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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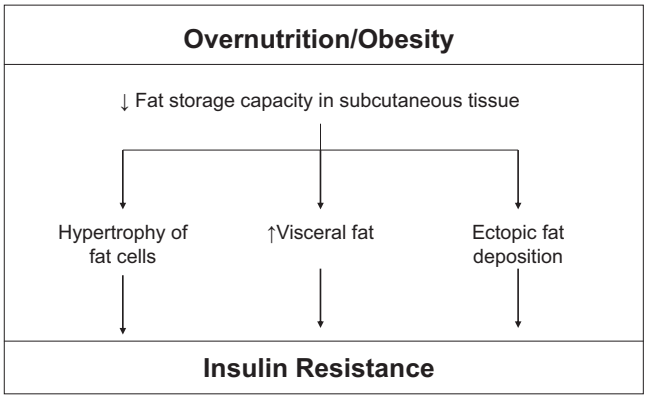

FIG. 1. Potential links between obesity and IR.

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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REFERENCES

1. Rabinowitz D, Zierler KL. Forearm metabolism in obesity and its response to intra-arterial insulin: characterization of insulin resistance and evidence for adaptive hyperinsulinism. J Clin Invest 1962;41:2173–2181
2. Olefsky J, Reaven GM, Farquhar JW. Effects of weight reduction on obesity. Studies of lipid and carbohydrate metabolism in normal and hyperlipoproteinemic subjects. J Clin Invest 1974;53:64–76
3. Kursawe R, Eszlinger M, Narayan D, Liu T, Bazuine M, Cali AM, Adamo ED, Shaw M, Pierpont BM, Shulman GI, Cushman SW, Sherman A, Caprio S. Cellularity and adipogenic profile of the abdominal subcutaneous adipose tissue from obese adolescents: association with insulin resistance and hepatic steatosis. Diabetes 2010;59:2288–2296
4. Salans LB, Knittle JL, Hirsch J. The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. J Clin Invest 1968;47:153–165
5. Hirsch J, Knittle JL. Cellularity of obese and nonobese human adipose tissue. Fed Proc 1970;29:1516–1521
6. Stern JS, Batchelor BR, Hollander N, Cohn CK, Hirsch J. Adipose-cell size and immunoreactive insulin levels in obese and normal-weight adults. Lancet 1972;2:948–951
7. Foley JE, Lillioja S, Zawadzki J, Reaven G. Comparison of glucose metabolism in adipocytes from Pima Indians and Caucasians. Metabolism 1986;35:193–195
8. Björntorp P, Sjöström L. Carbohydrate storage in man: speculations and some quantitative considerations. Metabolism 1978;27:1853–1865
9. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes 2007;56:1010–1013
10. Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. J Clin Endocrinol Metab 2005;90:2282–2289
11. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83:847–850
12. Skurk T, Alberti-Huber C, Herder C, Hauner H. Relationship between adipocyte size and adipokine expression and secretion. J Clin Endocrinol Metab 2007;92:1023–1033
13. Jernås M, Palming J, Sjöholm K, Jennische E, Svensson PA, Gabrielsson BG, Levin M, Sjögren A, Rudemo M, Lystig TC, Carlsson B, Carlsson LM, Lönn M. Separation of human adipocytes by size: hypertrophic fat cells display distinct gene expression. FASEB J 2006;20:1540–1542
14. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. Arch Intern Med 2007;167:642–648
15. McLaughlin T, Sherman A, Tsao P, Gonzalez O, Yee G, Lamendola C, Reaven GM, Cushman SW. Enhanced proportion of small adipose cells in insulin-resistant vs insulin-sensitive obese individuals implicates impaired adipogenesis. Diabetologia 2007;50:1707–1715
16. Taksali SE, Caprio S, Dziura J, Dufour S, Calí AM, Goodman TR, Papademetris X, Burgert TS, Pierpont BM, Savoye M, Shaw M, Seyal AA, Weiss R. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 2008;57:367–371
17. Goran MI, Nagy TR, Treuth MS, Trowbridge C, Dezenberg C, McGloin A, Gower BA. Visceral fat in white and African American prepubertal children. Am J Clin Nutr 1997;65:1703–1708
18. Arslanian S, Suprasongsin C. Differences in the in vivo insulin secretion and sensitivity of healthy black versus white adolescents. J Pediatr 1996;129:440–443
19. Osei K, Schuster DP. Ethnic differences in secretion, sensitivity, and hepatic extraction of insulin in black and white Americans. Diabet Med 1994;11:755–762
20. Petersen KF, Dufour S, Savage DB, Bilz S, Solomon G, Yonemitsu S, Cline GW, Befroy D, Zemany L, Kahn BB, Papademetris X, Rothman DL, Shulman GI. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc Natl Acad Sci U S A 2007;104:12587–12594