Can Glucocorticoid Homeostasis Explain the Antiatherogenic Effect of Peripheral Adiposity?

To the Editor:

Tankó et al. observed that peripheral adiposity in elderly women may be associated with a relatively reduced risk of insulin resistance, dyslipidemia, and vascular calcification. They suggested that this benefit reflects an antiatherogenic effect of peripheral fat. However, we believe their findings support the concept that subtly increased glucocorticoid activity may exert dysmetabolic and atherogenic effects. It is well known, for example, that supraphysiologic levels of glucocorticoids, as seen in Cushing syndrome, increase central adiposity at the expense of peripheral adiposity and muscle mass. In recent years, there has been increasing evidence that connects physiologically elevated endogenous glucocorticoid activity with visceral obesity—a phenomenon that may be mediated at the central level via increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and at the peripheral level via increased conversion of cortisone to cortisol by 11-β-hydroxysteroid-dehydrogenase type 1 in adipose tissue. Increased activity of neuroendocrine stress axes—including elevated hypothalamic-pituitary-adrenal axis tone—has been linked to the metabolic syndrome and may contribute to the clustering of low HDL cholesterol, high triglycerides, insulin resistance, hypertension, and visceral obesity. In addition, there is in vitro evidence that glucocorticoids may contribute to vascular calcification.

In sum, the association between peripheral adiposity and favorable vascular risk factor profiles observed by Tankó et al. may not be due to direct atheroprotective effects of peripheral fat per se. It is plausible that this association reflects a variation in endogenous glucocorticoid tone between the different groups—high glucocorticoid tone associated with central fat distribution and low glucocorticoid tone associated with peripheral fat distribution. It would be interesting to know whether other features of increased glucocorticoid activity, such as osteoporosis and decreased muscle mass, were more prevalent in those women with a more central fat distribution.

Daniel J. Brotman, MD
John P. Girod, DO
Department of General Internal Medicine
Cleveland Clinic Foundation
Cleveland, Ohio
brotmad@ccf.org


Reply

We thank Drs Brotman and Girod for their interesting comment on our article. They direct our attention to a possible alternative explanation for the proposed role of peripheral fat mass (PFM) as an independent antiatherogenic factor. They propose that the inverse association between PFM and atherosclerosis may reflect endogenous variation in the tone of the HPA axis with resulting high glucocorticoid levels associated with central fat distribution and low glucocorticoid levels associated with peripheral fat distribution. Unfortunately, our study design does not allow meaningful extrapolation from measures of plasma cortisol. However, to validate their hypothesis, we have retrieved measures of bone and muscle mass from all participating women as reliable surrogate variables reflecting long-term HPA-axis activity. To our great surprise, we have found that in all 4 groups, women with central adiposity had the highest bone mineral density (BMD) and the highest amount of muscle mass on the legs. BMD at the lumbar spine (0.950±0.135 versus 0.864±0.178 g/cm²; *P*<0.05), distal forearm (0.389±0.010 versus 0.336±0.010 g/cm²; *P*<0.001), and hip (0.840±0.16 versus 0.780±0.22 g/cm²; *P*<0.05) were all significantly higher in women with central compared with peripheral adiposity. Similarly, total leg lean mass was also significantly higher in patients with central adiposity: 13.36±0.19 versus 11.27±0.21 kg, respectively (*P*<0.001). After adjustment for body mass index, BMD at the distal forearm and leg lean tissue mass continued to show significant differences. Thus, these results do not seem to provide support for a significant contribution of the HPA axis to the findings of our study. We believe that it is still important to look for other underlying mechanisms to explain the independent antiatherogenic effect of PFM observed in our study.

László B. Tankó, MD, PhD
Yu Z. Bagger, MD
Peter Alexandersen, MD
Claus Christiansen, MD
Center for Clinical and Basic Research A/S
Ballerup, Denmark
ltb@ccbr.dk

Philip J. Larsen, MD, PhD,
Rheoscience A/S
Rødovre, Denmark

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Daniel J. Brotman and John P. Girod

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