Normoalbuminuric Renal-Insufficient Diabetic Patients

A lower-risk group

VINCENT RIGALLEAU, MD, PHD[1]
CATHERINE LASSEUR, MD[2]
CHRISTELLE RAFFAITIN, MD[1]
MARIE-CHRISTINE BEAUVIEUX, PD, PHD[3]
NICOLE BARTHE, PD[4]
PHILIPPE CHAUVEAU, MD[2]
CHRISTIAN COMBE, MD, PHD[2]
HENRI GIN, MD, PHD[1]

OBJECTIVE — About 20% of diabetic patients with chronic kidney disease (CKD) detected from the new American Diabetes Association recommendations (albumin excretion rate >30 mg/24 h or estimated glomerular filtration rate [GFR] <60 ml/min per 1.73 m^2) may be normoalbuminuric. Do the characteristics and outcome differ for subjects with and without albuminuria?

RESEARCH DESIGN AND METHODS — A total of 89 patients with diabetes and a modification of diet in renal disease (MDRD) estimated GFR (e-GFR) <60 ml/min per 1.73 m^2 underwent a 51Cr-EDTA B-isotopic GFR determination and were followed up for 38 ± 11 months.

RESULTS — The mean MDRD e-GFR (41.3 ± 13.1 ml/min per 1.73 m^2) did not significantly differ from the i-GFR (45.6 ± 29.7). Of the subjects, 15 (17%) were normoalbuminuric. Their i-GFR did not differ from the albuminuric rate and from their MDRD e-GFR, although their serum creatinine was lower (122 ± 27 vs. 160 ± 71 μmol/l, $P < 0.05$): 71% would not have been detected by measuring serum creatinine (sCr) alone. They were less affected by diabetic retinopathy, and their HDL cholesterol and hemoglobin were higher ($P < 0.05$ vs. albuminuric). None of the CKD normoalbuminuric subjects started dialysis (microalbuminuric: 2/36, macroalbuminuric: 10/38) or died (microalbuminuric: 3/36, macroalbuminuric: 7/38) during the follow-up period (log-rank test: $P < 0.005$ for death or dialysis), and their albumin excretion rate and sCr values were stable after 38 months, whereas the AER increased in the microalbuminuric patients ($P < 0.05$), and the sCr increased in the macroalbuminuric patients ($P < 0.01$).

CONCLUSIONS — Although their sCr is usually normal, most of the normoalbuminuric diabetic subjects with CKD according to an MDRD e-GFR below 60 ml/min per 1.73 m^2 do really have a GFR below 60 ml/min per 1.73 m^2. However, as expected, because of normoalbuminuria and other favorable characteristics, their risk for CKD progression or death is lower.

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Twenty-five to forty percent of patients with diabetes have kidney damage (1), and diabetes is the first cause of end-stage renal disease in most countries (2). The early detection of chronic kidney disease (CKD) in diabetic patients is therefore of critical importance. The conventional approach for screening is the determination of the albumin excretion rate (AER). However, a substantial proportion of normoalbuminuric diabetic patients may present with a reduced glomerular filtration rate (GFR): their rates have been reported to be ~20% based on GFR <60 ml/min per 1.73 m^2 in type 2 diabetes (3) and in type 1 diabetes based on GFR <90 ml/min per 1.73 m^2 with more advanced glomerular lesions (4). In accordance with the National Kidney Foundation guidelines (5), this has led the American Diabetes Association to recommend the screening of CKD in diabetic patients based both on the AER (threshold: 30 mg/24 h) and the Cockcroft and Gault equation or modification of diet in renal disease (MDRD) equation estimated GFR (threshold: 60 ml/min per 1.73 m^2) (6).

