INSULIN RESISTANCE AS A MEDIATOR OF OBESITY-RELATED COMPLICATIONS

Overweight/obesity affects more than 60% of American adults, costing over 78 billion dollars annually in terms of treatment, primarily related to comorbid conditions such as diabetes, hypertension and cardiovascular disease. 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. Indeed, IMGU varies sixfold among normal glucose-tolerant individuals of the same body weight. 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. 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, as well as elevations in plasma hsCRP (inflammation) and asymmetric dimethylarginine (ADMA) (endothelial dysfunction). 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. 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. 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. 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. Visceral fat is an attractive factor for causing insulin resistance due to its greater catecholamine-stimulated lipolysis and inflammation, 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, 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
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. 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. Also supportive of this hypothesis are studies in Zucker fatty and ob/ob mice showing that blockade of IKKβ-mediated inflammatory pathways during overfeeding prevents hyperglycemia and hyperinsulinemia, and others showing that knockout of MCP-1 or CCR-2, important mediators of macrophage recruitment, reduce macrophage accumulation in adipose tissue, insulin resistance and hepatic steatosis in diet-induced obese mice. 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. Administration of salicylic acid clearly reduces hyperglycemia in diabetic patients, but in nondiabetic obese subjects improvement in glycemia appeared to result from decreased clearance of insulin rather than improved insulin sensitivity. Thus, although much excitement exists regarding this theory, proof of causality for insulin resistance in humans has yet to be established.

**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.

**ACKNOWLEDGEMENTS**

TM has received grant support from Amylin/Lilly. TM serves as an expert witness for diabetes cases. TM has also received grant support from National Institutes of Health/ National Institute of Digestive Diseases and Diabetes, R01 DK080436, R01DK071309. The author acknowledges Dr Samuel W Cushman for his mentoring. Publication of this supplement was partially supported by Nutrilite Health Institute with an unrestricted educational contribution to Stanford Prevention Research Center.

**REFERENCES**

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999--2008. JAMA 2010; 202: 235--241.
2. Finklestein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. Health Aff 2009; 28: w622–w831.
McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G. Prevalence of insulin resistance and associated cardiovascular risk factors among normal, overweight, and obese individuals. *Metabolism* 2004; 53: 495–499.

Yeni-Komshian H, Caratoni M, Abbasi F, Reaven GM. Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 480 healthy nondiabetic volunteers. *Diabetes Care* 2000; 23: 171–173.

McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in prevalence of risk factors for cardiovascular disease and type 2 diabetes in obese individuals: impact of differences in insulin sensitivity. *Arthritis Int Med 2007; 167: 642–648.*

Yip J, Gacchini FS, Reaven GM. Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. *J Clin Endocrinol Metab* 1998; 83: 2773–2777.

Facchini FS, Hua N, Abbasi F, Reaven GM. Insulin resistance as a predictor of age-related-diseases. *J Clin Endocrinol Metab* 2001; 86: 3574–3578.

Zavaroni I, Bonini L, Gasparini P, Barillai AL, Zuccherelli A, Dall’Aglio E et al. Hyperinsulinemia in a normal population as a predictor of non-insulin-dependent diabetes mellitus, hypertension, and coronary heart disease: the Barilla factory revisited. *Metabolism* 1999; 48: 989–994.

McLaughlin T, Abbasi F, Lamendola C, Liang L, Reaven G, Schaaf P et al. Comparison of inflammatory markers in subcutaneous adipose tissue obtained from equally obese insulin resistant and insulin sensitive women. *Diabetologia* 2008; 51: 2303–2308.

Goldfine AB, Forneva V, Jablonski KA, Pyle L, Staten MA, Shoelson SE. TNS1-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Ann Intern Med* 2010; 152: 346–357.

Koska J, Ortega E, Bunt JC, Gasser A, Impson J, Hanson RL et al. The effect of salsalate on insulin action and glucose tolerance in obese non-diabetic patients: results of a randomized double-blind placebo-controlled study. *Diabetologia* 2009; 52: 385–393.

McLaughlin T, Yee G, Glassford A, Lamendola C. Use of a two-stage insulin suppression test to assess the relationship between insulin-suppression of lipolysis and insulin-mediated glucose uptake in overweight/obese, non-diabetic women. *Metabolism* 2011; 60: 1741–1747.

Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. *Lancet* 2010; 375: 2267–2277.

Boden G. Obesity, insulin resistance and free fatty acids. *Curr Opin Endocrinol Diabetes Obes* 2001; 18: 139–143.

McLaughlin T, Abbasi F, Lamendola C, Kim H, Reaven GM. Metabolic changes following sibutramine-assisted weight loss in obese individuals: role of free fatty acids in the insulin resistance of obesity. *Metabolism* 2001; 50: 819–824.

Miyazaki Y, Glass L, Trip psychotic C, Matsuda M, Cusi K, Mahankali A et al. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia* 2001; 44: 2210–2219.

Bajaj M, Baig R, Suramammal K, Hardies LJ, Coletta DK, Cline GW et al. Effect of pioglitazone on intramyocellular fat metabolism in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010; 95: 1916–1923.

Spalding KL, Arner E, Westmark P, Bernhard S, Buchholz RA, Bergmann O et al. Dynamics of fat cell turnover in humans. *Nature* 2008; 453: 783–787.

Faust IM, Johnson PR, Stern JS, Hirsch J. Diet-induced adipocyte number increase in adult rats: a new model of obesity. *Am J Physiol* 1978; 4: E279–E286.

Kashiwagi A, Mott D, Bogardus C, Liljio S, Reaven GM, Foley JE. The effects of short-term overfeeding on adipocyte metabolism in Pima Indians. *Metabolism* 1985; 34: 364–370.

McLaughlin T, Sherman A, Tsao P, Gonzalez O, Yee G et al. Enhanced proportion of small adipose cells in insulin-resistant vs insulin-sensitive obese individuals implicates impaired adipogenesis. *Diabetologia* 2007; 50: 1707–1715.

Yang X, Jansson P, Nagaev I, Jack MM, Carvalho E, Sunnhaugen KS et al. Evidence of impaired adipogenesis in insulin resistance. *Biochem Biophys Res Comm 2004; 317: 1045–1051.*

McLaughlin T, Deng A, Yee G, Lamendola C, Reaven G, Tsao P et al. Inflammation in subcutaneous adipose tissue: relationship to adipose cell size. *Diabetologia* 2010; 53: 369–377.

Kim JR, Gavrilova O, Chen Y, Reitman ML, Shulman GI. Mechanism of insulin resistance in AZIP/F-1 fatless mice. *J Biol Chem* 2000; 275: 8456–8460.

Petersen KF, Oral EA, Dufour S, Befroy D, Artyan G, Yu C et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *J Clin Invest* 2002; 109: 1345–1350.

McLaughlin T, Liu T, Yee G, Abbasi F, Lamendola C, Reaven G et al. Pioglitazone increases the proportion of small cells in human subcutaneous adipose tissue. *Obesity* 2010; 18: 926–931.