# Sex differences in adipose tissue remodeling: mechanisms and role in disease risk associated with obesity

**AFFINITY RESEARCH COLLABORATIVE**

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The amount and anatomical location of stored fat differs in females and males. Females store more fat in peripheral depots (hips and thighs) and are typically 'pear-shaped', while males store most of their fat in central (abdominal) depots (both subcutaneously and in visceral depots) and develop an apple shape with age/obesity. The amount of abdominal fat, particularly the amount of visceral fat, varies within each sex and this variation is in large part genetically determined. Fat distribution is of medical importance because it is tightly correlated with risk of chronic disease, including type 2 diabetes, cardiovascular disease, infertility and cancer. In association with their lower body fat distribution, females are at overall lower risk for metabolic disease than males. Data from recent epidemiological and clinical studies and animal models indicate that the amount of gluteal-femoral fat exerts a protective effect on disease risk that is independent of total body fat, through unknown mechanisms.

The adipose organ serves two main functions that are critical for survival: 1) a highly regulated fuel reservoir that stores food energy in highly specialized cells (adipocytes) when available and releases it when needed, and 2) an endocrine tissue that synthesizes and secretes hormones (most notably leptin and adiponectin) that regulate virtually every physiological system, including reproduction, immunity, and metabolism (systemic fuel homeostasis). Adipose tissues located in different anatomical regions are functionally distinct and differ in cellular composition, blood flow and innervation. Visceral adipose tissues are characterized by the presence of lymph nodes, which exert local paracrine effects on the function of adipocytes. In addition to adipocytes, adipose tissues include preadipocytes, endothelial cells, pericytes, resident macrophages and other immune cells.

With the stress of obesity, adipose tissues, particularly visceral ones, attract macrophages and other immune cells, creating a pro-inflammatory paracrine milieu that contributes to adipocyte dysfunction and in the extreme, adipocyte death. While normal remodeling events likely contribute to the health of adipose tissues, with the chronic or extreme stress, inflammation within adipose tissue is thought to have deleterious consequences for adipocyte function. The resulting altered secretion of hormones and other secreted proteins and metabolites is thought to instigate systemic insulin resistance, hyperlipidemia and chronic inflammation. In rodent models, high fat induced obesity causes an almost complete remodeling of the male visceral adipose tissue (epididymal) with death of adipocytes by a process that is neither clearly apoptosis or necrosis, followed by a recruitment of preadipocytes and restoration of the adipose mass and function. This process appears to occur at a much slower pace in humans, and its pathophysiological importance in the metabolic consequences of obesity is not known.

Our recent studies show that the magnitude of the inflammation and adipose remodeling is markedly lower in female than male mice, and in subcutaneous compared to visceral adipose tissues of both sexes. Perhaps as a consequence, females are protected from the insulin resistance associated with high fat diet-induced obesity. Ovariectomy increases inflammation and insulin resistance, and administration of estrogen to ovarectomized females preferentially decreases the size of abdominal fat depots, decreases

inflammation and enhances muscle fat oxidation through both genomic and non-genomic mechanisms. Whether there are intrinsic differences in functional capacities of adipocytes of male and female origin, and how early programming, particularly exposure to sex steroids, affects adipose tissue growth and function through epigenetic mechanisms remain unknown. The effects of sex steroids may be in part indirect, mediated by though central effects via sympathetic connections, Finally, although there is little doubt that sex steroids play a critical role in determining sex differences in fat distribution and function, recent studies also point to the importance of sex differentiation (presence of the Y chromosome, differential dose of X genes or imprinting). A major long-term goal of our ARC will be to dissect the roles of these factors in determining fat distribution and function.

To gain insight into the mechanisms that control sex- and depot- differences in adipose tissue function, we conducted microarray analysis of visceral and subcutaneous adipose depots of mice, and humans (male, female, ovarectomized, pre- and post-menopausal women and age-matched males). These data confirmed the sex difference in inflammation, and pointed to a number of candidate genes. We considered this descriptive experiment as a resource and first step in defining genetic and hormonal determinants of sex- and depot-differences in fat distribution, and their physiological and pathophysiological consequences.

