Editorial

Hyperglycemic endothelial dysfunction: does it happen and does it matter?

Robert P. Hoffman

Section of Endocrinology, Department of Pediatrics, The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA

Correspondence to: Professor Robert P. Hoffman, MD. Section of Endocrinology, Nationwide Children's Hospital, 700 Children's Drive, ED422, Columbus, Ohio 43205, USA. Email: Robert.hoffman@nationwidechildrens.org.

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In the September issue of *Arteriosclerosis, Thrombosis and Vascular Biology*, Loader *et al*. (1) present the results of a meta-analysis on the effect of acute hyperglycemia on vascular function. The authors did an extensive search of literature and report on findings in 39 studies that measured endothelial function and/or vascular smooth muscle function during euglycemia and during acute induction of hyperglycemia. The studies varied considerably in terms of subject type, age, method of induction of hyperglycemia, and method of measurement of endothelial function. The authors in the analysis specifically focus on differences between studies that measured macrovascular versus microvascular endothelial function.

The results showed that there may be publication bias present, but that as a whole endothelial function is impaired by acute induction of hyperglycemia and vascular smooth muscle function is not. They specifically found that acute hyperglycemia impaired macrovascular, but not microvascular, endothelial function. The authors emphasize this point several times but also note that fewer studies of microvascular endothelial function (9 *vs*. 30 studies) were performed which may have limited their ability to detect an effect. This is an important limitation because, as they acknowledge, impairments of microvascular endothelial function may lead to impairment of macrovascular function by altering shear stress in the conduit arteries. Clinically, there is no clear evidence regarding whether impairment of macrovascular or microvascular endothelial function is more significant or whether one precedes the development of the other. It is clear, however, that abnormal endothelial function precedes the development of structural vascular changes, such as increases in carotid artery intima medial thickness (2,3). This is also supported by the authors' finding of no effect of hyperglycemia on vascular smooth muscle function.

The fact that endothelial dysfunction is the earliest discernable, pathophysiological precursor to atherosclerotic cardiovascular disease is what makes understanding the effects of hyperglycemia on endothelial function so important. As Loader and colleagues (1) point out, the frequency of pathological hyperglycemia is increasing with increasing obesity and type 2 diabetes and there is also a progressive increase in sugar-sweetened beverage consumption, all of which are going to increase the frequency of hyperglycemia within the population and within a given individual. Thus, if acute hyperglycemia does cause acute endothelial damage, as demonstrated by their results, we are facing the potential of marked increases in future cardiovascular disease. Interestingly, there is evidence both *in vivo* (4) and *in vitro* (5) that increased glucose variability causes more severe endothelial damage than prolonged hyperglycemia. This is a scary possibility as high glucose variability would be expected in individuals who frequently consume sugar-sweetened beverages.

Two key caveats must be considered regarding these findings. Loader *et al*. (1) review the methods of endothelial function measurement but do not describe the precise outcome measures in the studies. Measurement of endothelial function usually involves a ratio or percent change of some post- to pre-intervention measure. The measure may be brachial artery diameter, forearm blood flow, or forearm vascular resistance and the intervention will usually either

be acetylcholine infusion or vascular occlusion. The former directly stimulates endothelial nitric oxide release and the latter creates a shear stress which increases endothelial nitric oxide release. The problem is that if there is a change in the pre-intervention baseline measures it is difficult to truly interpret what changes in the ratio really mean. In many of the studies reviewed, the hyperglycemic intervention would cause not only an increase in glucose but likely a significant increase in insulin as well and insulin is a well-known vasodilator (6) that acts through endothelial stimulation (7). Beyond this hyperglycemia without changes in plasma insulin has been shown to markedly increase baseline forearm blood flow in healthy adults (8) and youth with type 1 diabetes (9). If there is a ceiling effect as to how much vasodilation can be maximally achieved the increase in pre-intervention blood flow would mathematically necessitate a decline in the post- to pre-intervention ratio while maximal vasodilation and endothelial function is unimpaired. Against this potential explanation, however, is a study by Greyling *et al*. (10) which found that increasing blood flow through increasing temperature prevented a hyperglycemic-induced fall in conduit artery flow mediated vasodilation. They hypothesized that this was due to increased shear stress due to increased flow.

The second caveat is that hyperinsulinemia accompanying hyperglycemia may confound the results in many of the reviewed studies. Of the reviewed studies, only in the report by Dye *et al*. (9) of adolescents with type 1 diabetes is it likely that insulin levels are not increased during hyperglycemia and there is likely to be a wide degree of variability to the degree of increase. Endothelial function is impaired during low dose and high dose euglycemic clamp (11). Thus, for most of the studies cited by Loader *et al*. (1) the effect of hyperglycemia cannot be easily separated from the effects of hyperinsulinemia. Beyond this there are likely other hormones involved as demonstrated by the potential protective effects of glucagon like peptide 1 in the study by Ceriello *et al*. (12). From a clinical standpoint separating the effects of hyperglycemia from those of hyperinsulinemia may not matter since the two will usually accompany one another in most clinic situations except in type 1 diabetes or type 2 diabetes with extreme β-cell failure.

In summary, the meta-analysis by Loader *et al*. (1) indicates that induction of hyperglycemia has an acute impact on endothelial function although the exact reasons for the effect are not clear. It is likely that if frequently repeated this hyperglycemia-induced endothelial damage will have significant adverse clinical consequences. Further research will be needed to determine what vascular measurement changes (pre- or post-intervention) are responsible for this decline, on the effects of hyperglycemia on microvascular function, and on the independent roles of glucose, insulin and other hormones. In addition, if we are to prevent future cardiovascular disease we will need to develop interventions to block the effect of hyperglycemia. Early studies with ascorbic acid have shown potential effectiveness (11,13-15).

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Footnote

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