Nonalbuminuric Renal Insufficiency in Type 2 Diabetes

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OBJECTIVE — To determine the prevalence and characteristics of patients with type 2 diabetes who have impaired renal function, defined as a glomerular filtration rate (GFR) <60 ml · min^{-1} · 1.73 m^{-2}, and normoalbuminuria.

RESEARCH DESIGN AND METHODS — A cross-sectional survey of 301 outpatients attending a single tertiary referral center using the plasma disappearance of isotopic ^{99m}Tc-diethylene-triamine-penta-acetic acid to measure GFR and at least two measurements of urinary albumin excretion rate (AER) over 24 h to determine albuminuria.

RESULTS — A total of 109 patients (36%) had a GFR <60 ml · min^{-1} · 1.73 m^{-2}. The overall prevalence of normo-, micro-, and macroalbuminuria was 43 of 109 (39%), 38 of 109 (35%), and 28 of 109 (26%), respectively. Compared with patients with macroalbuminuria, those with normoalbuminuria were more likely to be older and female. After excluding patients whose normoalbuminuric status was possibly related to the initiation of a renin-angiotensin system (RAS) inhibitor before the start of the study, the prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was 23%. Temporal changes in GFR in a subset of 34 of 109 (32%) unselected patients with impaired renal function were available for comparison over a 3- to 10-year period. The rates of decline in GFR (ml · min^{-1} · 1.73 m^{-2} · year^{-1}) of −4.6 ± 1.0, −2.8 ± 1.0, and −3.0 ± 07 were not significantly different for normo- (n = 12), micro- (n = 12), and macroalbuminuric (n = 10) patients, respectively.

CONCLUSIONS — These results suggest that patients with type 2 diabetes can commonly progress to a significant degree of renal impairment while remaining normoalbuminuric.

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A reduced glomerular filtration rate (GFR), mainly estimated from creatinine clearance measurements, has been reported to occur in some long-standing normoalbuminuric type 1 diabetic patients (1,2). Work from our group has suggested that this phenomenon can also occur in both type 1 or type 2 diabetes and that it may be more common in type 2 diabetes (3). Furthermore, in comparison to patients with type 1 diabetes, albuminuric patients with type 2 diabetes have a great deal of renal ultrastructural heterogeneity (4,5). This structural heterogeneity raises the possibility that different GFR and AER relationships are seen in patients with type 2 compared with those with type 1 diabetes. We have therefore further investigated the association between GFR and AER in patients with type 2 diabetes. In particular, we determined the prevalence and characteristics of patients with impaired renal function, defined as a GFR <60 ml · min^{-1} · 1.73 m^{-2}, and an AER within the normoalbuminuric range.

RESEARCH DESIGN AND METHODS

— A total of 625 patients attending the diabetes clinic at Austin Health, a tertiary referral center and teaching hospital of The University of Melbourne, Victoria, Australia, were studied between 1990 and 2001 as part of an ongoing project investigating the pathogenesis of diabetic renal disease. Isotopic estimations of GFR were routinely performed regardless of a patient's albuminuric status. The type of diabetes was classified according to World Health Organization criteria (6), and patients with type 1 or secondary diabetes were excluded (n = 168). Patients with type 2 diabetes who had recurrent urinary tract infections or hematuria (n = 9), known nondiabetic renal disease (n = 15), severe intercurrent illness such as a malignancy (n = 10), symptomatic cardiac failure (n = 2), no isotopic estimation of GFR, or only one estimation of AER (n = 120) were also excluded from this analysis. The remaining 301 patients were then classified according to their GFR and AER status.

Laboratory methods

AER was measured using fresh 24-h urine collections. On completion of each collection, a midstream specimen of urine was examined by microscopy and culture to exclude urinary tract infection and hematuria. Albumin concentrations were determined by radioimmunoassay (RIA) or immunoturbidimetry (Dade-Behring, Marburg, Germany). These methods and the equivalence of the RIA and turbitimer assays have been previously reported (7). GFR was measured by the plasma disappearance of isotopic ^{99m}Tc-diethylene-triamine-penta-acetic acid (DTPA) using the Brochner-Mortensen correction (8).