We envision expanding our studies with analysis of sexual dymorphisms in cell- and tissue specific gene networks, proteomes, secretomes, and metabolomes using human and animal tissues, and primary and cultured cell models. Members of our group created a mouse model of altered fatness and fat distribution in males and females secondary to early testosterone exposure, providing an opportunity to evaluate the role of epigenetic mechanisms. This and other mouse models (e.g. conditional knockouts of sex steroid receptors and key gene targets) will be invaluable for translational studies directed at understanding the redistribution of adipose tissue observed in humans with aging, menopause, hypogonadism, and polycystic ovarian syndrome. Women with PCOS have an abdominal body fat distribution and high free T in women). In contrast, hypogonadal men have increased abdominal, particularly visceral adipose tissue, which is reversed by T administration. Whether the relative growth of visceral adipose tissue after menopause is mediated by the fall in estrogen, and why androgens have differential effects on fat distribution and function in males and females remains an important gap in knowledge. Adipose tissues are active in the metabolism of sex steroids, but the regulation of these processes and their role in adipose tissue physiology and metabolism is poorly defined. Members of the ARC have addressed the mechanisms by which obesity leads to adipose dysfunction and disease. Available evidence supports a role for local hypoxia and impaired capillarization in adipose inflammation, remodeling and its metabolic consequences. Thus, one goal of this ARC is to address the possibility that these processes are targets of sex steroids.

We therefore wish to further investigate, **using multidisciplinary approaches**, the role of sex steroids and genetic sex on these processes. Our overarching hypothesis is that sex steroids and sex chromosomes mediate depot- and sex-specific adipose morphology and function. The objectives of this interdisciplinary ARC are to address the following major questions:

1) How are female fat protected from inflammation and remodeling? Do sex steroids directly or indirectly affect angiogensis and the vascularity of specific adipose depots with consequences for local hypoxia and its consequences? Is there a role for sex steroids in regulating the chemotaxis of immune cells into adipose tissues?

2) How does female gluteal/femoral adipose tissue confer protection from metabolic disease? Is there a unique metabolic or humoral signal?

3) What is the role of sex steroids in determining fat distribution and depot-specific function? What are the primary targets of sex steroids in adipose tissues in vivo and in vitro, in mouse and human?
4) What are the genetic determinants of fat distribution in men and women?
5) Are there intrinsic/genetic differences between male and female adipocytes/adipose tissue and do they persist after culture or transplant?
6) What is the role of physiological factors such as innervation and blood flow in determining sex- and depot-specific adipose tissue function in vivo?

To achieve these goals**, interdisciplinary expertise and tools are needed**. Members of this ARC have the resources and technological expertise to address these questions, including: bioinformatics, mass spectroscopy methods to measure sex steroids 'stored' in adipose tissues, flow cytometry to define the cell types within adipose tissue and how they change with stress and sex steroid status, confocal imaging of adipose capillarization and morphology, analysis of mechanisms of adipocyte birth and death (apoptosis and necrosis), animal models of sex-specific altered fatness and fat distribution, access to specific patient populations and expertise in clinical investigation, in vivo and in vitro analysis of adipose tissue function, access to large population studies to understand genetic contributions to sex-specific fat distribution and its association to disease risk.

This ARC will also provide ample opportunities for training in multidisciplinary translational research for post-doctoral fellows, clinical fellows, and graduate students in Molecular Medicine and Nutrition Graduate Programs. If you are interested in joining this ARC please contact skfried@bu.edu.

**Members of this ARC currently include:**

| Name | Affiliation | Main focus/expertise |
|---|---|---|
| Susan K. Fried, Ph.D. | BUSM-Med/Endo/BONRC | Adipose biology, in vitro adipocyte models |
| Steven R. Smith, M.D. | Pennington | Human adipose phenotyping |
| Andrew S. Greenberg, M.D. | Tufts/HNRC | Adipose inflammation/function |
| Caroline Apovian, M.D. | BUSM/BONRC | Endocrinology, obesity |
| Noyan Gokce, M.D. | BUSM | Cardiology, vascular biology |
| Shalander Bhasin, M.D. | BUSM-Med/Endo | Androgens/Mass Spec steroids |
| Steven Farmer, Ph.D. | BUSM-biochem | Adipogenesis |
| Martin Obin, Ph.D. | Tufts/HNRC | adipose remodeling/immunity |
| Barbara Corkey, Ph.D. | BUSM | adipocyte biology, ROS |
| Paul Pilch, Ph.D. | BUSM-biochem | insulin signaling |
| Kostya Kandror, Ph.D. | BUSM-biochem | adipocyte cell biology |
| Gerald Denis, Ph.D. | BUSM | development, transcription |
| Deborah Clegg, Ph.D. | UT Southwest | central regulation of adiposity |
| Andrea Coviello, M.D. | BUSM-Endo | PCOS |
| Ulla Hansen, Ph.D. | BU –Biology/Bioinformatics | Estrogen action, gene networks |