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A Lifetime on the Hips: Programming Lower-Body Fat to Protect Against Metabolic Disease

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In the 60 years since Vague (1) described that an "android" pattern of adipose tissue (AT) distribution was associated with diabetes, atherosclerosis, gout, and kidney stones, many of the physiological mechanisms underlying this relationship have been illuminated. To date, most of the effort has been directed at understanding how accumulation of intra-abdominal fat, also known as visceral AT (VAT), promotes insulin resistance (IR). IR is the common defect underlying glucose intolerance, central obesity, dyslipidemia, and hypertension. This phenotypic cluster, called the metabolic syndrome, is associated with a doubling of cardiovascular disease risk and a fivefold increased risk of type 2 diabetes (2).

VAT is likely to promote IR in several ways. Enlarged adipocytes in VAT were originally thought to promote hepatic, and eventually systemic, IR via increased portal free fatty acid (FFA) flux (3). Other factors are likely to be involved, however, because although FFA flux from VAT does increase in obesity, it is not the major determinant of portal FFA concentrations (4). In obesity, VAT also may contribute to IR via alterations in its secreted products (adipokines), as well as proinflammatory molecules such as tumor necrosis factor-α, interleukin-6 (IL-6), C-reactive protein (CRP), and monocyte chemoattractant protein-1 (MCP-1) (5).

Independently of VAT, parallel studies have established that a gynoid pattern of AT distribution, characterized by greater amounts of subcutaneous AT (SAT) in the lower body, is associated with improved glucose tolerance and lipid profile and that this fat pattern may protect against cardiovascular disease (6,7). These protective effects often vary with sex, but they are well supported by population-based studies using simple anthropometry (8). Taken together, a large body of research shows that VAT and lower-body SAT exert opposing influences on the risk of metabolic disease in humans.

How does lower-body SAT protect against metabolic disease? In women with lower-body obesity, gluteal SAT (GSAT) takes up more meal-related fatty acids than in either upper-body obese women or men (9). GSAT is thought to function as a "metabolic sink," protecting nonadipose tissues from excessive FFA exposure and development of IR (10). Once sequestered in GSAT, these lipids are relatively more resistant to mobilization than when they are stored in other depots (11). Compared with VAT and abdominal SAT (ASAT), GSAT also produces greater amounts of palmitoleate, a lipid-signaling molecule that improves insulin action in liver and skeletal muscle (12).

Many key studies on GSAT have been performed by Fredrik Karpe, Keith Frayn, and colleagues at the University of Oxford (reviewed in 13). In this issue of *Diabetes*, these investigators extend their previous work by studying relationships between regional adiposity (measured by DEXA), IR (by HOMA-IR), and fasting plasma concentrations of insulin, triglycerides, HDL cholesterol, and CRP. Notably, the new study was conducted in a sample of 3,399 healthy adults (14). When overall adiposity was accounted for, the amount of GSAT in both males and females was negatively associated with fasting insulin, IR, and dyslipidemia. In males, GSAT was negatively associated with CRP concentrations. As in other studies (15), ASAT mass was positively correlated with both IR and dyslipidemia.

To further investigate the protective effects of GSAT, transcriptomic analysis was performed in paired samples of GSAT and ASAT, an approach that revealed marked

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COMMENTARY

differences in developmental gene expression, particularly of Homeobox (*HOX*) genes. The most differentially expressed genes were *HOXA5* (higher in ASAT) and the long noncoding RNA *HOTAIR* (higher in GSAT), which is known to repress transcription of *HOXD* genes via chromatin remodeling (16). When all of the differentially expressed genes were grouped using gene ontology, four sets of genes were downregulated in GSAT: Two sets were related to sequence-specific DNA binding, one was related to morphogenesis, and the last was related to pattern specification.