Clinical evaluation

As part of the patient's usual clinical evaluation, the following information was recorded in the patient's history and then abstracted for this study: age and sex, type and duration of diabetes, height and

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Abbreviations: AER, albumin excretion rate; CHD, coronary heart disease; CVD, cerebrovascular disease; DTPA, ^{99m}Tc-diethylene-triamine-penta-acetic acid; GFR, glomerular filtration rate; PVD, peripheral vascular disease; RAS, renin-angiotensin system; RIA, radioimmunoassay.

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

weight (for the calculation of BMI), and the presence or absence of the following—a history of coronary heart disease (CHD), cerebrovascular disease (CVD), peripheral vascular disease (PVD), treatment for hypertension (anti-HT use), use of inhibitors of the renin-angiotensin system (RAS), and smoking history. Retinal examination was performed by direct ophthalmoscopy after pupillary dilatation in the ophthalmology clinic. Systolic and diastolic blood pressures were measured after 5 min of recumbency using the appearance and disappearance of the Korotkoff sounds.

Patient classification

Patients were divided on the basis of their GFR estimation, i.e., $<$ or $\geq$60 ml · min^{-1} · 1.73 m^{-2}, and further classified according to albuminuria status, i.e., normo- (<20 μg/min), micro- (20–200 μg/min), or macroalbuminuria (>200 μg/min), as determined by the geometric mean of at least two measurements collected within the same 12-month period as the GFR estimation. The overall prevalence and clinical characteristics of patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was compared with those who had mico- or macroalbuminuria. The prevalence of normoalbuminuria associated with a GFR $<$ or $\geq$60 ml · min^{-1} · 1.73 m^{-2} was also determined.

In patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria, the results of all previous AER measurements were then reviewed to identify any patients whose normoalbuminuric status was possibly related to RAS inhibitor use before the start of this study. After exclusion of these patients, an adjusted prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was calculated.

In 34 of 109 (32%) unselected patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2}, an additional estimation of GFR had been performed 3–10 years before the commencement of this study. These values were used to determine temporal changes in GFR for the normo-, micro-, and macroalbuminuric groups.

Statistics

Continuous data are expressed as mean ± SEM, and categorical data as number (percent) except where specified. Serum creatinine values are expressed as median (interquartile range). Logarithmic transformation of AER and triglycerides was performed before statistical analysis. AER results are expressed as geometric mean ×/÷ tolerance factor. Differences in continuous variables were compared using Student's *t* tests (two groups) or one-way ANOVA (three or more groups) with subgroups then compared by Fisher's protected least significant difference post hoc test. Differences in categorical variables were compared using χ^2 analysis. Pearson correlation was used to analyze univariate associations between continuous variables.

A level of $P < 0.05$ was considered statistically significant, and 95% levels of confidence were used for confidence intervals. Statistical analysis was performed using Stata (1997; StataCorp, College Station, TX) and StatView (1998; SAS Institute, Cary, NC).

