Relevance of human fat distribution on lipid and lipoprotein metabolism and cardiovascular disease risk

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Abstract

Purpose of review

Upper body abdominal and lower body gluteofemoral fat depot masses display opposing associations with plasma lipid and lipoprotein and cardiovascular disease (CVD) risk profiles. We review developments on adipose tissue (AT) fatty acid (FA) metabolism in the context of body fat distribution and how that might be related to adverse lipid and lipoprotein profiles and CVD risk.

Recent findings

Recent data have confirmed the paradoxical relationship of upper abdominal and lower body gluteofemoral adiposity and CVD risk. Mechanistically this is likely to reflect the different ways fat depots handle lipid storage and release, which impacts directly and indirectly on lipid and lipoprotein metabolism. The upper body enhances immediate fat storage pathway with rapid uptake of dietary-derived FAs, whereas the lower body fat depot has a reduced lipid turnover accommodating a slower fat redistribution. Body fat distribution and the fat depots' ability to undergo appropriate expansion when fat storage is required, rather than overall body fatness, appear as the important determinant of metabolic health.

Summary

A focus on fat distribution in overweight people, preferably using precise imaging methods, rather than quantifying total body fatness, is likely to provide the medical community with better tools to stratify and treat patients with obesity-related complications.

Key words: Body fat distribution, adipose tissue expandability, adipose tissue metabolism, lipid-lipoprotein profile, cardiovascular risk

Introduction

Although obesity *per se* is positively associated with cardiovascular disease (CVD), this relationship is complex due to several independent associations with CVD risk markers such as hypertension, hyperlipidaemia, insulin resistance or even type 2 diabetes. It is also recognised that total body fatness can have divergent associations with CVD dependent of fat distribution. The recognition of the fact that different fat depots handle lipid metabolism in very different ways [1] and its consequence on whole body lipid and lipoprotein homeostasis will be reviewed in this article. We will pursue the argument that obesity *per se* is a less important determinant of metabolic dysfunction, instead it is likely to be body fat distribution and the regional fat depots capability to accommodate adequate fat storage that determines metabolic health [2].

Fat depots: an overview

The major compartments for dedicated fat storage in the human body includes the subcutaneous adipose tissue (SAT) depot, defined as upper body abdominal SAT (aSAT) and the lower body gluteofemoral fat depots, which together account for >80% of overall body fat mass [3]. Additionally, the intra-abdominal depots which includes visceral adipose tissue (VAT), composed of two major compartments (omental and mesenteric) represents approximately 10% of overall body fatness in women whereas this proportion may reach up to 25% in men [4]. Closer examination of the aSAT depot has led to the identification of two anatomically and biologically distinct compartments: a superficial layer of SAT (sSAT) and a deeper SAT (dSAT) compartment, separated anatomically by Scarpa's fascia [5-7]. The adverse effects of excessive 'upper body adiposity' has often been linked to VAT, and the role of aSAT in the regulation of metabolic health has been less recognized until recently. The conventional anthropometric measurement of abdominal obesity is waist circumference (WC) but this surrogate marker does not distinguish between aSAT and VAT. Precise imaging techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DEXA) provide better estimates of fat depot masses, particularly in the abdominal region.

Upper body abdominal vs lower body gluteofemoral fat depots

Epidemiological studies have shown that upper and lower body adiposity measured using WC and hip circumference (HC) have paradoxical effects on metabolic health and CVD events and these effects are independent of total body fatness measured with body mass index (BMI) [8-10]. Using DEXA body composition measurements of 4,950 participants in the Oxford Biobank, we have recently shown that upper body fat depots (android and visceral fat) are associated with increased risk of hypertriglyceridaemia, impaired fasting glucose, hypertension and insulin resistance, while lower body fat depots (gynoid and leg fat) have opposite associations when adjusted for total body fat mass [11]. Compared with conventional anthropometry it was very

clear that precise instruments of quantifying fat depot masses enhanced the ability to observe the paradoxical associations between regional fat masses.

Upper body abdominal fat depots

Large cohort studies such as the Framingham Heart Study and the Jackson Heart Study using CT-imaging, have shown that excess VAT is a predictor of CVD, independently of total body fat mass or SAT [12-15]. In a 10-year longitudinal study of Japanese men, cases developing coronary heart disease (CHD) were approximately 22% more VAT than controls [16]. Adverse effects like insulin resistance or dyslipidaemia dependent on abdominal adiposity is likely to result from both dysfunctional aSAT and VAT accumulation; this becomes clinically apparent among individuals with increased waist-to-hip ratio (WHR) [17, 18]. Although accumulation of fat in aSAT is considered to be less detrimental than excessive VAT depot, disproportionate expansion of dSAT compared to sSAT has been associated with CVD risk factors; dSAT shares morphological and functional similarities to VAT [7, 19]. However, these models might be too simplistic as attempts to remove VAT in randomized trials using surgical omentectomy do not appear to show any metabolic benefit [20-25].

