. At 9:00 a.m., a bolus injection of 1 μg K/Cg-125I-EDTA was given over 30 s. Seven samples were collected at 5, 12.5, 50, 80, 180, 240, and 300 min, with time 0 being the midpoint of the infusion interval. GFR was measured eight times: at baseline and every year from the 2nd until the 8th year of the follow-up period. The coefficient of variation of the bolus injection, because of measurement errors related to the calculation of the radioactivity concentration of the dose injected of each sample using a 40-min time for count measurement in duplicate, was 2.6 ± 0.3%. The coefficient of repeated measurements, which accounts for physiological variability in different days in the same subject, was 3.5 ± 0.8%. Further details have been provided previously (20,21). GFR courses of individuals were modeled using a first-order linear function cubic B-splines. Group comparisons were based on five component vectors of fitted GFR values using a permutation approach to a Hotelling’s T2 statistic (22). A similar, although not identical, approach had been previously used by Nosadini et al. (4). Blood samples were collected after an overnight fast for lipid measurement. Serum triglycerides and total cholesterol were measured by enzymatic techniques using commercially available Konelab 20 Autoanalyzer (Thermo Clinical Chemistry). Venous, Venna, Flinsapre, NOSTADINI AND ASSOCIATES

**Ultrasound Determination of the R/I.** A Sienna Sonoline ultrasound machine (Siemens, Milan, Italy) with a 3.5-MHz convex-array transducer was used. The B-mode measurements were performed at the same time as the Doppler measurement of the R/I. The ultrasonographic procedure that we adopted has been described previously (14,15,23,24). Briefly, the maximal length, width, and depth of the kidney were determined, and the renal volume was calculated as one-half the product of the three dimensions. The renal parenchymal width was measured from the capsulated to the tip of a renal pyramid in both kidneys. Intrarenal Doppler signals were obtained from two to three representative proximal segmental arteries (the first vessels branching of the main renal artery) from both kidneys. The peak systolic velocity (Vp) and the minimal diastolic velocity (Vm) were determined, the R/I was calculated as (Vp/Vm)×100, and the renal resistive index calculated as R/I+0.5. The renal resistive index measurements were averaged. The reproducibility of R/I index measurements was tested in 45 patients by two independent investigators in 3 days in 3 consecutive weeks to calculate the intraobserver-intrasession variability, the interobserver-inter session variability, and the interobserver-intrasession variability. The respective values for coefficient of variation were 1.7, 3.3, and 4.3%, respectively. The renal resistive index was appreciated by color-flow imaging. Stenosis was suspected if a segment of the vessel showed color-flow abnormality. The maximal systolic-flow velocity was measured at the site of “aliasing” (disturbance) (Vmax) and the point most distal to the site (Vpmax). The area of stenosis (as percentage of the total area) was calculated according to the continuity equation as 100 × (1 – (Vpmax/Vpmax)). According to this technique, an area of stenosis >75%, which approximately results in a reduction in the diameter of the vessel >50%, was diagnosed only when Vmax was higher than Vpmax by a factor >4.

**Percutaneous kidney biopsies.** Percutaneous kidney biopsies were performed under ultrasound guidance in the patients at baseline. Tissue was examined under a dissecting microscope to make sure of an adequate number of glomeruli in the kidney specimen. A 1-mm core was immediately snap frozen in liquid nitrogen for immunofluorescence. A second fraction was placed in Zenker’s fixative embedded in paraffin and processed for light microscopy. The patterns of renal lesions in the 157 type 2 diabetic patients with hypertension and microalbuminuria were classified as described previously using light microscopy technique by A.S. and R.F. (4,11,25,26), who were unaware of the clinical features of the patients as follows.

**Category 1.** Sixty-six patients had typical diabetic nephropathy. These biopsies showed established diabetic glomerulopathy with proportionally more capillary basement membrane thickening and mesangial expansion and septal formation in the thickened glomerular capillary wall, which was seen in type 1 diabetic patients. These patients had proliferative diabetic retinopathy.