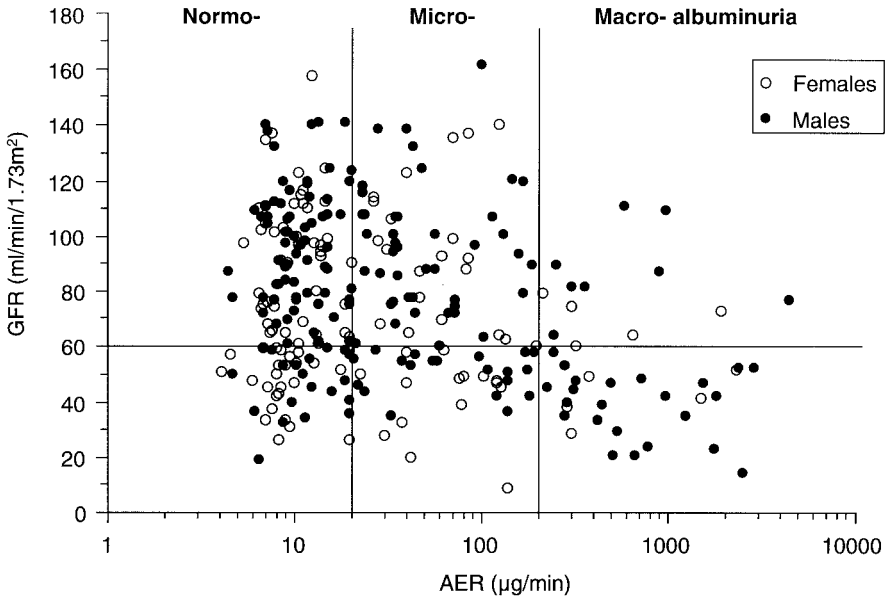

Figure 1— *The distribution of 301 patients with type 2 diabetes attending a single tertiary referral clinic divided on the basis of GFR, i.e., $<$ or $\geq$60 ml · min^{-1} · 1.73 m^{-2} and AER, i.e., normo- (<20 μg/min), micro- (20–200 μg/min), or macroalbuminuria (>200 μg/min). There was a significant correlation between a decreasing GFR with increasing levels of AER (r = −0.29, P < 0.0001). The overall relationship between GFR with AER was similar for both males and females. Although patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} with normoalbuminuria were more likely to be female, those with macroalbuminuria were more likely to be male.*

RESULTS — The relationship between GFR and AER for all 301 patients with type 2 diabetes in this study is shown in Fig. 1. There was a significant correlation between a decreasing GFR with increasing levels of AER ($r = -0.29$, $P < 0.0001$). A total of 192 of 301 (64%) patients had a GFR ≥60 ml · min^{-1} · 1.73 m^{-2} while 109 of 301 (36%) had a GFR <60 ml · min^{-1} · 1.73 m^{-2}. For the 109 patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} the prevalence of normo-, micro-, and macroalbuminuria in a cross-sectional survey was 43 (39%), 38 (35%), and 28 (26%), respectively. For the 192 patients with a GFR ≥60 ml · min^{-1} · 1.73 m^{-2} the prevalence of normo-, micro-, and macroalbuminuria was 115 (60%), 64 (33%), and 13 (7%), respectively. When the 301 patients were stratified according to their AER status regardless of their GFR, 158 (52%) had normo-, 102 (34%) had micro-, and 41 (14%) had macroalbuminuria. For the 158 normoalbuminuric patients, 43 (27%) had a corresponding GFR <60 ml · min^{-1} · 1.73 m^{-2} (AER 9.3 ×/÷ 1.1 μg/min) and 115 (73%) had a GFR ≥60 ml · min^{-1} · 1.73 m^{-2} (AER 10.5 ×/÷ 1.0 μg/min).

The demographic, clinical, and biochemical characteristics of the subgroup of 109 patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} stratified according to their AER status are shown in Table 1. Normoalbuminuric patients were significantly older ($P < 0.01$) and more commonly female ($P < 0.01$) in comparison to those with macroalbuminuria. There were no differences in the duration of di-

Table 1—*Clinical and laboratory characteristics of 109 patients with type 2 diabetes attending a single tertiary referral clinic with a GFR <60 ml · min^{-1} · 1.73 m^{-2}*

	Normo-albuminuria	Micro-albuminuria	Macro-albuminuria	*P*
n	43	38	28	
AER (μg/min)	9.3 ×/÷ 1.1	61 ×/÷ 1.2	671 ×/÷ 1.2	<0.0001
Age (years)	73 ± 1	72 ± 2	67 ± 2	<0.01
Females (%)	56	45	18	<0.01
Duration of diabetes (years)	14 ± 1	16 ± 1	15 ± 2	0.64
BMI (kg/m^2)	30.8 ± 1.0	29.3 ± 0.7	31.6 ± 1.4	0.26
Retinopathy (%)	26	50	41	0.11
CHD (%)	49	51	64	0.42
CVD (%)	21	27	18	0.67
PVD (%)	23	35	46	0.12
Smoking (%)	38	53	62	0.19
HbA_{1c} (%)	7.3 ± 0.3	7.9 ± 0.2	7.9 ± 0.3	0.23
SBP (mmHg)	138 ± 3	147 ± 3	147 ± 3	0.02*
DBP (mmHg)	75 ± 2	78 ± 1	77 ± 1	0.37
TC (mmol/l)	4.4 ± 0.2	4.5 ± 0.2	4.3 ± 0.2	0.91
LDL-C (mmol/l)	2.6 ± 0.1	2.8 ± 0.1	2.5 ± 0.2	0.43
HDL-C (mmol/l)	1.15 ± 0.05	1.19 ± 0.06	0.97 ± 0.05	0.02*
TG (mmol/l)	1.9 ×/÷ 1.1	1.8 ×/÷ 1.1	2.0 ×/÷ 1.1	0.86
GFR (ml · min^{-1} · 1.73 m^{-2})	47 ± 2	47 ± 2	39 ± 2	0.01
Creatinine (μmol/l)	110 (87–146)	112 (101–136)	150 (123–200)	0.001
RAS inhibitor (%)	74	74	81	0.76
Anti-HT (%)	95	95	96	0.95