Abdominal adiposity, particularly VAT, has been shown to be associated with dyslipidaemia characterised by raised concentrations of total and very-low-density lipoprotein (VLDL)-triglycerides (TG), low high-density lipoprotein (HDL)-cholesterol, and an abundance of smaller and denser LDL particles despite relatively normal total and low-density lipoprotein (LDL)-cholesterol levels [26]. This dyslipidaemic profile could be fuelled by excess flux of fatty acids (FA) to the liver. However, the relevance of the quantitative contribution of non-esterified fatty acid (NEFA) delivery from VAT has been questioned as it only accounts to ~15% of the total systemic NEFA circulation, while majority of the NEFA is delivered by SAT [27, 28]. VAT is more metabolically active (greater fat storage and release) leading to higher lipid turnover than other fat tissues, greater lipolytic rates in response to stress hormones, and a lesser response to the anti-lipolytic effect of insulin, thus promoting atherogenic lipid and lipoprotein profiles compared

to aSAT (Figure 1) [29]. Although it is suggested that the aSAT depot may help to regulate lipid metabolism by sequestering lipids destined to ectopic fat depots [30, 31], the heterogeneity of the aSAT depot makes this questionable. The deeper aspect of the depot (dSAT) appears to have similarities to VAT [7], and an expansion of dSAT may therefore impact negatively on effective fat storage with effects on lipid and lipoprotein metabolism.

Lower body gluteofemoral fat depots

The CVD and diabetes-protective properties of the lower body gluteofemoral fat depots across a wide range of age, BMI and co-morbidities is well-established [11, 32-36]. Gluteofemoral fat, as measured by thigh circumference, HC or leg fat mass, is associated with lower total- and LDL-cholesterol, lower total- and VLDL-TG levels, and higher HDL-cholesterol levels [37-40]. In the INTERHEART study, an independent association between larger HC and lower risk for myocardial infarction has been shown [9]. In the prospective European Prospective Investigation into Cancer and Nutrition–Norfolk study, larger HC was associated with a lower hazard ratio for CHD [8]. In a cross-sectional study involving 683 university students, higher levels of leg fat mass, as measured using DEXA, have been associated with a more favourable lipid profile, regardless of total body fatness, cardio-respiratory fitness or physical activity levels [41]. Change in leg fat mass after a 14-weeks intervention with diet and exercise was inversely associated with LDL-cholesterol levels and a number of CVD risk factors in overweight and obese women [42]. The positive health effects of gluteofemoral fat could probably be related to its various inherent properties such as its ability to serve as a long-term storage reservoir for excess fat, thus acting as a "metabolic sink", and protecting other tissues from excessive exposure to lipids [32, 43]. The tissue is characterised by a low lipid turnover compared with abdominal fat depots [30]. During energy deficit, the gluteofemoral depots shrink more slowly than abdominal depots [44-46]. Absence of gluteofemoral fat, such as in familial partial lipodystrophy, is almost invariably associated with dyslipidaemia and liver fat accumulation.

What is the evidence that fat depots handle lipid and lipoproteins differently?

Factors that regulate lipid trafficking in fat depots is balanced between the rate of lipolysis and the rate of fat storage originating from chylomicron or VLDL-TG. There is also a small fraction of direct uptake of NEFA by adipose tissue (AT). The aSAT is characterised by a greater FA uptake from diet-derived FA and a high turnover that is easily stimulated by adrenergic receptor activation. In contrast, the gluteofemoral AT depots are characterised by a reduced turnover and a higher capacity to accommodate lipids undergoing redistribution (recirculating FA from VLDL-TG or from NEFA pool) (Figure 1) [1]. The uptake of diet-derived FA occurs less efficiently in the gluteofemoral fat than in the abdominal fat depots [28, 47]. This is balanced by less FA release from gluteofemoral AT in the postabsorptive state or during adrenergic lipolytic stimuli [28, 48]. Direct measurements of lipid turnover after oral administration of radiolabelled FA show faster short-term uptake of diet-derived lipids in subcutaneous abdominal than in femoral fat depot [47, 49, 50]. Administration of isotopically labelled FA followed by serial biopsies of abdominal and femoral AT showed higher incorporation (~50%) of diet-derived FA in the abdominal than in the femoral fat depot [49]. Additional metabolic studies consistently demonstrated higher uptake of chylomicrons-derived FA in abdominal AT than in femoral AT [51-53].

