CORRESPONDENCE

To the Editor:

Niskanen et al[1] recently reported that the *Pro12Ala* polymorphism of the *PPAR-γ2* gene is related to increased levels of oxidized low-density lipoprotein (LDL) autoantibodies in patients with type 2 diabetes mellitus and suggested that the genotype may modulate the oxidative modification of LDL in hyperglycemia.

In a cross-sectional biomolecular study of 900 subjects (Pizarra study, a town in the province of Málaga, southern Spain),[2,3] we examined the relation between *Pro12Ala* polymorphism of the *PPAR-γ2* gene, levels of antioxidized LDL autoantibodies, and diabetes mellitus. The prevalence of nondiabetic persons was 60.3%, of impaired fasting glucose 12.4%, of impaired glucose tolerance 12.4%, of unknown diabetes mellitus 9.0%, and of known diabetes mellitus 5.9%. The homeostatic model assessment (HOMA) pattern of insulin resistance was also studied in all subjects (data not yet published). Oxidized LDL autoantibodies were measured by enzyme-linked immunosorbent assay (ELISA).[4] The overall level of oxidized LDL autoantibodies was 0.30 ± 0.12 optic density (OD). No differences were found depending on the presence of *PPAR-γ2* polymorphisms. Differences found in levels of oxidized LDL autoantibodies according to various carbohydrate metabolism disorders disappeared after adjusting for age and sex. Previously we found a negative relation between levels of antioxidized LDL autoantibodies and plasma LDL-cholesterol.[4] In this study, 13% of the variance in oxidized LDL autoantibodies was explained by age ($\beta = -0.0027$; SE$\beta = .00037$; $P < .0001$) and LDL-cholesterol ($\beta = -0.0003$; SE$\beta = 0.00011$; $P = .008$), independently of *PPAR-γ2* genotype and presence of carbohydrate metabolism disorder. Differences found in oxidized LDL autoantibody levels in the presence of a carbohydrate metabolism disorder disappeared after adjusting for age and LDL levels.

There are several explanations for the differences between our study and that of Niskanen et al. First, Niskanen et al measured antioxidized LDL autoantibodies modified with Cu^{2+}, whereas the antioxidized LDL autoantibodies in our study were modified with malonaldehyde bis(dimethyl acetal) (MAD). Nevertheless, both antioxidized LDL autoantibody techniques are reported to be valid.[5,6] Second, the probability of error in Niskanen's study was .043, which is very near the accepted rejection level of .05. This could have resulted in a type I error. Third, their control group was selected from the reference population instead of the whole normal study population. Furthermore, only half the diabetic patients initially selected for the study were studied genetically. Finally, the prevalence of the *PPAR-γ2* Ala12 allele was slightly different in our study (nondiabetic persons 0.15, IFG 0.11, IGT 0.12, and diabetes mellitus 0.11; difference not significant [NS]) compared to Niskanen's study (nondiabetic persons 0.12, diabetic patients 0.11; NS).

Our study also included different degrees of glucose tolerance as well as a measurement of insulin resistance but no slope in risk was found between *PPAR-γ2* and insulin resistance or oxidized LDL autoantibodies.

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REPLY

To the Editor:

We thank Dr Gomez-Zumaquero and colleagues for their interest in this evidently very complex issue. The response refers to the Pro12Ala polymorphism of *PPAR-γ2* gene, which according to our study may modulate the levels of oxidized LDL antibodies in patients with long-standing type 2 diabetes.[1] As in all association studies in genetics, there may be population-specific frequencies or differences in expression. The methods of measuring oxidized LDL antibodies in our study as well as in the study by Gomez-Zumaquero both seem to be valid. However, we have found in several studies in our laboratory that oxidized LDL antibody levels are different when Cu- and MDA-

modified LDL has been used as an antigen. Therefore, the results are not directly comparable. Furthermore, the interpretation of our adjusted *P* value of .043 in diabetic patients as very close to type 1 error on the cross-sectional analysis of the 10-year follow-up is oversimplification. The study population was followed-up for 10 years, and even at the time of diagnosis of diabetes there was a trend to this association ($P = .077$ and after adjustment $P = .091$). Therefore Gomez-Zumaquero and coworkers should follow-up their diabetic patients[2,3] and repeat their measurements to exclude time- and genotype-related changes in oxidized LDL antibodies in their population. As to the control population in our study, it has been thoroughly described in earlier publications[4] and consisted of a representative random sample from the population register which has a 100% coverage of the Finnish population. Finally, we agree with Gomez-Zumaquero et al, that the relationship between oxidized LDL antibodies and atherosclerosis is very complex and in fact, in this same diabetic study population, oxidized LDL antibodies did not predict cardiovascular events or association with carotid intima-media thickness.[5]

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