Data are mean ± SEM, geometric mean ×/÷ tolerance factor, or median (interquartile range). Patients were stratified on the basis of AER, i.e., normo- (<20 μg/min), micro- (20–200 μg/min) and macroalbuminuria (>200 μg/min). *After adjustment for differences in age or sex, there were no significant differences in SBP ($P = 0.15$) or HDL-C ($P = 0.66$). CHD, coronary heart disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

abetes, BMI, prevalence of retinopathy, history of vascular disease, smoking history, HbA_{1c} levels, diastolic blood pressure, total cholesterol, LDL cholesterol, and triglyceride levels among patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} associated with normo-, micro-, or macroalbuminuria. Systolic blood pressure readings were lowest in normoalbuminuric patients, but this difference compared with micro- and macroalbuminuric patients was no longer apparent after adjustments for age and sex between the groups. HDL cholesterol levels also no longer varied among the groups of patients after the above adjustments were made.

Overall there were no significant differences in the use of any anti-HT agent and specifically RAS inhibitors for patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normo-, micro-, or macroalbuminuria (Table 1). The results of retrospective AER measurements in the 43 patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria were also reviewed to determine whether the initiation of RAS inhibitor therapy resulted in reversion of micro- or macro- to normoalbuminuria (Fig. 2). Eleven patients (26%) had never received a RAS inhibitor. For these patients there was no evidence to suggest reversion from persistent micro- or macro- to normoalbuminuria occurred with the use of non–RAS anti-HT agents (AER sampling period of 56 ± 12.7 months). In 15 of 43 (35%) patients, a RAS inhibitor had been initiated in our clinic; however, 9 of these 15 patients displayed persistent normoalbuminuria before this (AER sampling period of 34.8 ± 5.6 months). By contrast, in 6 of these 15 patients (40%), there was clear reversion of either micro- or macroalbuminuria to normoalbuminuria with RAS inhibition. In the remaining 17 of 43 (40%) patients, a RAS inhibitor had already been initiated before they attended our clinic and, thus, retrospective AER measurements before this time were not available for review.

The prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was then calculated after excluding 23 of 43 patients whose normoalbuminuric status was possibly altered by the use of a RAS inhibitor (i.e., the 17 patients on a RAS inhibitor before attending the clinic and the 6 patients with micro- or macroalbuminuria before the initiation of therapy). After this adjustment the prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was 20 of 86 (23%).

The age (normo- 76 ± 1, micro- 72 ± 2, and macro- 67 ± 2 years, $P < 0.01$) and sex differences (female: normo- 65%, micro- 45%, and macro- 18%, $P < 0.01$) between patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} and various levels of albuminuria were preserved after the exclusion of normoalbuminuric patients who did not have a documented history of normoalbuminuria before the initiation of a RAS inhibitor.

Temporal changes in GFR in a subset of 34 of 109 (32%) unselected patients with impaired renal function were available for comparison. The rate of change was calculated by subtracting a GFR measured 3–10 years previously from the most recent GFR used to classify patients as having a GFR <60 ml · min^{-1} · 1.73 m^{-2}. The mean interval between GFR measurements (years) of 4.9 ± 0.5, 5.6 ± 0.6, and 6.6 ± 0.6 together with the rate of decline in GFR (ml · min^{-1} · 1.73 m^{-2} · year^{-1}) of −4.6 ± 1.0, −2.8 ± 1.0, and −3.0 ± 07 were not significantly different for normo- ($n = 12$), micro- ($n = 12$), and macroalbuminuric ($n = 10$) patients, respectively.