**Category 2.** Forty patients had atypical patterns of renal injury. These patients had absent or only mild glomerular diabetic changes with dispropor-
R/I PREDICTS RENAL FUNCTION IN TYPE 2 DIABETES

TABLE 1
Demographic and clinical characteristics of the hypertensive, microalbuminuric type 2 diabetic patients at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>≥80</th>
<th>&lt;80</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>59</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 8</td>
<td>64 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>13 ± 4</td>
<td>12 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic/diastolic blood pressure (mmHg)</td>
<td>132/80 ± 11/5</td>
<td>133/79 ± 13/7</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma cholesterol (mg/dl)</td>
<td>221 ± 15</td>
<td>189 ± 16</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Plasma triglycerides (mg/dl)</td>
<td>187 ± 32</td>
<td>147 ± 31</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>7.3 ± 0.6</td>
<td>7.4 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>40/19</td>
<td>60/38</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>41</td>
<td>12</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Carotid artery disease (%)</td>
<td>31</td>
<td>9</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Peripheral artery disease (%)</td>
<td>40</td>
<td>19</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Renal histological category 1 (n)</td>
<td>36/59</td>
<td>30/98</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Renal histological category 2 (n)</td>
<td>19/59</td>
<td>21/98</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Renal histological category 3 (n)</td>
<td>4/59</td>
<td>47/98</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>39</td>
<td>12</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

Data are means ± SD. Blood pressure and glucose control values were those during the entire period of follow-up with drug treatments.

The analysis of kidney specimens was carried out according to the score system described by Mauer et al. (25) and Fioretto et al. (26). The study was approved by the ethical committee of the University of Padova and Sassari.

**Statistical analysis.** Data are reported as means ± SE or SD when normally distributed and as medians with ranges when the data were not normally distributed. The unpaired and paired Student's t test for parametric parameters, the Wilcoxon test for nonparametric parameters, and the quadratic chi² test for the comparison of the data expressed as percentages were evaluated using the software SPSS analysis approach. Because the number of subjects in each of the two groups of comparison was uneven, we used the formula of Fleiss et al. (27) to calculate the size of the cohort of patients we needed, assuming a difference between groups with regard to the primary end point of 1 − P = 0.4, with P being the relative frequency of the exposed controls and an odds ratio statistically significant at P < 0.05 with a size dimension of the sample ≥80. The number of patients in the group with R/I ≥80 was 59, and the number in the group with R/I <80 was 98 (27,28). Kaplan-Meier analysis with log-rank test was used as appropriate to assess the differences between groups, after correction for metabolic and systemic parameters. The number of years of follow-up was calculated from the date of ultrasonography until the date of the last documented visit in the out patient clinic, encompassing the GFR measurement (on average after 7.8 years). For multivariate analysis, the effect of multiple variables on worsening of renal function was evaluated using stepwise forward Cox regression analysis (with P < 0.10 as threshold level of significance for the removal of the variable from the analysis or the definition of nonsignificance and P < 0.05 as the threshold for entry into the model). The variables investigated were the R/I; age; duration of the disease; sex; clinical, biochemical, electrocardiographic, or ultrasound signs of atherosclerosis in the heart, legs, or central nervous system; AER; average systolic, diastolic, and A1C patterns during the 7.8-year follow-up period; and baseline GFR and lipid circulating values.

