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

Ishwarlal Jialal[1] and Sridevi Devaraj[2]

Diabetes Care 2014;37:e106–e107 | DOI: 10.2337/dc13-2420

Lopes-Virella et al. (1) recently reported on a substudy of the Diabetes Control and Complications Trial (DCCT) and claimed that in addition to the soluble tumor necrosis factor receptors (TNFR)-1 and -2, a biomarker of endothelial dysfunction, soluble E-selectin (sE-selectin) is also a predictor for macroalbuminuria in type 1 diabetes (T1D). The data on TNFR-1 and -2 confirm previous work from the Joslin group with respect to prediction of chronic kidney disease (CKD) (2). However, the interpretation of the data with respect to biomarkers of endothelial function is of great concern. In this study, four biomarkers of endothelial function were reported, two specific (sE-selectin and soluble vascular cell adhesion molecule-1 [sVCAM-1]) and two less specific (soluble intracellular adhesion molecule-1 [sICAM-1] and plasminogen activator inhibitor 1 [PAI-1]).

While they conclude that increasing sE-selectin predicts macroalbuminuria, they present confusing data with respect to sVCAM-1. They show that low levels of sVCAM-1 predict macroalbuminuria after covariate adjustment (see Table 3 in ref. 1). Also, they show an inverse correlation of sVCAM-1 with LDL-cholesterol, HbA_{1c}, and triglycerides, but positive correlations with sE-selectin. If VCAM-1 is accepted like E-selectin as a biomarker of endothelial dysfunction, then the consensus is that levels are increased and not decreased when these noxious insults impact the endothelium. The unexpected negative and biologically implausible correlations with LDL-cholesterol, HbA_{1c}, and triglycerides are ignored. An obvious explanation that may contribute to this paradoxical finding of decreased sVCAM-1 in T1D with macroalbuminuria is sample integrity, as it appears that these samples were drawn in 1999–2000 and the stability of the biomarkers over time could have been compromised. The authors do not state clearly if there was thawing and freezing of the frozen samples. Undertaking comparative electrophoretic studies on fresh samples and the samples reported in this study could help elucidate this by confirming absence of proteolysis of VCAM-1. Until then the authors cannot draw any firm conclusions with respect to endothelial dysfunction and macroalbuminuria on the basis of one of four biomarkers of endothelial function in T1D. Furthermore, the Joslin group failed to show that biomarkers of endothelial dysfunction predicted CKD.

Finally, the authors did not mention in the article and may be unaware that there is increased Toll-like receptor (TLR) activity in patients with T1D, and the TNF pathway is triggered by activation of certain TLRs (3). Pertinent to the role of TLRs, studies show that knockout of TLR-2 results in an amelioration of albuminuria and diabetic nephropathy (4). Other groups have showed a similar benefit with knockout of TLR-4. Hence, the TLR pathway is the more valid explanation for the increase in TNF and TNFR-1 and -2. A role for the TNF in diabetic nephropathy cannot be excluded at this point (5). Also, the authors fail to report on TNF levels, as TNFRs are decoy receptors for TNF and the increase in TNFR-1 and -2 is probably a compensatory mechanism to limit further tissue damage by TNF. In the Joslin studies (2), total TNF predicted CKD but significance appeared to be lost in the multivariate model. While Lopes-Virella et al. (1) coupled with the Joslin studies support a role of these biomarkers as predictors of CKD, a definite role of TNF and TNFR cannot be excluded until clinical trials are conducted.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. Lopes-Virella MF, Baker NL, Hunt KJ, et al.; DCCT/EDIC Research Group. Baseline markers of inflammation are associated with progression to macroalbuminuria in type 1 diabetic subjects. Diabetes Care 2013;36:2317–2323
2. Gohda T, Niewczas MA, Ficociello LH, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. J Am Soc Nephrol 2012; 23:516–524
3. Devaraj S, Dasu MR, Rockwood J, Winter W, Griffen SC, Jialal I. Increased toll-like receptor (TLR) 2 and TLR4 expression in monocytes from patients with type 1 diabetes: further

[1]*Division of Endocrinology, Metabolism and Diabetes, Department of Internal Medicine, University of California, Davis, Davis, CA*
[2]*Department of Pathology and Immunology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX*
Corresponding author: Ishwarlal Jialal, ishwarlal.jialal@ucdmc.ucdavis.edu.

evidence of a proinflammatory state. J Clin Endocrinol Metab 2008;93:578–583
4. Devaraj S, Tobias P, Kasinath BS, Ramsamooj R, Afify A, Jialal I. Knockout of toll-like receptor-2 attenuates both the proinflammatory state of diabetes and incipient diabetic nephropathy. Arterioscler Thromb Vasc Biol 2011;31:1796–1804
5. Navarro-González JF, Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol 2008;19:433–442