Obesity, insulin resistance and type 2 diabetes: The knowns and the unknowns

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Fundamentally in all ethnicities, excess weight is the strongest risk factor for type 2 diabetes and, accordingly, BMI forms a major aspect of all risk factor scores for diabetes. When individuals gain weight through lifestyle changes, they become more insulin resistant but do so at different rates or at different BMI thresholds depending on several factors, such as their gender, ethnicity and family histories of diabetes.

For example, we know now that men are more insulin resistant than women and, at nearly any given age, except perhaps the elderly, develop type 2 diabetes at a lower average BMI than do women (Logue et al, 2011). Considerable other data suggest that nearly all ethnic groups outside of European Caucasians are more insulin resistant for a given BMI, and, consequently, develop diabetes at lower average BMIs (Razak et al, 2007).

But how well are the mechanisms linking obesity to insulin resistance and type 2 diabetes understood, and what uncertainties remain? At a superficial level it appears that individuals who remain highly insulin sensitive despite considerable weight gain have an excellent ability to expand (safer) subcutaneous fat stores (Koster et al, 2010). By contrast, in those whose subcutaneous storage capacity is diminished (owing to poor expandability of this tissue for reasons as yet inadequately defined, perhaps related to a family history of diabetes or certain ethnicities), with continued weight gain, excess fat is likely to be placed more rapidly elsewhere. This so-called "ectopic fat" appears to accumulate in many places, including the intra-abdominal and peri-vascular cells, and critically into skeletal muscle, the liver and possibly the pancreas. Rising waist circumference is a relatively simple clinical sign associated with ectopic fat gain, while rising liver enzymes, in particular alanine transaminase (more so than aspartate transaminase) and gamma glutamyl transpeptidase, especially when seen in conjunction with parallel triglyceride changes, indicate liver fat gain (Sattar et al, 2007). Ectopic fat, in turn, renders organs insulin resistant by mechanisms that might include rising tissue levels of metabolically toxic lipid derivatives such as ceramides or diglycerides or other products, which, in turn, interfere with insulin signalling pathways (Samuel et al, 2010). Interestingly, excess perivascular fat may also be relevant to diabetes risk by altering nutrient flow via altered "vasocrine" signalling (Yudkin et al, 2005).

The role of hyperinsulinaemia in driving excess liver fat, and thus in contributing to hepatic insulin resistance, remains uncertain. Hyperinsulinaemia can drive *de novo* hepatic lipogenesis in the context of continued excess calorie intake but excess carbohydrate intake may also directly contribute to liver fat gain (Stefan et al, 2008). Thus, circular arguments linking hyperinsulinaemia, hepatic fat and hepatic insulin resistance often emerge. Whatever the truth of the matter, rising hepatic fat levels are linked to an elevated risk for developing type 2 diabetes.

Of course, people who develop type 2 diabetes also experience the failure of their beta-cells to cope with the peripheral insulin resistance. Certainly, some people are more genetically prone to beta-cell insufficiency (as recognised in the many genetic "hits" for type 2 diabetes; Ashcroft and Rorsman, 2012). However, the extent to which differential gain in ectopic fat within the pancreas may render some overweight or obese individuals susceptible to developing diabetes, but not others, is an area of future interest. This is especially the case since there is now clear evidence that bariatric surgery can lead to a "remission" of type 2 diabetes even in people who had previously been on insulin therapy (Dixon et al, 2008). Likewise, the recent elegant study showing remission in diabetes with parallel changes in liver and pancreatic fat and liver and pancreatic function with a very-low-calorie diet adds broad support to the ectopic fat concept for type 2 diabetes (Lim et al, 2011).

Finally, as research on obesity–diabetes links continues, we must remind our patients that lifestyle changes aimed at losing weight or stopping weight gain are fundamental to their good progress. Interestingly, a recent trial (Andrews et al, 2011) suggests that to achieve weight loss and associated improvements in glycaemic control, measures aimed to influence dietary changes should come before targeting activity levels. ■

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