Body fat distribution and obesity

Obesity is a complex chronic disease linked to increased risk of developing chronic cardiometabolic diseases, especially type 2 diabetes mellitus. Obesity-related complications are result of white adipose tissue (AT) dysfunction and are linked to body fat distribution. Dysfunctional AT is characterised by adipocyte hypertrophy, adipokine dysregulation, chronic low-grade inflammation, altered lipid metabolism, decreased AT blood flow (ATBF), mitochondrial dysfunction, and altered oxygenation. Abdominal (upper body) fat accumulation is associated with an increased incidence of obesity-related cardiometabolic complications. In contrast, fat accumulation in the lower body (gluteofemoral) is associated with decreased cardiometabolic disease risk. In this thesis we investigated the differences between upper and lower body AT biology, focusing on blood flow, the oxidative machinery, and inflammatory signatures of abdominal and femoral subcutaneous AT in humans with normal weight or obesity. A second aim was to investigate the influence of prolonged exposure to various oxygen levels on the inflammatory phenotype of abdominal and femoral adipocytes. In Chapter 2 the importance of AT oxygenation is discussed based on an extensive review of the relevant literature, concluding that AT oxygen partial pressure (pO_2) may play a key role in the metabolic and inflammatory perturbations seen in most individuals with obesity. In Chapter 3 we demonstrated that measurement of abdominal and femoral intravascular ATBF with percutaneous Doppler ultrasound is technically feasible and that fasting abdominal ATBF was significantly higher than femoral ATBF. Moreover, the postprandial increase in abdominal subcutaneous ATBF was significantly higher than the ATBF increase in femoral AT. In Chapter 4 we investigated the inflammatory signatures of abdominal and femoral subcutaneous AT in postmenopausal women with normal weight and obesity. We compared the *in vivo* fractional release of adipokines from abdominal and femoral AT in both groups, examined adipocyte morphology and gene expression of adipokines in these AT depots. Furthermore, we determined gene expression and secretion of adipokines *in vitro* using differentiated human primary abdominal and femoral subcutaneous adipocytes derived from the same study participants. The findings demonstrate that upper and lower body AT are characterized by distinct inflammatory signatures in postmenopausal women with normal weight or obesity. In Chapter 5 we examined the oxidative signatures of abdominal and femoral subcutaneous AT and adipocytes in the same group by investigating *in vivo* fractional O_2 extraction and CO_2 release across these AT depots, OXPHOS protein expression and mtDNA copy number in AT and adipocytes, and the oxygen consumption rates in differentiated abdominal and femoral adipocytes. AT oxygen extraction and adipocyte oxygen consumption were lower in abdominal than femoral AT in postmenopausal women, with no significant depot-differences in OXPHOS protein expression and mtDNA content. In addition, we found lower OXPHOS protein expression in AT and adipocytes in women with obesity versus normal weight. In Chapter 6 we investigated the impact of changes in pO_2 levels on adipocyte gene expression and secretion in differentiated human multipotent abdominal and femoral adipose-derived stem cells from the same individuals. Low physiological pO_2 (5%) decreases gene expression and secretion of pro-inflammatory factors in both abdominal and femoral adipocytes derived from individuals with obesity, while these responses were not present in adipocytes derived from individuals with normal weight. In conclusion, the studies described in this thesis provide important insights into the differences between upper and lower body AT

biology, in particular blood flow, the oxidative machinery, and inflammatory signatures of abdominal and femoral subcutaneous AT in humans with normal weight or obesity. Furthermore, the present work has contributed to a better understanding of the impact of prolonged exposure (14 days) to various oxygen levels (as present in human AT) on the inflammatory phenotype of abdominal and femoral adipocytes.