The MDRD equation is superior to the Cockcroft and Gault equation: it is more accurate (7,8), more robust when glucose control is poor (9), and not biased by body weight (10), which is of considerable importance because of the frequent association of type 2 diabetes, and CKD (11), with obesity. Most of the recent reports on CKD in diabetic patients rely on MDRD e-GFR (12–16). This equation may however not be ideal for screening CKD, as it is known to underestimate normal and high GFR (17,18): some of the MDRD-based CKD diagnosis may stem from this underestimation (19), particularly in normoalbuminuric patients. Furthermore, the progressive nature of normoalbuminuric CKD has been argued from studies based on measured GFR, reported by one group (3,20), and its association with complications relies on reports in Asian diabetic subjects, who are known to have a high incidence of CKD (14). Whether this applies to MDRD-diagnosed normoalbuminuric CKD in Caucasians remains to be demonstrated.

To evaluate the significance of normoalbuminuric CKD in diabetes, we compared the isotopic GFR and serum creatinine of normoalbuminuric versus albuminuric diabetic patients with CKD according to an MDRD e-GFR <60 ml/min per 1.73 m^2. The baseline characteristics of the patients, and their outcome

From the [1]Department of Nutrition-Diabétologie, Hôpital Haut-Lévêque, Pessac, France; the [2]Department of Nephrologie, Université Victor Segalen-Bordeaux 2, Hôpital Pellegrin, Bordeaux, France; the [3]Department of Biochimie, Hôpital Haut-Lévêque, Pessac, France; and the [4]Department of Médecine Nucléaire, Hôpital Pellegrin, Bordeaux, France.

Address correspondence and reprint requests to Vincent Rigalleau, Nutrition-Diabétologie, Hôpital Haut-Lévêque, Avenue de Magellan, 33600 Pessac, France. E-mail: vincent.rigalleau@wanadoo.fr.

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Abbreviations: AER, albumin excretion rate; CKD, chronic kidney disease; e-GFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

during a 38-month follow-up, were also compared.

RESEARCH DESIGN AND METHODS

— A total of 89 patients (49 men, mean age 64 ± 11 years) were recruited from the Nutrition-Diabetology and Nephrology departments of the Centre Hospitalier Universitaire de Bordeaux. The inclusion criteria were as follows: *1*) diabetes (a total of 22 patients had type 1 diabetes and 67 had type 2 diabetes) and 2) CKD according to an MDRD e-GFR <60 ml/min per 1.73 m^2, not requiring renal replacement therapy at inclusion.

The patients gave written informed consent to participate in the study, which was approved by the ethical committee of our institution. This study was supported by a clinical research program in the Bordeaux University Hospital.

Analytical methods

The AER was determined on one 24-h urine collection during a short hospitalization, with an immunonephelometric analyzer (Behring Nephelometer 2) using an appropriate kit (Nantiserum VO human albumin; Dade Behring). Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640; Olympus Optical, Tokyo, Japan), using the Jaffé method with bichromatic measurements according to the manufacturer's specifications, and daily calibration of the analyzer. This procedure did not change in our laboratory during the study. Clearance of the radionuclide marker was measured after intravenous injection of ^{51}Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning at 9:00 A.M., after a light breakfast. After a single bolus of 100 μCi (3.7 MBq) of ^{51}Cr-EDTA, four venous blood samples were drawn at 75, 105, 135, and 165 min, and urinary samples were collected at 90, 120, 150, and 180 min, as previously described (21). The final result was the mean of the four clearance values. If for one period, the urine flow was too low or if a clearance value was not within ±20% of the mean of the three others, this value was excluded and the mean was calculated for the other three clearances. Less than 5% of the values were excluded this way. The ^{51}Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003; Packard Instruments, Meriden, CT).

Follow-up, care, and outcome

This prospective study began in June 2001. It was based on a cooperative follow-up between diabetologists and nephrologists with the establishment of a joint medical file for each patient. This cooperative follow-up was complementary and included one visit with the diabetologist every 4 months and one visit with the nephrologist every year if 40 < MDRD e-GFR ≤60 ml/min per 1.73 m^2, every 4 months if 20 < MDRD e-GFR ≤40 ml/min per 1.73 m^2, and then one visit every 1 or 2 months if MDRD e-GFR ≤20 ml/min per 1.73 m^2. Mean duration of the follow-up was 38 ± 11 months.

