RESPONSE TO COMMENT ON LOPES-VIRELLA ET AL.

Baseline Markers of Inflammation Are Associated With Progression to Macroalbuminuria in Type 1 Diabetic Subjects. Diabetes Care 2013;36:2317–2323

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Diabetes Care 2014;37:e108–e109 | DOI: 10.2337/dc13-2976

We appreciate the comments of Drs. Jialal and Devaraj (1) on our article (2). Our study was run concomitantly with the study reported by Joslin investigators (3) and reached similar conclusions concerning the predictive value of soluble tumor necrosis factor (TNF) receptors in nephropathy progression. We mentioned their results in our discussion. We did not mention the possible role of increased Toll-like receptor (TLR) activity in triggering the TNF pathway as other alternative explanations could better explain our findings. We previously published data showing that oxidized LDL immune complexes (oxLDL-ICs) are associated with and predict the development of proteinuria (4) and that oxLDL-ICs are much stronger activators of the TNF pathway than oxLDL, which activates innate immunity through the interaction with TLR-4 (5).

The concern over the relationship between soluble vascular cell adhesion molecule-1 (sVCAM-1), lipid parameters, and the development of macroalbuminuria is quite valid. We had the same concerns and for that reason the findings were not incorporated in the abstract or conclusions, but only in the text. We are confident that sample integrity is not behind the controversial findings for sVCAM-1. *1*) Frozen samples received from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study were aliquoted when the sample was first unthawed and all the aliquots were frozen immediately. A fresh frozen aliquot was retrieved for any measurement performed thereafter, avoiding thawing and unthawing of samples. *2*) A randomly selected subgroup of samples collected during 1997–1999 in which adhesion molecules were run at the time of collection were rerun in 2009 in frozen aliquots, and the levels were not statistically different from the original measurements. *3*) Our levels for soluble intracellular adhesion molecule-1 and sVCAM-1 were higher than those reported in 2008 in the same samples by the Harvard group (5), who similarly did not find an association between sVCAM-1 levels and change in albumin excretion rate levels over time. Specifically, they used mixed-effects regression to examine the relationship between sVCAM-1 tertiles and change in albumin excretion rate throughout DCCT.

We decided to report the sVCAM-1 data regardless of our inability to logically explain the results as we firmly believe that properly collected data, even when discordant from current dogma, should be reported. Although the reason for the apparent discrepancy is not obvious now, possible reasons may emerge in the future and it is important for advancement of science to record "unexpected" findings when there is no valid reason to exclude them.

Sufficient data are presently available to allow us to conclude that endothelial dysfunction is associated with nephropathy in type 1 diabetes (6–8). Whether specific adhesion molecules or clusters of adhesion molecules are more predictive of disease progression than others may depend on the stage of disease at the time of the sample collection and the outcome being assessed. Adhesion molecule families are functionally distinct and their impact may be seen at different stages of disease. The data reported by several investigators, including our own, will help in the design of future, more detailed studies.

Funding and Duality of Interest. This work was supported by the grant R01-DK-081352 funded by National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK). This work was also supported by the Research Service of the Ralph H. Johnson Medical Center, Department of the Veterans Affairs. The DCCT/EDIC was sponsored through research contracts from the Division of Diabetes, Endocrinology and Metabolic Diseases (NIDDK) of the NIH. Additional support

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The contents of this article do not represent the views of the Department of Veterans Affairs or the U.S. government.

was provided by the National Center for Research Resources through the General Clinical Research Centers program and by Genentech, Inc., through a Cooperative Research and Development Agreement with the NIDDK. No other potential conflicts of interest relevant to this article were reported.

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