Immortalized preadipocytes grown and differentiated in culture maintain intrinsic properties such as replication, adipogenesis, and susceptibility to apoptosis that are determined by their depot of origin (17). In the newly published report, Pinnick et al. (14) refined the concept of depot-specific transcriptional "memory" by identifying differences in gene expression between ASAT and GSAT (sequence-specific DNA binding genes such as *HOXA5*, *HOTAIR*, *IRX2*, *TBX5*, *HOXA6*, *HOXC11*, and *SHOX2*) that persisted in adipocytes differentiated in vitro (Fig. 1). Examination of the promoter regions of two genes, *TBX5* and *HOTAIR*, revealed depot-specific patterns of DNA methylation that were consistent with altered expression. In adipocytes derived from ASAT, knockdown of *TBX5* (which was normally more highly expressed in ASAT than GSAT) reduced cellular proliferation, lipid content, and expression of mature adipocyte genes. Greater understanding of these depot-specific factors may allow us to manipulate regional adiposity and, in turn, influence an individual's risk of obesity-related metabolic diseases.

The pathways by which GSAT confers its protective effects also are explored in the current study by correlating gene expression with individual metabolic syndrome components. In both GSAT and ASAT, obesity was positively associated with inflammatory gene expression, while being negatively associated with energy-generating gene expression. Notably, these relationships were much stronger in ASAT, which led the authors to conclude that in obesity GSAT may resist the shift toward a proinflammatory, hypometabolic state. Similarly, measurements of arteriovenous differences in cytokine concentrations in ASAT and GSAT showed that despite comparable adipocyte size distribution and leptin production, ASAT released more than four times as much proinflammatory IL-6 per gram of tissue and tended to produce more MCP-1. A variety of AT-immune cells (macrophages, T cells, B cells) have been implicated in the pathogenesis of IR, and all of them can produce IL-6. Immune cell profiling of ASAT and GSAT in this study might have revealed the major source of IL-6 in ASAT. Further studies are certainly warranted.

The study by Pinnick et al. (14) adds considerably to our understanding of how AT distribution influences