The care program objectives included glycemic control according to the French 1999 recommendations (A1C <8.0%; if possible, 6.5% without severe hypoglycemia in type 2 and <7.0% in type 1 diabetes), but also control of associated factors such as hypertension (objective: <130/80 mmHg) and dyslipidemia (objective: LDL cholesterol <1.3 g/l). We prescribed 0.8 g protein·kg^{-1}·day^{-1} according to the National Kidney Foundation recommendations (22), except for patients with clinical signs of undernutrition or who were ≥65 years of age.

The primary outcome was requirement for dialysis, or death. The secondary outcomes were the AER and serum creatinine for living nondialyzed patients at the end of the follow-up.

Statistical analysis

The results are expressed as means ± SD. The normoalbuminuric patients were compared with the albuminuric (micro- and macroalbuminuric) patients by ANOVA and unpaired Student's *t* tests for the continuous variables and by χ^2 test for the categorical variables. Similar analysis was performed after categorizing the subjects as normoalbuminuric (AER <30 mg/24 h), microalbuminuric (30 ≤ AER <300 mg/24 h), and macroalbuminuric (AER ≥300 mg/24 h), with a Bonferroni correction. For the primary outcome (death or dialysis), prognostic curves were obtained using the Kaplan-Meier estimation method and compared by log-rank test; the patients who did not present any event (death or dialysis onset) were censored at the end of the follow-up. For the secondary outcome, the baseline and final characteristics of the patients were compared by paired Student's *t* tests. All the analysis was performed using SPSS software, version 10.0. The significance level was fixed at $P < 0.05$.

RESULTS

Baseline characteristics

A total of 89 patients were included. Their mean diabetes duration was 18 ± 10 years, mean MDRD e-GFR was 41.3 ± 13.1 ml/min per 1.73 m^2 (11–59.9), it did not significantly differ from their isotopic GFR (45.6 ± 29.7, $P = 0.12$), although 15 subjects had an isotopic GFR >60 ml/min per 1.73 m^2. A total of 15 subjects (17%) were normoalbuminuric. The proportion of subjects whose isotopic GFR was >60 ml/min per 1.73 m^2 was lower in the normoalbuminuric group (13.3%) than the normoalbuminuric group (25.7%, NS by χ^2). The normoalbuminuric subjects were less frequently affected by diabetic retinopathy, but they had higher HDL cholesterol and hemoglobin levels. For these characteristics, the difference was mainly due to the macroalbuminuric group, with intermediary values in the microalbuminuric group. There were also tendencies ($P < 0.07$) for more women, less cigarette smoking, fewer previous cardiac events, a lower duration of diabetes, and a higher total cholesterol level in the normoalbuminuric group. The type of diabetes, A1C, and blood pressure did not differ (Table 1).

Most of the normoalbuminuric patients (71%) had serum creatinine levels in the normal range. Despite their lower serum creatinine levels, their MDRD e-GFR did not significantly differ from the albuminuric group, and the MDRD underestimation was not significant in either group ($P = 0.051$ between isotopic and MDRD e-GFR in the microalbuminuric group). The correlation between MDRD e-GFR and the reference isotopic measurement was even better for the normoalbuminuric group, and the accuracy of the MDRD (percent estimations within ±10, 30, and 50% of the isotopic GFR) tended to be better for them. The coexistence of normal AER and CKD could therefore not be attributed to the MDRD underestimation of GFR in our patients.

Outcome

Primary outcome. Ten of the albuminuric patients died during the follow-up, whereas all the normoalbuminuric subjects were alive at its end. Twelve of the albuminuric patients required dialysis during the follow-up (10 from the macroalbuminuric patients, $P < 0.01$ by χ^2), whereas none of the normoalbuminuric patients did. Figure 1 shows the log sur-

