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Metabolic heterogeneity of obesity: role of adipose tissue

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Obesity is not synonymous with insulin resistance. Why some but not all individuals develop insulin resistance with weight excess is not clear, but a number of plausible hypotheses with ample support now exist. This article reviews regional fat distribution, inflammation, lipotoxicity/ectopic fat and impaired adipogenesis as leading theories as to why excess body weight has the potential to promote insulin resistance.

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INSULIN RESISTANCE AS A MEDIATOR OF OBESITY-RELATED COMPLICATIONS

Overweight/obesity affects more than 60% of American adults,[1] costing over 78 billion dollars annually in terms of treatment, primarily related to comorbid conditions such as diabetes, hypertension and cardiovascular disease.[2] It has now been shown that not all overweight/obese individuals are at equal risk for complications of obesity. This may be related to the development of insulin resistance, which generally indicates resistance to insulin-mediated glucose uptake (IMGU). Despite the fact that 85% of total body IMGU occurs in skeletal muscle, it has long been noted that IMGU ironically correlates more highly with fat mass than with muscle mass. A more recently noted twist in this observation is that despite the association with increasing body fat, insulin resistance does not invariably affect all overweight/obese individuals.[3–5] Indeed, IMGU varies sixfold[6] among normal glucose-tolerant individuals of the same body weight.[4] Furthermore, when followed prospectively for up to 14 years, the most insulin-resistant subgroup of weight-matched non-obese individuals demonstrate an eightfold increased incidence of diabetes/impaired glucose tolerance, a fourfold increased incidence of cardiovascular disease and a twofold increased risk of hypertension.[6–8] When otherwise healthy obese individuals are stratified according to the degree of insulin resistance, marked differences in metabolic and cardiovascular risk factors are apparent, with the insulin-resistant subgroup exhibiting significantly higher blood pressure, higher fasting plasma triglyceride and lower HDL–cholesterol concentrations, elevations in fasting and 2 h plasma glucose,[5] as well as elevations in plasma hsCRP (inflammation)[9] and asymmetric dimethylarginine (ADMA) (endothelial dysfunction).[10] Despite the heterogeneity in metabolic risk factors described above, it is clear that in susceptible individuals insulin resistance is weight responsive. The clearest example of this is the observation that when insulin-resistant and insulin-sensitive individuals lose an equal amount of body weight via dietary intervention, the insulin-resistant, but not the insulin-sensitive, subgroup experiences statistically significant improvements in insulin sensitivity, as well as in associated risk factors such as plasma triglycerides, hsCRP and ADMA.[9–11] Thus, those individuals who develop insulin resistance as a result of weight gain can also reverse it with weight loss, whereas others appear impervious, or at least resistant, to developing these metabolic changes in response to increased body fat. This important observation implies that (1) factors other than fat mass *per se* are important in determining insulin resistance and associated metabolic consequences of weight gain/obesity, and that (2) the insulin-resistant subgroup of overweight/obese individuals should be targeted for intensive weight-loss interventions given their higher risk profile and documented metabolic improvements in response to weight loss.

WHY DO SOME BUT NOT OTHER INDIVIDUALS DEVELOP INSULIN RESISTANCE IN RESPONSE TO WEIGHT GAIN/OBESITY?

Regional fat distribution

There are several theories regarding the relationship between excess body fat and development of insulin resistance that might explain why some but not all individuals develop insulin resistance. First is the regional pattern of fat deposition. A multitude of observational studies have shown that upper-body obesity is associated with increased risk for diabetes and cardiovascular disease.[12–13] We and others have further shown a correlation between relative and absolute amount of fat located in the intra-abdominal cavity (generally referred to as visceral fat) and insulin resistance.[14–19] Whether this fat poses risk in excess of total body fat is not completely clear. Although many studies show similar correlations between subcutaneous and visceral abdominal fat and insulin resistance, a few limited to obese individuals show that, after adjustment for total body fat, visceral fat is independently associated with insulin resistance.[14–20] Visceral fat is an attractive factor for causing insulin resistance due to its greater catecholamine-stimulated lipolysis and inflammation,[21,22] and direct drainage via the portal vein to the liver where free fatty acids (FFAs) contribute to hepatic triglyceride synthesis and glucose output. On the other hand, visceral fat accounts for less than 15% of total body fat and contributes less than 15% of systemic FFAs, a likely contributor to whole-body insulin resistance. Furthermore, quantification of IMGU before and after human omentectomy showed no significant difference,[23] thus casting further doubt on the assertion that visceral fat causes insulin resistance.