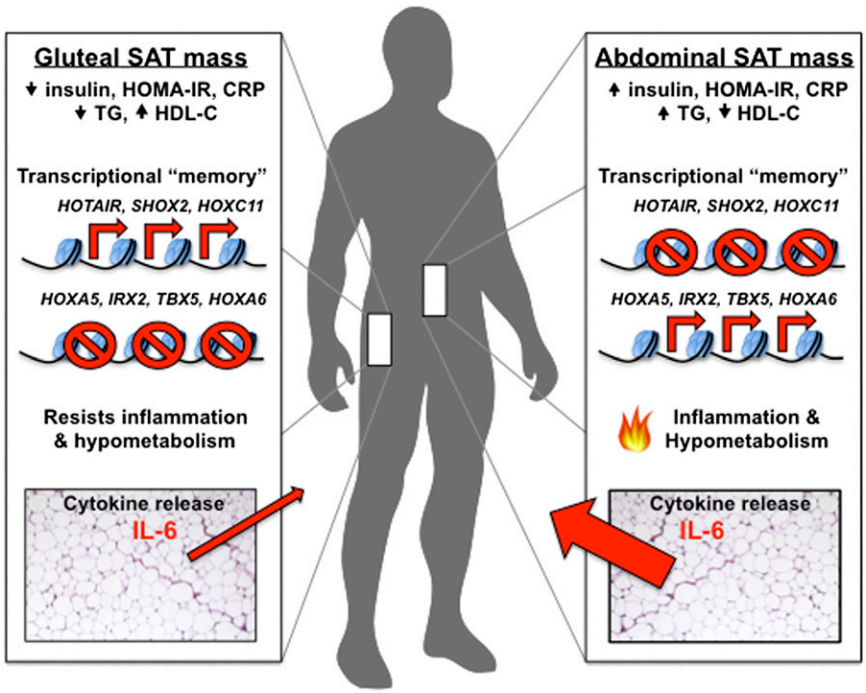

Figure 1—A depot-specific transcriptional "memory" contributes to the opposing effects of GSAT and ASAT depots on metabolism. Independently of total fat mass, GSAT and ASAT masses display opposing relationships with fasting insulinemia, insulin resistance, and dyslipidemia (gluteal, beneficial; abdominal, detrimental). Pinnick et al. (14) identify depot-specific gene expression signatures in a number of developmental genes (increased expression of *HOTAIR*, *SHOX2*, and *HOXC11* in GSAT and *HOXA5*, *IRX2*, *TBX5*, and *HOXA6* in ASAT) that are maintained in preadipocytes isolated from these depots and in mature adipocytes differentiated in vitro. In obesity, these intrinsic differences between depots are thought to enable GSAT to resist many of the deleterious changes in gene expression (inflammation and hypometabolism) that occur in ASAT. Arteriovenous measurements from these depots revealed that ASAT secreted more than four times as much proinflammatory IL-6 as GSAT, despite comparable leptin production and adipocyte size distribution.

metabolism. Determining how GSAT resists metabolic dysfunction in obesity may reveal new therapeutic targets for glucose intolerance, IR, and dyslipidemia. In individuals with android obesity or partial lipodystrophy, for example, a selective expansion of GSAT could divert lipids away from deleterious AT depots, sparing liver and skeletal muscle from lipotoxicity. This idea is reminiscent of the hyperplasia in SAT observed following thiazolidinedione treatment (18) and in transgenic *ob/ob* mice overexpressing adiponectin (19). Similarly, intra-abdominal transplantation of SAT, but not VAT, prevents high-fat diet–induced inflammation and glucose intolerance in mice (20). Diverting energy into GSAT therefore could improve metabolism, possibly giving a positive meaning to the old saying: "A moment on the lips, a lifetime on the hips."

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References

1. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. Am J Clin Nutr 1956;4:20–34

2. Cornier MA, Dabelea D, Hernandez TL, et al. The metabolic syndrome. Endocr Rev 2008;29:777–822

3. Björntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis 1990;10:493–496

4. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest 2004;113:1582–1588

5. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97

6. Snijder MB, Dekker JM, Visser M, et al.; Hoorn Study. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn Study. Diabetes Care 2004;27:372–377

7. Okura T, Nakata Y, Yamabuki K, Tanaka K. Regional body composition changes exhibit opposing effects on coronary heart disease risk factors. Arterioscler Thromb Vasc Biol 2004;24:923–929

8. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. Int J Obes Relat Metab Disord 2004;28:402–409

9. Santosa S, Hensrud DD, Votruba SB, Jensen MD. The influence of sex and obesity phenotype on meal fatty acid metabolism before and after weight loss. Am J Clin Nutr 2008;88:1134–1141

10. Lemieux I. Energy partitioning in gluteal-femoral fat: does the metabolic fate of triglycerides affect coronary heart disease risk? Arterioscler Thromb Vasc Biol 2004;24:795–797

11. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes 1999; 48:839–847

12. Pinnick KE, Neville MJ, Fielding BA, Frayn KN, Karpe F, Hodson L. Gluteofemoral adipose tissue plays a major role in production of the lipokine palmitoleate in humans. Diabetes 2012;61:1399–1403

13. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. Int J Obes (Lond) 2010;34:949–959

14. Pinnick KE, Nicholson G, Manolopoulos KN, et al.; the MolPAGE Consortium. Distinct developmental profile of lower-body adipose tissue defines resistance against obesity-associated metabolic complications. Diabetes 2014;63:3785–3797

15. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116:39–48

16. Rinn JL, Kertesz M, Wang JK, et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007;129: 1311–1323

17. Tchkonia T, Giorgadze N, Pirtskhalava T, et al. Fat depot-specific characteristics are retained in strains derived from single human preadipocytes. Diabetes 2006;55:2571–2578

18. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784–2791

19. Kim JY, van de Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest 2007;117: 2621–2637

20. Hocking SL, Stewart RL, Brandon AE, et al. Intra-abdominal transplantation of subcutaneous adipose tissue in mice prevents high-fat diet-induced inflammation and glucose intolerance (Abstract). Diabetes 2014;63(Supp. 1):A435