**RESULTS**

The clinical characteristics of the two groups of type 2 hypertensive, microalbuminuric, diabetic patients with R/I at baseline ≥80 and <80 are shown in Table 1. Patients with R/I ≥80 showed slightly higher circulating lipid patterns and stronger smoking habits. Blood pressure control was reasonably tight, with average levels of systolic and diastolic blood pressure <140/90 mmHg even if not <130 mmHg as for systolic levels, as recommended by the guidelines for the treatment of hypertension in diabetes. BMI was 27 ± 0.4 and 28 ± 0.6 kg/m² at baseline, respectively, in the groups. Patients with R/I ≥80 more frequently showed clinical, biochemical, and ultrasound evidence of atherosclerosis (41 vs. 12% coronary artery disease, 31 vs. 9% carotid artery disease, and 40 vs. 19% peripheral artery disease, Table 1). Patients with R/I ≥80 more frequently had renal histological patterns of category 1 and 2 than 3 (category 1, 61 vs. 30%; category 2, 32 vs. 19%; and category 3, 7 vs. 48%; see absolute number in Table 1). The number of patients who smoked was greater among patients with R/I ≥80 than with R/I <80. Kaplan-Meier curves for the primary end point (decrease of GFR ≥3.0 ml/min per 1.73 m² per year), corrected as for lipid, A1C patterns, blood pressure levels, renal histology category, and smoking habits, was two to three times more frequently observed in patients with R/I ≥80 (Fig. 1). The percentage of patients who showed a regression to normoalbuminuria during the follow-up period was four- to fivefold lower in patients with R/I ≥80 than in those with R/I <80 (Table 2). On the contrary, overt proteinuria did not develop more frequently in patients with R/I ≥80 than in patients with R/I <80 (24 vs. 5%, P < 0.01). Average AER levels decreased significantly in patients with R/I ≥80 but not in those with R/I <80 (Table 2). Multivariate analysis revealed a number of variables that differed significantly between patients with R/I ≥80 or with R/I <80 with regard to the primary end point (decrease of GFR ≥3.0 ml/min per 1.73 m² per year). The strongest risk factor was the R/I index (Table 3). Also, the presence of combined artery disease, renal histological category, and smoking habits played a discriminatory role, which was, however, not so important in comparison with the R/I index, as evidenced by the lower relative risks associated with these variables (Table 3).

The size of the cohort of patients with a R/I value ≥80 or <80 with systolic blood pressure >140 mmHg was too low to allow statistical comparisons. The cohort of patients, within the entire population, who showed an average value of systolic blood pressure >140 mmHg (19%) had a greater decline of GFR than those in whom systolic blood pressure was steadily maintained <140 mmHg (−2.56 ±
other patients (rate of decay in the patients using simvastatin than in the within the entire population. We observed a slightly lower treated. Therefore we just compared the rate of decay of different R/I to allow a statistical comparison with those vastatin was too low inside each group of patients with any comparison. The number of patients treated by sim-

NS).

greater in patients with an R/I DIABETES, VOL. 55, JANUARY 2006 237

FIG. 1. Kaplan-Meier analysis, corrected for lipid, A1C, blood pressure levels, and smoking habits, of time to the predefined primary end point, e.g., an yearly decline of GFR ≥−3 ml/min per 1.73 m² in the 59 patients with an R/I index ≥80 and in the 98 patients with an R/I index <80 during the 7.8-year follow-up period. The percentage of patients with a yearly decrease of GFR ≥−3 ml/min per 1.73 m² was two to three times greater in patients with an R/I ≥80.

0.111 vs. −1.23 ± 0.12 ml/min per 1.73 m² per year, P < 0.05). The number of patients with steady values of diastolic blood pressure >90 mmHg was too small to allow any comparison. The number of patients treated by simvastatin was too low inside each group of patients with different R/I to allow a statistical comparison with those treated with different hypocholesterolemic drugs or untreated. Therefore we just compared the rate of decay of GFR between patients treated by simvastatin or untreated within the entire population. We observed a slightly lower rate of decay in the patients using simvastatin than in the other patients (−1.96 ± 0.29 vs. −2.77 ± 0.37, P < 0.07, NS).

DISCUSSION

Microalbuminuria is not merely a predictor of diabetic nephropathy but also constitutes evidence of renal dam-
age. This has been demonstrated by Adler et al. (29) and by our research group (11), who showed in microalbuminuria altered mRNA expression of several glomerular proteins.

Patterns of glycemic control accomplishing an average A1C level of 7.0% are able to delay the onset of overt diabetic nephropathy in type 2 diabetic patients (17). We achieved an average level of A1C of 7.3–7.4%, despite thorough efforts to obtain a tighter glycemic control. Nevertheless even in the UKPDS study (17), a nontrivial fraction of the patients had A1C levels >7.0%, and several other reports in type 2 diabetic patients with altered A1C showed A1C levels close to 8.0% (7–11).

