Response to Comment on: Sukumar et al. Nox2 NADPH Oxidase Has a Critical Role in Insulin Resistance–Related Endothelial Cell Dysfunction. Diabetes 2013;62:2130–2134

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We would like to thank Drs. Jandeleit-Dahm and Schmidt (1) for their interesting comments regarding our study examining the role of the Nox2 isoform of NADPH oxidase in insulin resistance–related endothelial cell dysfunction (2). We would also like to congratulate them on their own elegant and comprehensive piece of work examining the role of the Nox isoforms Nox1, Nox2, and Nox4 in the development of advanced type 1 diabetes–related atherosclerosis (3).

Based on their findings that Nox1 may be more important in diabetes-related atherosclerosis than other isoforms of NADPH oxidase, the authors raise concerns regarding our conclusions that Nox2 has a critical role in insulin resistance–related endothelial dysfunction. They also reported that holoinsufficiency of Nox2 in mice rendered diabetic using streptozotocin led to a substantial mortality rate.

It is important to recognize the fundamental differences between our studies and those of Jandeleit-Dahm and colleagues (3). Jandeleit-Dahm and colleagues and You et al. (4) administered streptozotocin to render mice diabetic. In the article by Jandeleit-Dahm and colleagues, this led to a severe model of advanced insulin-deficient diabetes leading to substantial weight loss, hyperglycemia, and increased triglycerides and cholesterol. Moreover, it is well established that streptozotocin-induced diabetes leads to immune dysfunction (5), which may account for the findings reported by Jandeleit-Dahm and colleagues regarding mortality in Nox2 deficient mice. A comparison between our study and that of Jandeleit-Dahm and colleagues is therefore difficult to make.

In our studies, we used two complementary models of human disease before the onset of hyperglycemia with the ApoE gene intact: *1*) endothelium-specific insulin resistance (mice expressing a mutant human insulin receptor specifically in the endothelium) and *2*) whole-body insulin resistance (mice with haploinsufficiency of the insulin receptor). We found no increase in Nox1 or Nox4 expression in endothelial cells from these mice, but did demonstrate increased Nox2. Mice with endothelium-specific insulin resistance deficient in Nox2 or mice treated with the Nox2 inhibitor gp91ds-tat did not have increased mortality.

In our studies, acute and chronic inhibition of Nox2 led to restoration of endothelial vasorelaxation and superoxide to the levels seen in wild-type littermates, providing compelling evidence that Nox2 is a critical determinant of endothelial dysfunction in insulin resistance. We did not examine the role of Nox2 in severe hyperglycemia–induced endothelial dysfunction and atherosclerosis. In the commentary to our article, Dr. Symons (6) raised a number of suggestions for future work, one of which was to assess the role of Nox2 in insulin resistance–related atherosclerosis; we are currently pursuing this avenue of work. The work from the laboratories of Drs. Jandeleit-Dahm and Schmidt and our own highlight the complexity of diabetes-related vascular disease and illustrate that a "one size fits all" approach is not appropriate for the treatment of this lethal complication of diabetes.

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