Using two different FA labels to simultaneously quantify extraction of dietary chylomicron-derived TG and VLDL-derived TG across abdominal and gluteofemoral AT depots, McQuaid and colleagues showed that chylomicron-derived TG were more efficiently extracted by abdominal AT, whereas no difference for VLDL-derived TG was observed [53]. Therefore, in relative terms the gluteofemoral AT depots have a preference for taking up FA from VLDL-TG compared with chylomicron-TG [53]. The extension of this observation is that VLDL-TG represents off-loading of lipids from the liver, which could suggest a hepato-femoral axis for fat storage. This would provide an explanation for the hepatic steatosis observed in patients lacking gluteofemoral AT depots, such as in familial partial lipodystrophy.

Sex difference in body fat distribution pattern

The difference in body fat distribution between men and women has been related to both sex-specific lipid-lipoprotein profiles and CVD risk [32, 54]. The female lower body fat depot is only reduced during periods of excessive energy demand [55]. After menopause, a switch in storage pattern from peripheral to central is observed and this is associated with a parallel increase in metabolic risks including adverse lipoprotein profile comparable to that seen in men [56]. However, an increase in total fat mass in men is rather immediately associated with accumulation in VAT [57]. Observations from transsexuals who have been treated with sex hormones have shown that the female-to-male transition induced by intramuscular testosterone injections show a progressive shift in body fat distribution from gluteofemoral to abdominal over a few months to 3 years [58-60]. Conversely, estrogen treatment in the male-to-female transition increases fat deposition in all SAT depots, while having little effect on the VAT depot [58, 60].

Sex difference in fatty acid metabolism and metabolic consequences

In women, diet-derived lipid storage increases in proportion to lower body fat mass, while no association was found between relative lipid uptake in aSAT and adiposity measures [61]. In men, the capacity of aSAT to rapidly assimilate fat is higher compared with that of the femoral fat depot [62]. Indirect assessment of lipid uptake by fat depots suggests that VAT more efficiently removes lipids from the circulation during the postprandial period in men than in women [47, 63]. Dietary FAs enter the circulation through chylomicron synthesis and may enter the liver in at least two ways [64]. FAs are released from TG-rich lipoprotein core of chylomicron by lipoprotein lipase. When this process occurs at a higher rate than the tissue uptake allows for, the excessive FAs spill over into the plasma NEFA pool and consequently contribute to the postprandial NEFA plasma concentrations reaching the liver. The chylomicron remnants with their remaining TG content are taken up by the liver. The FA spill over pathway is more pronounced in women compared to men, despite women having a greater fat mass [65]. This route could enhance recirculating FA

toward long term lipid storage and there could also be different handling of the FAs in the liver depending on whether they enter as NEFA or by lipoprotein remnant uptake.

Sex differences in VLDL-TG metabolism have been reported in several studies [66, 67]. Women channelled a larger proportion of VLDL-TG to femoral AT depot for storage in the postabsorptive state [68]. Furthermore, the more femoral AT there is, the greater the efficiency to VLDL-TG uptake by this depot [69]. Men have higher plasma VLDL-TG concentrations and higher VLDL-TG secretion rates than women at any degree of adiposity [67]. Although hepatic VLDL-TG secretion rate was an important determinant of plasma VLDL-TG concentrations in both women and men, VLDL-TG secretion explained 70% of VLDL-TG concentrations in plasma in men but only 30% in women, indicating that the female plasma TG concentrations are more reliant on catabolism.

Adipose tissue expandability

Upper and lower body AT respond differently to increasing demands for fat storage. Whilst the upper body subcutaneous AT depot displays a hyperplastic response (more fat in each fat cell), the gluteofemoral AT shows a proliferative response (new fat deposited in new fat cells) [70]. Expanding the fat stores in time of excess energy storage is a must to maintain metabolic health (Figure 2). The failure of AT expandability as a unifying hypothesis to explain complications of obesity was first muted by Eliot Danforth Jr [71]. Subsequently, this has been refined and underpinned by mechanistic insight by several groups [72, 73]. More recently, this concept has been given support using large-scale genetic resources. Yaghootkar and colleagues have shown that carriers of 'favourable adiposity alleles' have a higher BMI and body fat percentage but, paradoxically, lower risk of diabetes, hypertension and CVD disease a phenotype that would be consistent with metabolically healthy obese, than non-carriers of these favourable adiposity alleles [2], suggesting that the absence of expandability leads to obesity-related complications. It is possible that these individuals are characterised by a more uniform fat distribution which is geared towards subcutaneous, rather than VAT expansion [74]. According to this hypothesis, the

failure of appropriate AT expansion and fat storage leads to overflow of lipids which will be stored in ectopic non AT [75], which is usually the case in an obese individual characterised by greater VAT and lower peripheral subcutaneous fat. With this in mind the relationships between plasma lipids and regional AT depot masses becomes complex as there might be a direct positive relationship between VAT and raised lipids, whereas a lower subcutaneous AT mass is likely may either reflect leanness or a failure of expansion. The same duality is likely to exist for lower body fat depots.

