Higher Levels of Urinary Albumin Excretion Within the Normal Range Predict Faster Decline in Glomerular Filtration Rate in Diabetic Patients

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OBJECTIVE — To assess the relationship between albuminuria, including elevation within the normal range, and decline in glomerular filtration rate (GFR) in diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 5,449 Japanese diabetic patients were categorized according to sex and urinary albumin-to-creatinine ratio (ACR; <5, 5–9, 10–29, 30–99, 100–299, 300–999, 1,000–2,999, and ≥3,000 mg/g) and followed for at least 5 years. The rate of change in estimated GFR (eGFR) adjusted for age and baseline eGFR was compared among ACR categories.

RESULTS — A higher baseline ACR predicted a faster decline in eGFR for both sexes. Even within the normal range (<30 mg/g), ACR ≥10 mg/g in women and ≥5 mg/g in men was associated with a significantly greater rate of decline in eGFR relative to subjects with ACR <5 mg/g.

CONCLUSIONS — Elevated ACR, even within the normal range, is associated with a faster decline in eGFR in diabetic patients.

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Albuminuria and proteinuria are associated with subsequent progression of diabetic kidney disease (1–3). Recent studies suggest that elevated urinary albumin excretion, even within the normal range, is also associated with a greater risk of cardiovascular disease (4–6). Because normal urinary albumin excretion is defined using an arbitrary cutoff value (albumin-to-creatinine ratio [ACR] <30 mg/g [7]), we sought to determine whether diabetic patients with high-normal–range ACR have a faster decline in glomerular filtration rate (GFR).

RESEARCH DESIGN AND METHODS

— The study was conducted in accordance with the Declaration of Helsinki. Subjects were recruited from Japanese patients with type 1 and type 2 diabetes, 18 years or older, who visited the Diabetes Center, Tokyo Women's Medical University Hospital, between February 1995 and May 2003. Subjects were eligible for inclusion if they had at least two determinations of urinary ACR and at least one measurement of serum creatinine within the 12-month baseline period. Patients were excluded if they had been treated with renal replacement therapy at baseline or started renal replacement therapy within 5 years of the baseline assessment, or if they had <5 years of follow-up since the first measurement of serum creatinine. Patients were also excluded if their baseline value of estimated GFR (eGFR) was ≥200 ml/min per 1.73 m^2 (considered physiologically implausible [8]).

Geometric mean ACR was determined from two consecutive first-morning urine samples and used to categorize subjects as follows: normoalbuminuria (ACR <30 mg/g), microalbuminuria (ACR 30–299 mg/g), and macroalbuminuria (ACR ≥300 mg/g) (7). Subjects were further divided by sex into eight ACR subcategories: <5, 5–9, 10–29, 30–99, 100–299, 300–999, 1,000–2,999, and ≥3,000 mg/g.

The primary outcome was the rate of change in eGFR during the follow-up period. GFR was estimated using the following modified three-variable equation for Japanese, as recently proposed by the Japanese Society for Nephrology: $GFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female) (9). The rate of change in eGFR per year was determined using a simple regression analysis, applied to all estimates of GFR obtained during the follow-up period (10). Patients were followed at least 5 years.

The rate of change in eGFR, expressed as least-square mean ± SE, was compared among ACR categories and subcategories using ANCOVA (SAS/STAT version 9.13; Cary, NC). A P value <0.05 was considered significant.

RESULTS

— A total of 5,449 diabetic patients had sufficient baseline and follow-up data to qualify for inclusion. The study population (15% type 1 diabetes) included 2,359 women and 3,090 men with a mean (±SD) age of 53 ± 14 years (range 18–87). Mean baseline serum creatinine levels and eGFR were 0.65 ± 0.22 mg/dl (0.24–4.66) and 95.7 ± 25.8 ml/min per 1.73 m^2 (11.9–199.9), respectively. The mean follow-up period was 9.2 ± 2.4 years (5.0–13.1).

Among ACR categories and subcategories, higher levels of ACR were associated with a faster decline in eGFR for both women and men (Fig. 1 and the Supplemental Table, available in the online-only