Table 1—*Baseline characteristics of patients*

	Normoalbuminuric	Albuminuric	*P*	Microalbuminuric	Macroalbuminuric
n	15	74		36	38
AER (mg/24 h)	20.7 ± 6.2	712 ± 876	0.003	123.7 ± 78.7	1,270 ± 922*†
Serum creatinine (μmol/l)	122 ± 27	160 ± 71	0.04	135 ± 44	183 ± 84*†
% Serum creatinine <120 μmol/l	71	33	0.006	35*	30*
Isotopic GFR (ml/min per 1.73 m^2)	47.5 ± 19.9	45.2 ± 31.4	0.79	51.8 ± 27.4	39.0 ± 33.6
MDRD e-GFR (ml/min per 1.73 m^2)	45.6 ± 8.9	40.4 ± 13.7	0.17	43.8 ± 12.2	37.2 ± 14.5
Correlation between MDRD e-GFR and isotopic GFR	$r = 0.69$, $P < 0.005$	$r = 0.45$, $P < 0.001$		$r = 0.53$, $P < 0.001$	$r = 0.34$, $P < 0.05$
% MDRD estimations within					
Isotopic GFR ± 10%	26	24	0.84	22	26
Isotopic GFR ± 30%	73	60	0.56	61	60
Isotopic GFR ± 50%	86	79	0.72	83	76
Sex (% female)	66	40	0.058	52	29*
Diabetes type (% type 2)	80	75	0.48	73	76
Age (years)	68 ± 9	64 ± 12	0.17	65 ± 11	62 ± 13
Diabetes duration (years)	14 ± 5	19 ± 11	0.06	19 ± 12	19 ± 10
BMI (kg/m^2)	27.0 ± 4.5	26.9 ± 4.3	0.89	27.1 ± 4.4	26.7 ± 4.3
A1C (%)	9.0 ± 1.3	8.5 ± 1.6	0.31	8.6 ± 1.3	8.5 ± 2.0
Cholesterol (g/l)	2.37 ± 0.67	2.10 ± 0.48	0.07	2.03 ± 0.38	2.16 ± 0.56
LDL cholesterol (g/l)	1.26 ± 0.46	1.19 ± 0.40	0.54	1.14 ± 0.32	1.25 ± 0.47
HDL cholesterol (g/l)	0.64 ± 0.28	0.52 ± 0.17	0.04	0.56 ± 0.19	0.49 ± 0.15*
Triglycerides (g/l)	1.91 ± 1.86	1.76 ± 1.09	0.67	1.56 ± 0.09	1.96 ± 1.23
Systolic blood pressure (mmHg)	143 ± 16	147 ± 19	0.47	145 ± 19	149 ± 19
Diastolic blood pressure (mmHg)	79 ± 8	81 ± 10	0.56	79 ± 9	83 ± 10
Number of antihypertensive drugs	2.5 ± 1.8	2.4 ± 1.2	0.68	2.2 ± 1.0	2.5 ± 1.3
% on ACE inhibitors	40	59	0.25	69	50
% on angiotensin 2 receptor inhibitors	20	16	0.71	16	17
Hemoglobin level (g/dl)	13.3 ± 1.4	12.3 ± 1.4	0.01	12.6 ± 1.3	12.0 ± 1.4*
% With previous cardiac event	13	38	0.058	31	46
% With diabetic retinopathy	26	66	0.01	61*	71*
% Cigarette smoking	20	52	0.054	41	63*

Data are means ± SD unless otherwise indicated. *Means $P < 0.05$ vs. the normoalbuminuric group; †means $P < 0.05$ vs. the microalbuminuric group. The medium column gives the significance for the difference between the normoalbuminuric group and the other patients ($n = 74$).

vival curve, with dialysis or death as the end point.

Secondary outcome. The second AER and serum creatinine determination was performed in all the alive nondialized patients. The changes in AER, serum creatinine, and MDRD e-GFR did not significantly differ according to baseline normo-, micro-, and macroalbuminuria. However, normoalbuminuria persisted during the follow-up, and serum creatinine did not change in the normoalbuminuric group. By contrast, AER increased in the microalbuminuric patients ($P < 0.05$ vs. baseline), and serum creatinine increased in the macroalbuminuric patients ($P < 0.01$ vs. baseline). The MDRD e-GFR tended to decrease in the albuminuric patients ($P = 0.05$), and the comparison between baseline and final values only involved the subjects who did not have to start hemodialysis (12 albuminuric patients, none normoalbuminuric) (Table 2).