Inflammation

The second major hypothesis regarding the link between excess body fat and insulin resistance is inflammation. It has long been shown that increased body weight in humans is associated with

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increases in plasma markers of inflammation such as hsCRP and interleukin-6.[24] Evidence that systemic inflammation may originate in adipose tissue as a result of weight gain is found in examples of overfed mice that develop hypertrophic adipose cells surrounded by mononuclear cells in "crown-like structures", with evidence of cellular necrosis and lipid phagocytosis by surrounding macrophages.[25] Macrophages have also been found in human adipose tissue and their density, as measured by CD68 staining, appears to correlate with both adipose cell size and body mass index.[26] Also supportive of this hypothesis are studies in Zucker fatty and ob/ob mice showing that blockade of IKKB-mediated inflammatory pathways during overfeeding prevents hyperglycemia and hyperinsulinemia,[27] and others showing that knockout of MCP1 or CCR-2, important mediators of macrophage recruitment, reduce macrophage accumulation in adipose tissue, insulin resistance and hepatic steatosis in diet-induced obese mice.[28,29] Whether or not these processes have a clinically important role in mediating human insulin resistance is still not clear. In humans, although macrophages are present in association with obesity, few crown-like structures have been observed, and clear association with insulin resistance is reported in only one study in which comparison of equally obese insulin-resistant versus insulin-sensitive adults demonstrated modest but significant increases in CD45 density and in expression of seven of the nine inflammatory genes measured.[30] Administration of salicylic acid clearly reduces hyperglycemia in diabetic patients,[31] but in nondiabetic obese subjects improvement in glycemia appeared to result from decreased clearance of insulin rather than improved insulin sensitivity.[32] Thus, although much excitement exists regarding this theory, proof of causality for insulin resistance in humans has yet to be established.

Lipotoxicity/ectopic fat

Obese individuals have increased circulating FFAs, presumably due to increased lipolysis in adipose cells. We have shown that the degree to which insulin can inhibit lipolysis *in vivo* is proportional to the degree to which insulin can stimulate glucose uptake in skeletal muscle,[33] and thus insulin-resistant individuals demonstrate insulin resistance in fat as well as in muscle. It has been suggested that circulating FFAs are the cause of impaired IMGU in muscle, as FFA metabolites such as diacylglycerol have been shown to inhibit translocation of GLUT4 in response to insulin stimulation of receptors in skeletal muscle.[34] Furthermore, FFAs are known to stimulate inflammatory pathways that may contribute to insulin resistance, and increase hepatic glucose and triglyceride synthesis.[35] The causal role of FFAs in promoting insulin resistance is called into question to some degree in that weight loss yields similar reductions in ambient FFA concentrations in both insulin-resistant and insulin-sensitive individuals, whereas IMGU improves only among the insulin-resistant individuals, with no correlation between change in daylong FFA concentrations (measured over 8 h during administration of two standardized test meals) and improved muscle insulin sensitivity.[36] Interestingly, administration of thiazolidinediones, a class of compounds that promote adipogenesis and fat storage in adipose cells, reduces systemic[37] and intramyocellular FFAs,[38] both of which correlate with improvement in IMGU, suggesting that modulation of FFAs can alter insulin resistance.

Impaired adipogenesis and fat storage capacity

The fourth hypothesis relating differential responses in adipose tissue to insulin resistance is impaired adipocyte differentiation and fat storage potential. When body fat mass expands, adipose cells must either increase in size (hypertrophy) or number (hyperplasia). Although it was once thought that adipocyte number did not increase after adolescence, there is now data showing that the adipose number in adult humans is not fixed.[39] Further, limited data in mice and humans show that with weight gain in already obese organisms, the size of large adipose cells shows little increase, but increase in number of small cells is apparent.[40,41] Data from our laboratory and others show evidence of impaired adipogenesis in insulin-resistant vs insulin-sensitive individuals who are matched for body weight.[42,43] We found not only decreased expression of several 5/6 adipogenic genes measured but also an increased proportion of small cells, suggesting inability to attain terminal differentiation and maximal fat storage capacity. Thus, we hypothesized that weight gain among already overweight individuals requires an increase in adipogenesis or maturation of a pool of immature adipocytes, and that individuals relatively unable to do this experience stress on existing adipocytes with further hypertrophy, cellular stress, lipolysis and initiation of inflammatory response. Interestingly, the accumulation of small cells correlates with inflammatory gene expression, indicating that either the small cells exhibit pro-inflammatory properties or are markers of stress on mature adipocytes that have attained maximal fat storage capacity.[44] Mechanisms linking impaired adipogenesis to insulin resistance are not well elucidated, but a likely mediator is ectopic fat, as individuals with limited ability to store triglyceride in the subcutaneous adipose tissue would need to store fat in ectopic sites such as liver and skeletal muscle. Clear support for this notion is found in both genetically fatless mice, which develop steatosis, intramyocellular fat, hypertriglyceridemia and insulin resistance that resolves with surgical transplantation of subcutaneous fat pads,[45] and in human generalized lipodystrophy, which is characterized by metabolic disturbances found in common obesity, such as insulin resistance and hypertriglyceridemia.[46] Indeed, improvement in insulin sensitivity (and reduction of systemic FFA concentrations as described above) associated with thiazolidinediones may be partly related to potentiation of adipogenesis and fat storage in subcutaneous fat,[47] allowing for reduction of fat in liver, muscle and visceral sites.

SUMMARY

Obesity is not synonymous with insulin resistance. Why some but not all individuals develop insulin resistance with weight excess is not clear, but a number of plausible hypotheses with ample support now exist. How these interrelate, the underlying basis for differential triggers in predisposed individuals, and translation to human health will require further study, but ultimately may yield targeted treatment to protect high-risk individuals from the metabolic consequences of obesity.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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