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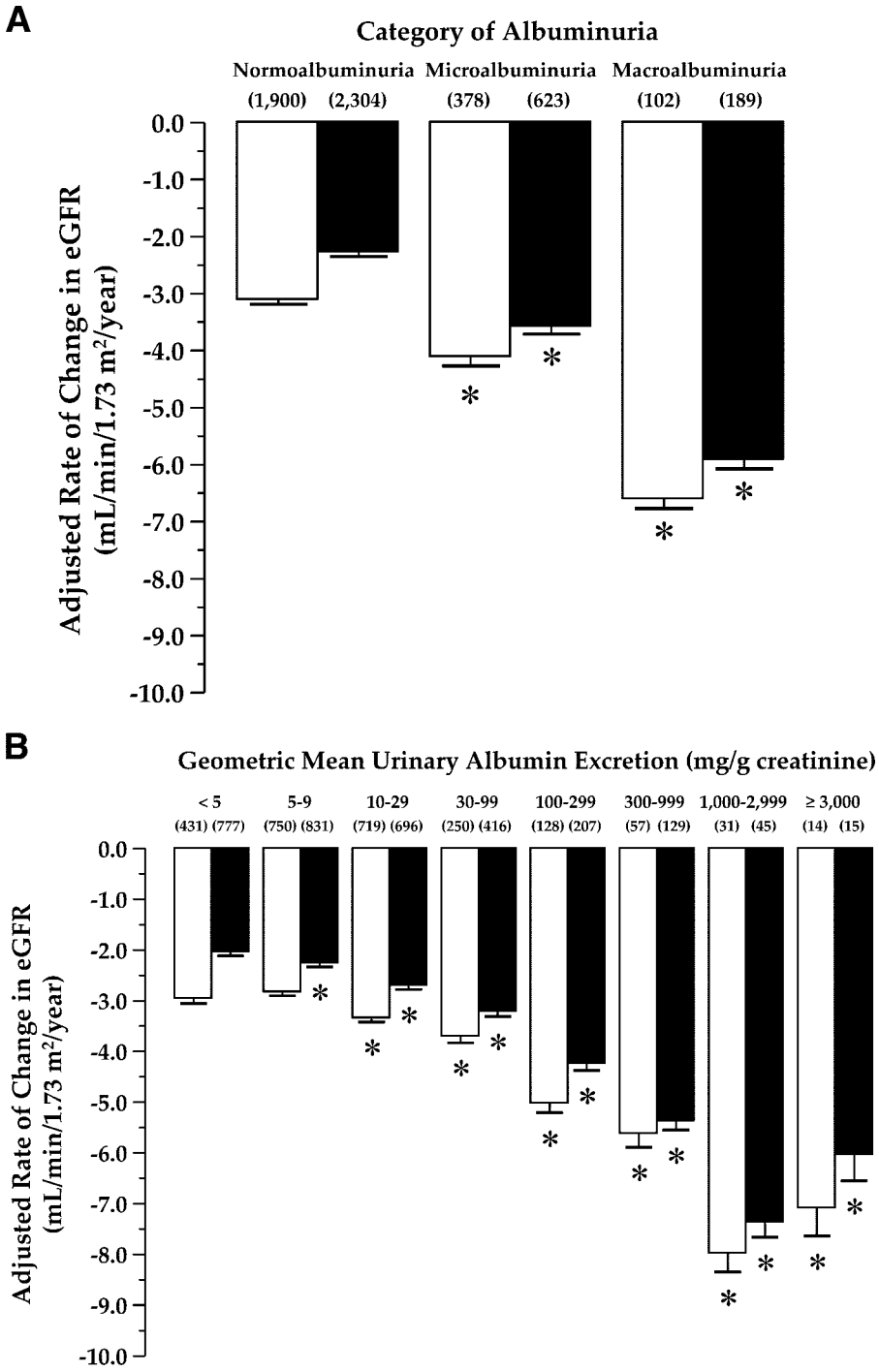

Figure 1—*Comparison of the rate of change in eGFR, adjusted for age and baseline eGFR, among traditional categories* (A) *and subcategories of the urinary ACR* (B)*, based on the geometric mean of two consecutive measurements. White and black bars represent least-square mean (±SE) for women and men, respectively.* *P < *0.05 vs. normoalbuminuria* (A) *and ACR <5 mg/g creatinine* (B)*, by ANCOVA.*

appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-2151/DC1). Even within the normal range (<30 mg/g), ACR ≥10 mg/g in women and ≥5 mg/g in men was associated with a significantly greater rate of decline in eGFR relative to subjects with ACR <5 mg/g. When analyzed for all eight ACR subcategories, women had a faster decline in eGFR than men ($P < 0.001$). For both sexes, the rate of decline in eGFR was maximal for the ACR 1,000–2,999 mg/g subcategory and slightly lower for the highest ACR subcategory.

CONCLUSIONS — In this large hospital-based observational cohort study in Japanese diabetic patients, we observed a greater rate of decline in eGFR in subjects with higher levels of ACR, even within the arbitrarily defined normal range. These data support previous studies showing a close relationship between albuminuria and rapid progression of diabetic kidney disease (1–3) and suggest such a relationship may extend to conventionally defined normoalbuminuria. Recent studies indicate the risk of cardiovascular disease and death increases for high-normal–range albuminuria (4–6), raising the issue whether a new definition of normoalbuminuria should be advocated (4–6,11).

The relationship between baseline ACR and rate of decline in eGFR was apparent for both sexes but with subtle differences. Although the rate of decline in eGFR tended to be greater in normoalbuminuric women, a stronger relationship was observed between higher ACR (in the normal range) and the rate of decline in eGFR in men. Our study suggests that the threshold of ACR identifying diabetic patients with a higher risk of progression of diabetic kidney disease may be lower in men than women, consistent with previous investigations advocating a lower cutoff value for albuminuria in men (12,13). The relatively fast rate of decline in eGFR in patients in this study compared with that reported in other studies (14) may be explained by differences in the duration of follow-up, higher baseline eGFR, presence of diabetes, racial factors, or other differences in this population.

This study addresses the association between baseline values of ACR and the change in GFR over time, without assessing intra-individual change in ACR. Thus, the study does not differentiate between patients in the normal range who had static or increasing values of ACR. Further studies are needed to determine whether increasing ACR values over time may predict a faster decline in GFR. Other limitations of this study include its ethnically and socially homogenous population and possible underestimation of the decline in eGFR in patients with higher levels of baseline ACR due to exclusion of patients starting renal replacement therapy during the 5-year follow-up. Nevertheless, the study's large sample size, long duration of follow-up, and consistent use of first-morning specimens (15) strengthen its potential relevance to clinical practice.

In conclusion, higher levels of ACR, even within the normal range, are associated with a faster decline in eGFR in diabetic patients. Further studies are needed to determine whether lower and/or sex-specific thresholds for ACR, or sensitive measurements of incremental rise in ACR over time, may be useful to indentify diabetic patients at a higher risk for progression of diabetic kidney disease.

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