CONCLUSIONS — The combination of impaired renal function and normoalbuminuria in patients with diabetes was first highlighted by Lane et al. (1), who identified eight women with type 1 diabetes with a low creatinine clearances and a normal AER. Subsequently, a study from our group showed that creatinine clearance could decline in patients with type 1 or type 2 diabetes, especially females, with no increase in AER (3). However, creatinine clearance is not always an accurate estimate of GFR (9,10). We have therefore performed this current study using the accepted gold standard estimate

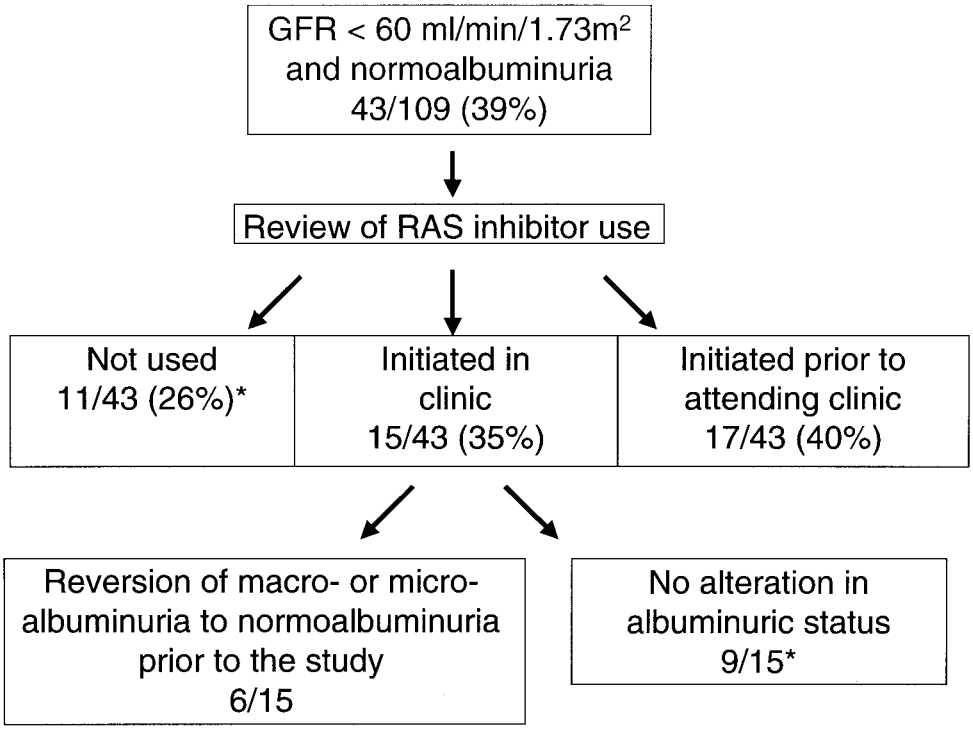

Figure 2— *The use of inhibitors of the RAS in relation to AER status in 43 patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} who were concurrently found to have normoalbuminuria. The normoalbuminuric status of 23 patients was possibly altered by the use of a RAS inhibitor (i.e., the 17 patients on a RAS inhibitor before attending the clinic and the 6 patients with micro- or macroalbuminuria before the initiation of therapy). *When only patients whose mormalbuminuric status was clearly not influenced by the initiation of a RAS inhibitor were included in the analysis, the prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria was 20 of 86 (23%). For these patients there was no evidence to suggest that reversion from persistent micro- or macroalbuminuria to normoalbuminuria occurred with the use of non–RAS anti-HT agents.*

of GFR in routine clinical practice, i.e., the plasma clearance of a radioisotopic marker (DTPA). The Brochner-Mortensen correction was used to modify a one-compartment model of DTPA clearance as uncorrected values are known to overestimate GFR (8). The study was limited to patients with type 2 diabetes because the relationship between AER and the various stages in the development of renal dysfunction is less well defined than in type 1 diabetes. Also, our work has suggested that the combination of impaired renal function and normoalbuminuria is more prevalent in patients with type 2 diabetes (3).