The R/I index is significantly correlated with increased blood pressure and decreased renal function (14,15,23,30). We suggest that R/I index ≥80 can predict the outcome of renal function in type 2 diabetic patients with microalbuminuria. This finding might be important from three different points of view. First, ischemic atherosclerotic injury, at the level of renal small vessels, might accelerate the decay of GFR, possibly further deteriorating the molecular structural characteristics of endothelial-podocyte system. Second, R/I index can be used to predict the outcome of renal function in type 2 diabetic patients with microalbuminuria. Third, an increased R/I index is closely associated, in type 2 diabetic patients with microalbuminuria, with patterns of glomerular lesions of typical or atypical diabetic nephropathy. The latter observation resembles the close relationship between proliferative diabetic retinopathy and patterns of glomerular and renal lesions typical of diabetic nephropathy that we have described previously (4,11,26). However, diabetic retinopa-

### TABLE 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R/I ≥80 at baseline</td>
<td>10.7 (3.3–15.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline GFR</td>
<td>1.8 (0.8–2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline AER</td>
<td>1.9 (0.7–3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Combined artery disease</td>
<td>5.2 (1.3–7.1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Renal histological category at base line</td>
<td>6.1 (2.0–12.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Duration of the disease</td>
<td>1.1 (0.6–1.8)</td>
<td>NS</td>
</tr>
<tr>
<td>A1C during follow-up</td>
<td>1.2 (0.4–2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure during follow-up</td>
<td>1.3 (0.6–2.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>4.3 (1.1–5.9)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are means (95% CI).

### TABLE 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (R/I &lt;80)</th>
<th>Group 2 (R/I ≥80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml · min⁻¹ · 1.73 m⁻²)</td>
<td>98 ± 2</td>
<td>97 ± 11</td>
</tr>
<tr>
<td>AER (µg/mg)</td>
<td>81 (32–240)</td>
<td>88 (31–261)</td>
</tr>
<tr>
<td>Normoalbuminuria (%)</td>
<td>—</td>
<td>31</td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>—</td>
<td>7†</td>
</tr>
</tbody>
</table>

Data are means ± SE, median (range), and %. *P < 0.05 baseline vs. 8 years. †P < 0.01 group 1 vs. group 2.
thy may not develop overt nephropathy (4). In fact, only type 2 diabetic patients with proliferative retinopathy are bound to show a rapid decline of GFR, but only 10–20% of type 2 diabetic patients have proliferative retinopathy (4,11,26). Moreover, the ophthalmoscopic examination, although mandatory to prevent and to treat diabetic proliferative retinopathy, is not less cumbersome than the evaluation of R/I to prevent and predict diabetic nephropathy. With regard to vascular events, the occurrences of carotid, peripheral, and coronary pathology are also less specific to predict the development of overt nephropathy than R/I index, because they may frequently be found also in type 2 diabetic patients without microalbuminuria and predisposition to develop overt nephropathy.

Thus we suggest that the R/I index might be useful to identify the cohort of microalbuminuric patients with more severe renal lesions and those prone to develop a rapid decay of GFR without performing routinely the invasive procedure of renal biopsy. Krolewski et al. (31,32) and Viberti et al. (33) demonstrated some years ago that a cohort of type 1 diabetic patients have a predisposition to develop overt diabetic nephropathy in association with increased Na/Li countertransport activity in erythrocytes, a marker of arterial hypertension. We have confirmed this observation in Caucasian type 2 diabetic patients (34). Arterial renal resistance, which also is frequently associated with arterial hypertension (30) and might reflect a more severe endothelial dysfunction, appears to be a further feature of this cohort of patients prone to develop overt nephropathy. Smoking habits certainly contributed to explain the rapid decline of GFR in our patients, but the role of R/I index emerged as the predominant risk factor (Table 3). Clearly, our findings need to be confirmed by other authors both in Caucasian and non-Caucasian type 2 diabetic patients.

ACKNOWLEDGMENTS


REFERENCES

