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, 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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appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-2151/DC1). Even within the normal range (0–10 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 identify diabetic patients at a higher risk for progression of diabetic kidney disease.

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