The overall prevalence of a GFR <60 ml · min^{-1} · 1.73 m^{-2} and normoalbuminuria in this study was 39% (43 of 109). After excluding patients that did not have a documented history of normoalbuminuria before the initiation of a RAS inhibitor, approximately one-quarter (23%) of patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} still had normoalbuminuria. A recent study of 105 longstanding normoalbuminuric patients with type 1 diabetes found that 23 (22%) had a low GFR (<90 ml · min^{-1} · 1.73 m^{-2}) estimated by either isothalamate or creatinine clearance (2). The exact prevalence of the relationship between low GFR and normoalbuminuria in patients with type 1 or type 2 diabetes is yet to be compared in the same study population using stringent GFR cutoffs estimated by isotopic techniques. Results from the Third National Health and Nutrition Survey (NHANES III) in which albuminuria and GFR were estimated from a random urinary albumin-to-creatinine ratio and serum creatinine levels, respectively, show that the finding of nonalbuminuric renal insufficiency in diabetes is not uncommon (11). In their community-based study, the prevalence of nonalbuminuric renal insufficiency in subjects with diabetes of similar age to those in our study, i.e., 60 to 79 years, was 34% for an estimated GFR <30 ml · min^{-1} · 1.73 m^{-2} and 47% for an estimated GFR 30–60 ml · min^{-1} · 1.73 m^{-2}. However, one of the limitations of their study was that the use of specific medications such as RAS inhibitors was not accounted for.

Glomerular lesions typical of diabetic nephropathy have been described in longstanding microalbuminuric patients with type 1 diabetes and a reduced GFR (1,2). In the absence of renal ultrastructural information, only limited conclusions can be drawn regarding the possible pathogenesis of impaired renal function and normoalbuminuria in patients with type 2 diabetes. There is a paucity of information available regarding the renal morphology of normoalbuminuric patients with type 2 diabetes, regardless of their GFR.

In contrast, only a minority of microalbuminuric patients with type 2 diabetes and preserved kidney function display renal structural changes that are typical of diabetic glomerulopathy. However, pathology that can be ascribed to well-recognized forms of nondiabetic renal disease appears to be rare. The most common renal changes reported for this clinical context include normal or near-normal renal structure and atypical patterns or injury including tubulointerstitial lesions, advanced glomerular arteriolar hylanosis, and global glomerular sclerosis (5). For macroalbuminuric patients with type 2 diabetes and various degrees of renal impairment, structural changes apart from those of diabetic glomerulopathy are also not an uncommon finding, but the exact prevalence of recognized nondiabetic forms of glomerular pathology is controversial (4,12–15).

In the present study, the prevalence of retinopathy, duration of diabetes, glycemic control, smoking history, history of vascular disease, lipid levels, and blood pressure (after adjustment for age and sex) were similar in patients with a GFR <60 ml · min^{-1} · 1.73 m^{-2} regardless of the association with normo-, micro-, or

macroalbuminuria. In comparison to macroalbuminuric patients, the association of a GFR <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and normoalbuminuria was more likely in older and female patients. A female predilection for normoalbuminuria and impaired renal function has been noted previously (1–3) and to date the reason for this association is unknown.

The main limitation of this study was that the results were predominantly obtained from a cross-sectional survey of patients with type 2 diabetes. Information regarding the biochemical, clinical, and renal status for patients at baseline, i.e., when patients had a normal GFR and normoalbuminuria, was not available. Significant differences in the above variables at baseline may therefore still exist for patients destined to reach a significant degree of renal impairment with or without a rise in AER. Another limitation was that temporal changes in GFR were only calculated for a limited subset of patients with a GFR <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and that the initial GFR for these patients was not always within the normal range.

For healthy nondiabetic individuals, the rate of decline in GFR with age has been reported to range between 0.6 and 1.0 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} $\cdot$ year^{-1} when estimated from serum creatinine or creatinine clearance (16–18). The rate of decline in renal function for a subset of normoalbuminuric patients in this study (-4.6 ± 1.0 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} $\cdot$ year^{-1}) is clearly greater than that related to aging alone. It should also be noted that the rate of decline in patients who had a GFR of <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and normoalbuminuria was not different to that observed for micro- and macroalbuminuric patients. This rate of decline in GFR is also similar to that reported in other studies of patients with type 2 diabetes and macroalbuminuria when GFR is estimated by isotopic methods (19–21) or from creatinine clearance (22,23).

In summary, the prevalence and characteristics of patients with type 2 diabetes at a single tertiary referral center who have nonalbuminuric renal insufficiency have been defined. One of the strengths of this study was that GFR was measured for all patients by the plasma clearance of a radioisotopic marker modified using the Brochner-Mortensen correction, and a GFR of <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} was used to define renal insufficiency. Although the majority of patients with impaired renal function were found to have micro- (35%) or macroalbuminuria (26%), a significant proportion (39%) had normoalbuminuria. After accounting for the use of RAS inhibitors, the prevalence of impaired renal function and normoalbuminuria was still not insignificant, i.e., 23%.

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