The High Creatine Kinase Phenotype is Hypertension- and Obesity-Prone

Dear Editor:

In a recent publication, Johnsen and colleagues[1] reported that baseline serum creatine kinase (CK) was correlated with blood pressure at follow-up, but the authors indicated that this association was attenuated when adjusted for body mass index (BMI). The authors concluded that the association between CK and blood pressure was modified by BMI. However, existing data indicate a causal role for CK in both hypertension and obesity, rendering the analysis with BMI as a confounding variable potentially invalid. CK rapidly regenerates adenosine triphosphate from phosphocreatine near highly energy-demanding processes such as ion transport and muscle contractility. Thus, the enzyme is thought to promote hypertension by enhancing sodium retention and cardiovascular contractility.[2] In line with this, a recent study showed a near-perfect correlation between expression of CK in human resistance arteries and systemic arterial blood pressure.[3] In addition, skeletal muscle CK, the main determinant of serum CK,[2] is associated with type II fiber predominance, resistance artery rarefaction, and hypertension.[4] Furthermore, the high CK, type II fiber–predominant skeletal muscle phenotype is obesity-prone.[5] These fast type II fibers designed for sprinting typically rely on glycolysis and cytoplasmic CK, and display an attenuated mitochondrial capacity for oxidation of glucose and fatty acids. Thus, the glucose and fatty acid uptake and utilization is limited, promoting the storage of lipid as fat tissue and obesity.[5,6] Importantly, CK inhibition leads to a shift from type II to type I fiber predominance and weight loss,[6] providing further evidence for a causal role of CK in obesity. Causal knowledge is a prerequisite for confounding analysis, and confounder identification must be grounded on an understanding of the causal network linking the variables under study.[7] Thus, adding BMI as a confounder to the regression analysis to assess the contribution of CK to blood pressure creates overadjustment bias, as the authors attempt to control for a variable that is causally related to the exposure.[8] Thus, we contend that since CK is known to promote obesity, BMI should not be included as a confounder to explain the association between CK and blood pressure.

Yentl C. Haan, MD;[1] Gert A. van Montfrans, MD, PhD;[1,2] Lizzy M. Brewster, MD, PhD[1,2,3]

[1]From the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [2]Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [3]Department of Social Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

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