

Response to Comment on: Wanic et al. (2008) Exclusion of Polymorphisms in Carnosinase Genes (*CNDP1* and *CNDP2*) as a Cause of Diabetic Nephropathy in Type 1 Diabetes: Results of Large Case-Control and Follow-Up Studies: *Diabetes* 57:2547–2551, 2008

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We thank Bakker et al. (1) for their concern about the factors affecting risk of end-stage renal disease (ESRD) and their appreciation of the issues relating to survival bias. In the original report (2), the Cox proportional hazards regression model of ESRD risk according to carnosinase genotype was adjusted for sex, duration of diabetes, age at examination, age at diagnosis of diabetes, and use of ACE inhibitor treatment. As reported, there was no effect of genotype on the risk. To address the reservations raised by Bakker et al., we ran additional Cox proportional hazards regression models including glomerular filtration rate (GFR), calculated using the Modification of Diet in Renal Disease equation, and the log of the albumin excretion rate (AER). Models including the original covariates as well as log AER and GFR did not reveal any difference in genetic risk, individually or combined.

In addition to identifying incident cases of ESRD, our prospective study of 445 patients with proteinuria allowed us to identify 27 fatalities before the onset of ESRD. To examine the potential bias introduced by early mortality, we ran additional Cox proportional hazards regression models treating these patients as cases of ESRD. Again, carnosinase genotype had no effect on risk. The hazard ratios for both the inclusion of non-ESRD deaths as cases and the inclusion of all covariates are reported in Table 1.

However, although we performed the analysis to address the concerns of Bakker et al., we do not agree that it is appropriate to adjust for renal function or level of proteinuria when investigating genetic factors contributing to progression to ESRD. When the outcome measured

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TABLE 1

Hazard ratios reported in the original manuscript as well as those adjusted for covariates and accounting for non-ESRD mortality

Polymorphism	Genotype	Reported	Adjusted*
rs12954438	A/A A/G	1.0 (Ref.)	1.0 (Ref.)
	G/G	1.02 (0.67–1.53)	0.96 (0.65–1.42)
rs890332	G/G A/G	1.0 (Ref.)	1.0 (Ref.)
	A/A	1.02 (0.67–1.53)	0.96 (0.65–1.42)
rs11151964	A/A A/G	1.0 (Ref.)	1.0 (Ref.)
	G/G	1.04 (0.69–1.56)	0.95 (0.65–1.39)
D18S880	55	1.0 (Ref.)	1.0 (Ref.)
	5X	1.34 (0.90–2.02)	1.01 (0.69–1.47)
	XX	0.79 (0.44–1.39)	0.65 (0.39–1.09)

Data are hazard ratio (95% CI). *Adjusted for sex, duration of diabetes, age at examination, age at diagnosis of diabetes, use of ACE inhibitors, GFR, and log AER. Also, this analysis treats as cases 27 patients who died prior to the onset of ESRD.

is ESRD, it is not appropriate to control for GFR or proteinuria at baseline (3–4) because these covariates are intermediate phenotypes for the outcome of interest. Their inclusion as exposures may reduce or eliminate the effect of genetic factors hypothesized to be contributing to the development of ESRD. In summary, we are still confident in our conclusion that genetic variants in the carnosinase genes do not confer any risk toward the progression to ESRD.

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