Comment on: Kaiyala et al. (2010) Identification of Body Fat Mass as a Major Determinant of Metabolic Rate in Mice. Diabetes;59:1657–1666

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The article by Kaiyala et al. (1) in the July issue of *Diabetes* represents a significant step forward for metabolic research. The emergence of regression as the gold standard for normalizing energy expenditure data in mice (2,3) will undoubtedly minimize a translational barrier between clinical and preclinical research communities. One concern when using this approach in other species has been whether fat mass should be included in the model (4,5) given that it may have a regulatory impact on metabolic rate. In most cases, the purpose for this normalization is to control for the variation in "metabolic mass," or tissue that significantly contributes to the maintenance energy requirements. Kaiyala's studies in obese *ob/ob* mice elegantly show that the influence of fat mass is primarily regulatory in nature, affecting metabolic efficiency rather than directly adding to the basal energy requirements.

My concern is that some readers may misinterpret the authors' recommendation: "Regression-based approaches that account for variation in both FM [fat mass] and LBM [lean body mass] are recommended for normalization of EE [energy expenditure] in mice." This message may be misconstrued to mean that both parameters should always be included in the model to normalize metabolic rate. Doing so would not only remove what little contribution fat mass directly adds to expended energy for tissue maintenance but also the more substantial impact that it has on regulating metabolic rate via leptin and other adiposity signals. Because many genetic manipulations and pharmaceuticals will affect these signals or their downstream pathways, controlling for this homeostatic influence may inadvertently discount the impact they have on metabolic efficiency or some other aspect of expenditure.

This field is long overdue for some consensus for presenting metabolic data. The work of Kaiyala et al. has the potential to move us toward that end, but only if the nuances of their observations are appropriately translated into a meaningful approach to normalization. To that end, I hope the authors would agree with the following clarification to their recommendation for metabolic studies in mice.

Always present unadjusted data because they provide the only direct and quantitative relationship to energy balance; ANCOVA, with lean mass as a covariate, should be used for the purpose of adjusting for metabolic mass (assuming the requirements for ANCOVA are met) because this compartment provides the best estimate of tissue that significantly contributes to basal maintenance requirements; and when fat mass is a predictor, it can be used as a covariate for a specific purpose, but only one that is more related to investigating its regulatory impact on metabolic rate.

The relevance of the work of Kaiyala et al. to other species, particularly humans, will surely be debated extensively. To initiate that debate, I would suggest that this study provides a solid step toward a normalization standard for metabolic research that extends beyond mice. Until there is good evidence or convincing arguments as to why this standard should be specific to mice, it will serve as my guide in both clinical and preclinical metabolic studies.

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