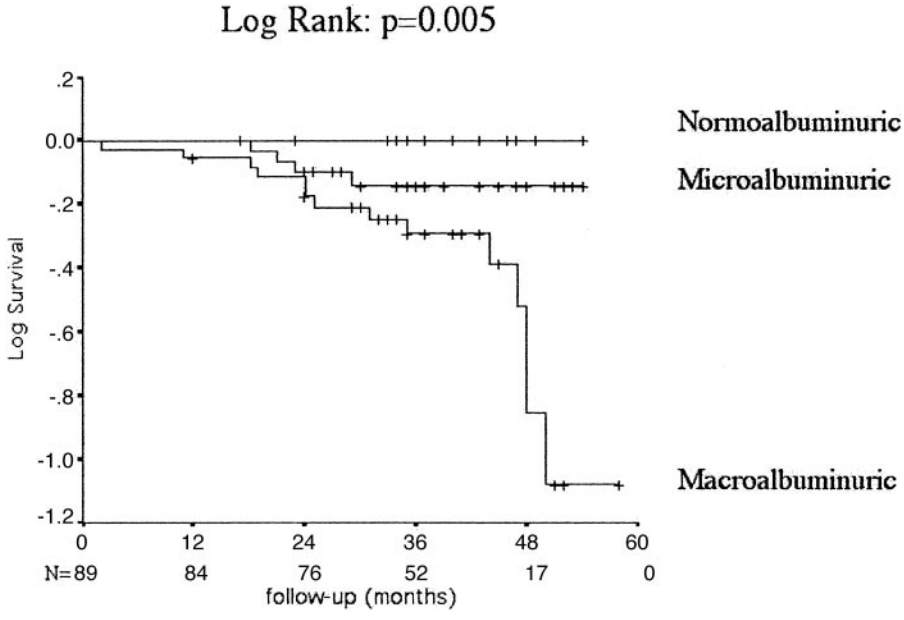

Figure 1—*Log survival plot (end point: death or dialysis).*

Table 2—*Outcome characteristics of patients at the end of follow-up*

	Normoalbuminuric	Microalbuminuric	Macroalbuminuric
n	15	36	38
Follow-up duration (months)	40 ± 8 (23–54)	38 ± 11 (17–54)	37 ± 13 (2–59)
AER (mg/24 h)	18.0 ± 9.0	271.1 ± 342.2*	1,508.3 ± 417.4
Serum creatinine (μmol/l)	123 ± 25	142 ± 44	265 ± 167†
MDRD e-GFR (ml/min per 1.73 m^2)	45.8 ± 8.5	43.0 ± 12.8	29.5 ± 21.1
Dialysis onset	0	2	10‡
Death	0	3	7

Data are *n*, means ± SD (range), or means ± SD. *$P < 0.05$ and †$P < 0.01$ vs. the result at the inclusion (shown in the Table 1). ‡$P < 0.01$ by χ^2 test.

CONCLUSIONS — Our first objective was to find out whether normoalbuminuric diabetic patients might represent an artificial group, stemming from overdiagnosed CKD due to the underestimation of high GFR by the MDRD equation. The isotopic determination of GFR in our patients argues against this hypothesis: although the MDRD underestimated their GFR, the difference was slight and not significant. The proportion of subjects for which isotopic GFR was >60 ml/min per 1.73 m^2 was indeed lower in the normoalbuminuric group (13.3%) than in the normoalbuminuric group (25.7%, NS by χ^2), and the correlation between estimated and measured GFR was better in the normoalbuminuric group. Most of these patients, therefore, really had a GFR <60 ml/min per 1.73 m^2, which would have been missed for 71% of them if their renal function had been assessed solely by a serum creatinine level >120 μmol/l. Despite its underestimation of GFR, mainly for GFR >60 ml/min per 1.73 m^2 (18,23), and the increase in the number of detected CKD (12,24), the use of the MDRD equation as recommended by the American Diabetes Association is of interest, especially when AER is normal.

