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Acute hyperglycemia impairs flow-mediated dilatation through an increase in vascular oxidative stress: winter is coming for excess sugar consumption

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In two editorials recently published in the *Journal of Thoracic Disease*, Robert P. Hoffman and John David Horowitz *et al*. separately reviewed the interaction between acute hyperglycemia and vascular function (1,2) with a focus on the results of our meta-analysis published in *Arteriosclerosis, Thrombosis and Vascular Biology* (3). We thank the authors for their interest in our research and for their contribution to further understanding the effects of acute hyperglycemia on cardiovascular health.

Hoffman importantly highlighted that although our meta-analysis defined the methods used to assess vascular function, the primary outcome of each study wasn't clearly described. Indeed, it can be confirmed that for all studies included in the meta-analysis, the percentage increase from baseline measurement in response to a specific test of vascular reactivity was the primary outcome for both microvascular data (e.g., acetylcholine and sodium nitroprusside iontophoresis) and macrovascular data (e.g., flow- and nitrate-mediated dilation); and was used to determine standardized mean difference between vascular function in the acute hyperglycemic and normoglycemic states. In agreement with Hoffman, if there is a ceiling effect to the maximal vasodilatory capability of a blood vessel, then variations in baseline measurements due to the potential vasodilating effects of increased blood glucose or blood insulin concentrations during acute hyperglycemia would limit interpretation of the results when expressing vascular data solely as the percentage increase from baseline (1). Given that only a few studies in the meta-analysis provided absolute values for baseline measurements of microcirculatory blood perfusion or brachial artery diameter, comparisons to detect differences in baseline data between the acute hyperglycemic and normoglycemic states were not possible. Such research deficiencies emphasize the need for future studies to clearly report absolute values of vascular function.

Further to this, Hoffman continued to address the potential confounding effects of the hyperinsulinemia that accompanies acute hyperglycemia. Indeed, insulin is a recognised vasodilator that contributes to vascular smooth muscle relaxation in an endothelium-dependent manner by stimulating the synthesis of nitric oxide via the PI3K/Akt pathway and the subsequent activation of endothelial nitric oxide synthase (eNOS) by phosphorylation at serine 1177 (4). Given that shear stress induces vasodilation through the same endothelium-dependent mechanism (5), it may be hypothesized that the impairment of the PI3K/Akt pathway that may be responsible for the acute hyperglycemia-mediated decrease in flow-mediated dilation may also cause a reduction in the vasodilatory action of insulin. Furthermore, it must be acknowledged that whilst blood glucose concentration increases rapidly following sugar consumption, increases in blood insulin concentration and its vasodilatory action are significantly delayed (6,7). Therefore, it is likely that the deleterious vascular effects of acute hyperglycemia may occur and be measured prior to any significant vasodilatory influence of insulin; moreover,

suggesting the redundancy of insulin's implication in potentially mediating heterogeneity between acute hyperglycemic and normoglycemic baseline measurements in vascular assessments performed soon after sugar consumption.

Considering that our meta-analysis highlighted the role of decreased nitric oxide bioavailability in acute hyperglycemia-mediated endothelial dysfunction, Horowitz *et al.* presented mechanisms that may contribute to impaired nitric oxide release (2). Nitric oxide synthesis is catalyzed by eNOS, which oxidizes L-arginine at its N-terminal oxygenase domain. However, L-arginine can also be converted to asymmetric N^G, N^G-dimethylarginine (ADMA) by protein arginine N methyltransferase (PRMT) (8) and arginase (9). The authors argue that elevated production of reactive oxygen species (ROS) during acute hyperglycemia may increase PRMT and arginase activity resulting in decreased bioavailability of L-arginine and increased ADMA. In addition to limiting substrate availability required for nitric oxide synthesis, ADMA directly competes with arginine for eNOS binding sites, thereby decreasing nitric oxide bioavailability. An increase in ROS (oxidative stress) during acute hyperglycemia may also impair eNOS activity by oxidizing its essential co-factor, tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2) (10). Such elevations in BH_2 concentration decrease the binding of BH_4 to the active site of eNOS, compounding the superoxide generation (11) that reduces nitric oxide bioavailability and subsequently impairs endothelial function.

Given that it is now clearly established that acute hyperglycemia induces transient oxidative stress that is responsible for endothelial dysfunction (12), there is a great interest in approaches that increase antioxidant defenses that can prevent endothelial dysfunction. Physical activity is one such method that is known to stimulate antioxidant mechanisms, which may enhance eNOS coupling and eNOS activation by phosphorylation at serine 1177 (13). Nevertheless, further experimental and clinical studies are needed to explore the ability of exercise training to prevent oxidative stress and the eNOS uncoupling phenomenon occurring during acute hyperglycemia.

In conclusion, our meta-analysis provided evidence that acute hyperglycemia induces endothelial dysfunction. Due to limited availability of microcirculatory studies, this effect was contained to the macrocirculation. However, further research is needed to clearly establish that acute hyperglycemia-mediated endothelial dysfunction might also occur in the microcirculation. Given that added sugar consumption has increased dramatically in recent decades, especially in children, highlights the importance of conducting such research that will inform public health policy on the role of excess sugar consumption in the pathogenesis of cardiovascular disease.

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Footnote

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