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

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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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
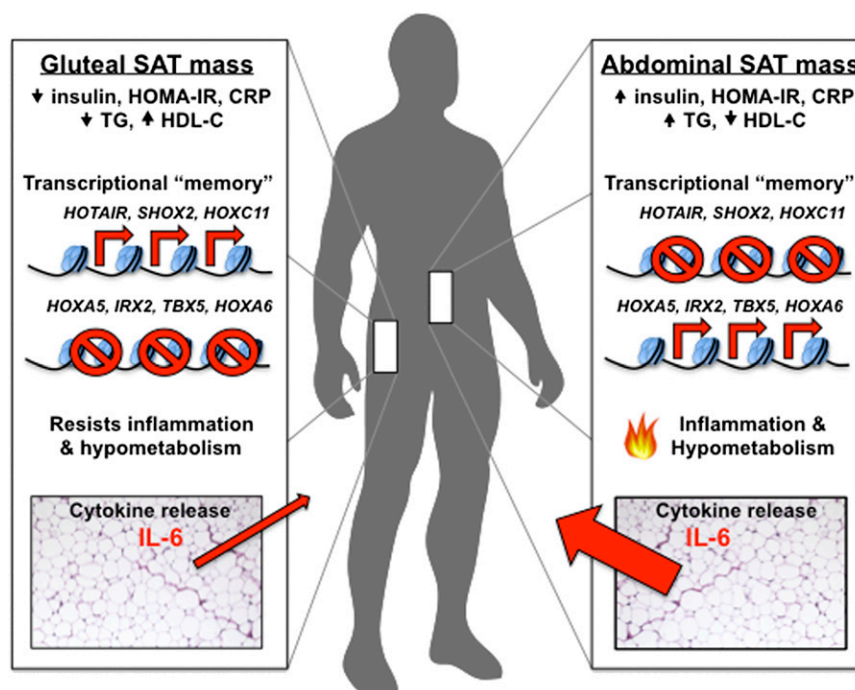
Figure 1—A depot-specific transcriptional "memory" contributes to the opposing effects of GSAT and ASAT depots on metabolism. Independently of total fat mass, GSAT and ASAT masses display opposing relationships with fasting insulinemia, insulin resistance, and dyslipidemia (gluteal, beneficial; abdominal, 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, intraabdominal 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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