Apart from their relatively low creatinine levels, our normoalbuminuric CKD patients displayed a number of specific characteristics: a higher proportion of women, a lower duration of diabetes, a low prevalence of retinopathy (3,4), fewer smokers (25), higher hemoglobin levels (26,27), and higher HDL cholesterol (28,29) are consistent with previous reports on the characteristics associated with the presence of an abnormal AER. As our normoalbuminuric patients were mainly women and slightly older, their low MDRD e-GFR was not unexpected: increasing age and female sex both reduce the MDRD estimation. Only a minority of these patients had diabetic retinopathy, suggesting that their renal impairment may not be due to diabetic nephropathy. However, around one-third of type 2 diabetic patients with renal biopsy–demonstrated diabetic glomerulopathy do not have retinopathy (30). Because blood pressure levels did not differ between the two groups, it seems unlikely that the low GFR of normoalbuminuric patients was due to nephroangiosclerosis; these patients were also less affected by previous cardiovascular events. However, they required as much antihypertensive therapy as did the albuminuric patients, which suggests that their renal impairment was not without consequence.

Although 17 is similar to the 20 normoalbuminuric patients studied by MacIsaac et al. (3), the small sample size is a limitation of our study, which probably explains why the differences between AER and e-GFR changes did not reach significance. Formulae estimations are known to underestimate the decline in GFR in diabetic patients (31). None of the normoalbuminuric patients died or started dialysis, and their stable AER and serum creatinine, whereas AER increased in microalbuminuric, and creatinine increased in the macroalbuminuric, both significantly, are however strong indications for a better outcome in the normoalbuminuric group. It must be noticed that most of the clinical events occurred in CKD patients with macroalbuminuria. The different characteristics we found may have contributed to this better outcome: male sex (32), a longer duration of diabetes (33), the presence of retinopathy (34), a lower hemoglobin level (32,35), and smoking (36) have all been reported to be associated with the progression of nephropathy in diabetes. However, the most probable is the persisting absence of albuminuria by itself: numerous reports have emphasized its importance for CKD progression (30,33–35,37,38) and coronary heart disease (39) in diabetes.

Some other limitations should be noted. As reflected by the scatter of the isotopic GFR in the albuminuric group (Table 1), their proportion of stages 4–5 CKD was higher (26/74 vs. 3/15 normoalbuminuric), which can explain that all the subjects who had to start dialysis were albuminuric. We feel nonetheless that the few severe and terminal CKD cases in the normoalbuminuric group is a reflection that it is, on the whole, a rather stable condition. Silveiro et al. (40) studied the evolution over 5 years of ^{51}Cr-EDTA–determined GFR in 32 normoalbuminuric type 2 diabetic subjects: their GFR decline (−0.18 ml/min per month) did not differ from normal subjects (−0.14), except for 13 subjects who were hyperfiltering at baseline (−0.61). Nine of our normoalbuminuric patients were treated by ACE inhibitors or angiotensin receptor blockers. Although their proportion did not differ from the albuminuric group, these treatments may have contributed to their good outcome, but we cannot be sure of this because we do not know whether they had abnormal AER before the initiation of these medications. Finally, because no renal biopsy was performed in our patients, their renal impairment may not have been due to diabetic nephropathy, which would account for their better outcome (30). However, we feel that whether our patients actually had diabetic nephropathy is not the issue: our purpose was to determine the outcomes in patients with diabetes and a reduced estimated GFR, classified as presenting CKD according to the new recommendations. Of such patients, 17% were normoalbuminuric in our study. Our isotopic determination of GFR confirmed that they really had GFR below 60 ml/min per 1.73 m^2, although most of them would have not been detected on the sole basis of their serum creatinine level. But they did not progress, and the necessity to measure estimated GFR by MDRD, and label these patients as having CKD, may result in adverse emotional and financial consequences. Further studies on the outcome of normoalbuminuric CKD in diabetes are required to demonstrate that the awareness of this condition is a benefit.

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