

Obesity and Insulin Resistance: An Ongoing Saga

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Although the adverse effects of excess adiposity on insulin-mediated glucose uptake (IMGU) are well-recognized (1,2), the mechanism and/or mechanisms that explain this relationship continue to be debated. The article by Kursawe et al. (3) in this issue of *Diabetes* provides another, and potentially important, mechanism linking excess adiposity and IMGU. However, to put their findings into perspective, it might be helpful to provide a brief history of other approaches to this issue.

The experimental methods utilized in earlier mechanistic studies are reminiscent of the study by Kursawe et al. (3) and led to the view that metabolic abnormalities associated with obesity were related to changes in fat cell size rather than number (4–7). For example, ex vivo studies on adipose tissue isolated from obese humans demonstrated that the larger the fat cell, the more diminished the response to insulin (4). Furthermore, insulin sensitivity of isolated fat improved following weight loss-associated decreases in fat cell size. Although these data indicated that differences in fat cell size affected insulin action, the fat cell is not a major consumer of glucose (8). Thus, these data do not necessarily explain why large fat cells would have an adverse effect on whole-body IMGU. Furthermore, why some individuals had large fat cells and others did not remained unanswered.

Another approach to understanding the link between obesity and insulin resistance (IR) has focused on differences in regional fat distribution. In particular, it has been argued that abdominal obesity, specifically an increase in visceral fat volume, is the fundamental culprit responsible for IR and associated abnormalities. Mechanistically, it has been proposed that enlarged visceral fat cells secrete a number of inflammatory cytokines that lead to IR (9–11). In this manner, fat cell enlargement and the fat cell as a source of circulating inflammatory markers have merged to create one theory accounting for the link between obesity and IR (12,13).

The fact that IR and its associated abnormalities are increased in obese individuals does not necessarily mean that all obese individuals are insulin resistant (14). McLaughlin et al. (15) have published studies using techniques very similar to those of Kursawe et al. (3), attempting to identify why equally obese adults can differ approximately threefold in terms of IMGU (14). They found a bimodal distribution of fat cell size in isolated

subcutaneous fat with a higher proportion of small cells to large cells in insulin resistant—as compared with insulin sensitive—individuals. Parenthetically, McLaughlin et al. did not find a difference in the diameter of large cells between these two groups. These findings, along with a lower gene-expression profile for adipose cell differentiation, led these authors to suggest that insulin resistant, obese individuals were less able to store excess fat in newly differentiated subcutaneous fat cells, leading to its deposition as ectopic fat in other organs and contributing to IR.

Kursawe et al. expand on this hypothesis and propose a comprehensive mechanism for obesity-associated IR. They suggest that impaired adipose differentiation and lipogenesis decrease fat storage capacity in the subcutaneous adipose tissue, necessitating displacement of fat to organs such as the liver and muscle. This ectopic fat deposition then leads to organ dysfunction and IR. To evaluate this hypothesis, they divided obese adolescents into two groups based on their relative proportion of visceral to subcutaneous fat and found that those with higher visceral fat were more insulin resistant, had a higher fraction of small to large cells, and lower gene-expression markers for adipogenesis and lipogenesis. They also found that the diameters of the large fat cells were greater in those with higher visceral fat, similar to reports of older studies. The authors interpreted these findings to represent a reduced capacity for fat storage in the small cells and resultant hypertrophy of the large cells.

While Kursawe et al. show significant differences in fat cell characteristics between obese adolescents with high and low visceral fat proportion, it is not clear that their findings lead to obesity-associated IR. For example, although increased peripheral fat and ectopic fat deposition are stated to be important for the pathogenesis of IR, triglyceride and free fatty acid concentrations and intramyocellular lipid content were not different between the two groups. Therefore, it is not clear what accounts for the differences in insulin sensitivity between them. Another paradox is the disparity in racial distribution between the high and low visceral fat groups. Only 22% of the high visceral fat group was comprised of African American adolescents compared with 50% in the low visceral fat group. It is well known that visceral fat proportion is lower in African Americans (16,17); however, as a group they may be more insulin resistant (18,19). Not only is this contrary to the model by Kursawe et al., but racial effects must be considered in interpreting their findings. Finally, the authors found evidence of cell hypertrophy in the high visceral fat group compared with the low visceral fat group, whereas McLaughlin et al. did not find this distinction between their groups based on insulin sensitivity (15). Whether this disparity reflects differences between adolescents and adults or some other difference based on grouping needs further evaluation.

Overall, Kursawe et al. introduce another potential link

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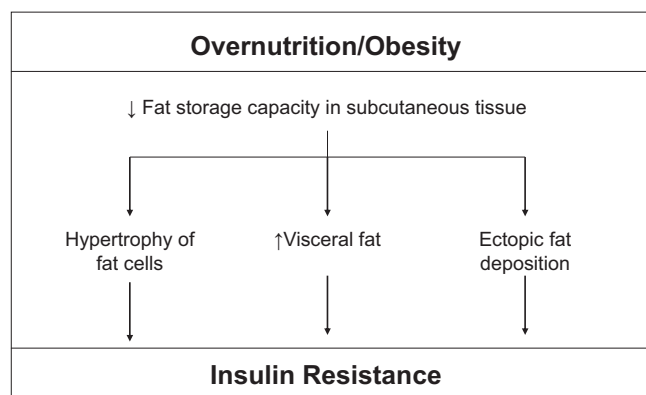


FIG. 1. Potential links between obesity and IR.

between obesity and IR that incorporates many previous hypotheses (Fig. 1). However, as with previous models, this one is not complete and raises additional questions. Most important, perhaps, is why the capacity for fat storage varies among equally obese individuals. In addition, as the study by Kursawe et al. is a cross-sectional evaluation, it remains unclear the relative role of small versus large cells or ectopic fat deposition in the initiation of events leading to IR. Thus, the primary role of visceral fat remains uncertain, and the book is not closed on the ongoing story between obesity and IR. Finally, it must be remembered that IR is not limited to obese individuals and can be demonstrated in nonobese persons without an increase in intraabdominal fat or circulating markers of inflammation (20).

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