COMMENTS AND RESPONSES

Pro12Ala Polymorphism in the *PPARG* Gene Contributes to the Development of Diabetic Nephropathy in Chinese Type 2 Diabetic Patients

Comment on the study by Liu et al.

We read with interest the article by Liu et al. (1) showing that the Pro/Pro genotype of the peroxisome proliferator–activated receptor (PPAR)-γ2 is a significant independent predictor of the development of diabetic nephropathy in a large population of Chinese type 2 diabetic patients. The study confirms, in a different ethnic group, what has already been shown in relatively small studies conducted in Caucasian diabetic patients (i.e., a population with lower prevalence of diabetic nephropathy and higher frequency of Pro12Ala genotype than the Chinese population), although none of these studies provides a complete evaluation of renal function (2–4). We report data that confirm the association between the Pro12Ala polymorphism of PPAR-γ2 and urinary albumin excretion rate (AER) in a large population of type 2 diabetic patients and expand current knowledge by also providing data on other parameters of renal function (i.e., urea, creatinine, and glomerular filtration rate [GFR]). We studied 750 type 2 diabetic male and female patients. The proportion of ProAla + AlaAla carriers was 12.1% ($n = 91$) and the distribution of the PPAR-γ2 genotype was in Hardy-Weinberg equilibrium and similar to that observed in other Caucasian populations. Urinary excretion rate was measured on a single occasion on a morning urine sample with the ELISA method and expressed as albumin-to-creatinine ratio; plasma urea and creatinine concentration was also measured, and GFR was estimated using the Modification of Diet in Renal Disease. Carriers of the Ala allele had lower AER than subjects with the Pro/Pro genotype (i.e., 40.7 ± 78.1 vs. 72.5 ± 257 μg/mg, $P = 0.018$), plasma urea and creatinine were also lower in this group (i.e., 36.3 ± 8.6 vs. 39.5 ± 12.6 mg/dl, $P = 0.021$ and 0.78 ± 0.17 vs. 0.85 ± 0.44 mg/dl, $P = 0.003$, respectively); accordingly, estimated GFR was significantly higher in carriers of the ALA allele (97.6 ± 22.9 vs. 94.4 ± 22.9 ml/min/1.73 m^2, $P = 0.04$) than Pro/Pro carriers. Furthermore the proportion of subjects with mildly impaired renal function (i.e., GFR <60 ml/min/1.73 m^2 or creatinine ≥1.2 mg/dl) was significantly lower in participants with the Pro12Ala than the Pro/Pro genotype (2.2% vs. 8.1%, $P = 0.05$; odds ratio 0.90 [CI 0.85–0.96]). As for possible confounders, we failed to find any difference between the two genotype groups with respect to age, diabetes duration, sex, BMI, waist circumference, systolic and diastolic blood pressure, A1C, total and HDL cholesterol, triglycerides, proportion of current smokers, and proportion of patients on antihypertensive medication or statins. High-sensitivity C-reactive protein and homeostasis model assessment of insulin resistance—the first a marker of subclinical inflammation and the second a marker of insulin resistance—are two conditions possibly associated with the development of diabetic nephropathy (5). They were similar in the two genotype groups (4.74 ± 7.4 vs. 6.3 ± 12 mg/l and 4.58 ± 3.8 vs. 4.95 ± 2.92 mg/l, respectively, for Pro/Pro or Ala carriers).

In conclusion, we confirm the association of the Pro12Ala polymorphism of PPAR-γ2 with lower AER in a large population of Caucasian type 2 diabetic patients and expand current knowledge by showing that the Pro12Ala polymorphism of PPAR-γ2 is associated with overall better renal function.

EMANUELA LAPICE, MD[1]
MICHELE PINELLI, MD[2]
GABRIELE RICCARDI, MD[1]
OLGA VACCARO, MD[1]

From the [1]Department of Clinical and Experimental Medicine, University of Naples Federico II, Naples, Italy; and the [2]Department of Cellular and Molecular Biology and Pathology, A. Califano DBPCM, University of Naples Federico II, Naples, Italy.

Corresponding author: Olga Vaccaro, ovaccaro@unina.it.

DOI: 10.2337/dc10-0596

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

E.L. researched the data and wrote the letter; M.P. researched the data; G.R. reviewed and edited the letter; and O.V. wrote, reviewed, and edited the letter.

References

1. Liu L, Zheng T, Wang F, Wang N, Song Y, Li M, Li L, Jiang J, Zhao W. Pro12Ala polymorphism in the PPARG gene contributes to the development of diabetic nephropathy in Chinese type 2 diabetic patients. Diabetes Care 2010;33:144–149
2. Caramori ML, Canani LH, Costa LA, Gross JL. The human peroxisome proliferator-activated receptor γ2 (PPARγ2) Pro12Ala polymorphism is associated with decreased risk of diabetic nephropathy in patients with type 2 diabetes. Diabetes 2003;52:3010–3013
3. Herrmann SM, Ringel J, Wang JG, Staessen JA, Brand E, Berlin Diabetes Mellitus (BeDiaM) Study. Peroxisome proliferator-activated receptor-γ2 polymorphism Pro12Ala is associated with nephropathy in type 2 diabetes: The Berlin Diabetes Mellitus (BeDiaM) Study. Diabetes 2002;51:2653–2657
4. De Cosmo S, Motterlini N, Prudente S, Pellegrini F, Trevisan R, Bossi A, Remuzzi G, Trischitta V, Ruggenenti P, BENEDICT Study Group. Impact of the PPAR-γ2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: evidence from BENEDICT. Diabetes 2009;58:2920–2929
5. Yang J, Zhang D, Li J, Zhang X, Fan F, Guan Y. Role of PPARγ in renoprotection in type 2 diabetes: molecular mechanisms and therapeutic potential. Clin Sci (Lond) 2009;116:17–26