Adipose tissue distribution and thermogenesis: relationships with metabolic disease

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It is well established that accumulation of intra-abdominal (visceral) fat leads to insulin resistance (IR), the common defect underlying glucose intolerance, central obesity, dyslipidaemia and hypertension. This phenotypic cluster, the metabolic syndrome, is associated with a marked increase in cardiovascular disease and type 2 diabetes risk. Several hypotheses have been proposed to explain the relationship between visceral adiposity and IR, including the portal or “overflow” hypothesis, secreted products of adipose tissue, and fat "expandability”.

Independently of visceral fat, accumulation of subcutaneous adipose tissue, particularly in the lower body, is associated with an improved lipid profile and protection against diabetes and cardiovascular disease. Although visceral and subcutaneous fat have a similar appearance, studies of isolated preadipocytes differentiated *in vitro* reveal that they possess intrinsic properties that are determined by their depot of origin.

We have studied the relationship between regional adiposity and glucose intolerance, IR and dylipidaemia by using an adipose tissue transplantation model. Under ketamine/xylasine anaesthesia (100mg/kg and 10/mg/kg, respectively, i.p), inguinal and epididymal adipose tissue depots were dissected out from donors and transplanted into littermates *via* a midline incision. Intra-abdominal transplantation of subcutaneous adipose tissue protected high-fat diet-fed mice against the development of glucose intolerance, IR, and hepatic triglyceride accumulation. Mice receiving subcutaneous fat grafts were also protected against systemic inflammation, which may be the primary effect of this procedure. Our findings indicate that factors derived from subcutaneous fat exert a considerable influence on hepatic glucose and lipid metabolism.

Recruitable beige/brite adipocytes expressing uncoupling protein-1 (UCP1) have an increased rate of metabolism, and may hold promise for treatment of obesity, hyperglycaemia and dyslipidaemia. We and others have identified these cells in human supraclavicular fat, and they may share an embryonic origin with smooth muscle. Beige/brite adipocytes are also present in smaller amounts in human omental and gastro-oesophageal (GO) fat; in females, higher UCP1 mRNA expression in omental and GO fat was significantly correlated with lower fasting FFA concentrations (P=0.012), independently of age and BMI. Beige/brite adipocytes may therefore contribute to whole-body lipid metabolism in humans.

These studies indicate that adipose tissue is highly heterogenous, and that in obesity, an individual’s risk of developing chronic metabolic diseases is determined, at least in part, by the opposing (beneficial and detrimental) influences of the major adipose tissue depots.