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Adipocyte size redux

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Adipocyte sizing methods have been extensively compared with each other since the late 60's (1–3) and multiple measures of adipocyte size were established to be associated with metabolic risk (4). Laforest and colleagues (5) address a related and important issue: which method best predicts metabolic risk. They found fairly good correlations among the three commonly used cell sizing methods (collagenase-isolated cells, histological tissue sections and electronic (Multisizer®) sizing of osmium-fixed adipocytes), yet intriguingly found that the median adipocyte size measured by electronic counting of osmium-fixed cells best correlated with measures of glucose homeostasis, lipid profiles, and circulating adipokine levels. Beyond the advantages/disadvantages of each method (4,5), these new findings bring up several issues that merit wider discussion.

Laforest et al. (5), like researchers before them (1), found that the size of osmium fixed adipocytes was larger (~25%), most likely due to the swelling of the fixed lipid droplet (1). Does it matter that 'actual' adipocyte size is likely overestimated after osmium fixation if it better predicts metabolic risk? It does matter because size affects adipocyte number estimates, another key predictor of metabolism, and for defining 'normal' sizes that can be compared among studies using different methods.

Assessment of adipocyte size distribution, which is often bimodal, is a cited advantage of the high throughput electronic sizing of osmium-fixed adipocytes (5,6). Although the smaller cells in the lower mode do not contribute substantially to the total volume of adipose tissue, the % small cells is important because it correlates with direct measures of insulin resistance (5). Although it is unclear why different numbers of these cells are detected by different sizing methods (see Figure 1 of Laforest et al. (4)), it would be interesting to determine if the % small cells correlated among the methods, and affected the prediction of metabolic risk. Also, the nadir separating the two populations and therefore the median size of 'small' adipocytes varies among individuals; thus 'small' is difficult to define and interpret.

The gold standard of scanning electron microscopy appears to detect fewer 'small adipocytes', i.e. those in the lower mode of the bimodal distribution is ~20–25% of the total as compared to 50–65% with the osmium/Coulter methods (5,6). Possibilities to explain this discrepancy include osmium fixation of lipid droplets within dead adipocytes, which vary in number among depots and as a function of metabolic health (7), although this contribution is likely small in human adipose tissue. An advantage of histological sections is that dead adipocytes can be identified by surrounding crown-like structures and excluded from size measurements (this issue has not previously addressed to my knowledge). In addition, it

seems possible that counting adipocytes at the limit of detection of the method, also in the same size range of debris, may lead to errors.

Laforest et al.'s paper reemphasizes adipocyte size as key obesity phenotype and points to the need to assure the rigor and reproducibility of adipocyte sizing methods that can be applied to clinical/translational obesity research.

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