Effect on the liver

Overall body fatness and abdominal visceral adiposity are both associated with liver fat accumulation, which in turn is associated with hepatic overproduction of VLDL-TG particles fuelling hypertriglyceridaemia [76]. Hepatic VLDL production is primarily substrate driven, with the most important substrates being NEFAs [77]. As the liver accumulates fat, there is overproduction of large VLDL particles [78]. NEFAs are taken up by the liver in proportion to their delivery rate [79]. The release of NEFAs from upper body SAT is a major determinant of systemic NEFA plasma concentrations, whereas VAT may contribute FAs specifically to the liver [80]. Thus, individuals with greater amounts of VAT are likely to have abnormalities in hepatic FA metabolism. Again, this relationship is more complex than anticipated and a dissociation between VAT volume and liver fat content has also been demonstrated [81].

Conclusion

The fat depots in the human body handle lipid storage and release differently and this impacts lipid and lipoprotein metabolism both directly and indirectly. Direct effects are seen on how various TG-rich lipoprotein species are handled differently by upper and lower body fat depots and also how the fat depots respond to lipolytic stimuli. Indirect effects, such as the impact on whole body fat storage capacity, is determined by body fat distribution, where the lower body fat depot appears to sequester excess fat better than upper body abdominal fat depots alleviating the formation of ectopic fat accumulation. Determinants of regional fat distribution, be it by genetic, epigenetic or hormonal influences, is a major determinant for lipid and lipoprotein metabolism with direct effects on CVD risk.

Key points

- Susceptibility to obesity related metabolic complications is not mediated by overall body fatness, but is largely dependent on the body fat distribution and the ability to sufficiently expand fat depots.

- Upper body abdominal and lower body gluteofemoral fat depots exhibits opposing associations with risk of cardiovascular disease and adverse lipid and lipoprotein profiles.

- The opposite relationship of abdominal and gluteofemoral fat depots to cardiovascular risk reflects differential ways in which these fat depots handle lipid and lipoproteins.

- Sex differences exist in lipids handling, which may explain the different implications of body fat depots in obesity-related lipid-lipoprotein profile and metabolic diseases in men and women.

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Conflict of Interest

None

Figure legends

Figure 1. Functional differences between adipose tissue (AT) depots. Abdominal AT (abdominal subcutaneous adipose tissue (ASAT) and visceral adipose tissue (VAT) depots) is the primary site for immediate storage of diet-derived fat. These fat depots have a high lipid turnover and undergo lipolysis in response to adrenergic stress stimuli. The gluteofemoral AT depot is characterised by a reduced lipid turnover with a high capacity to accommodate lipids undergoing redistribution consisting of recirculated fatty acids (from VLDL triglycerides or directly from the non-esterified fatty acid (NEFA) pool. The uptake of diet-derived fatty acids occurs less efficiently in the gluteofemoral fat than in the abdominal fat depot. This is balanced by less fatty acids release from gluteofemoral fat depot in the postabsorptive state or during adrenergic lipolytic stimuli. Consequently, this fat depot retains fatty acids well, which results in diminished exposure of ectopic tissues to lipids. AT, adipose tissue; VLDL, very low density lipoprotein; NEFA, non-esterified fatty acid

Figure 2. Relationship between body fat depots and obesity phenotypes against cardiovascular disease risk. Axis represent total fat percentage (total fat mass/total mass), visceral fat mass (VAT) and gluteofemoral fat mass (GF). Metabolically healthy normal weight (MHNW) individuals are characterised by relative ↑ GF and ↓ VAT; MHO (metabolically healthy obese) characterised by ↑↑ GF; MUNW (metabolically unhealthy, normal weight) characterised by ↑ VAT; and MUO (metabolically unhealthy obese) characterised by ↓ GF and ↑↑ VAT. At any given level of android fat, DEXA-measured peripheral fat (gynoid fat) is shown to be associate with reduced levels of fasting glucose, triglycerides, HOMA-IR (insulin resistance), and blood pressure. The differential association of upper and lower body fat depots with metabolic traits are evident in higher tertiles of fat mass index [11]. Thus, it is possible that such paradoxical associations are observed primarily in higher spectrum of obese phenotypes (MUNW and obese) characterized by greater total fat percentage. MHNW, metabolically healthy normal weight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obese.

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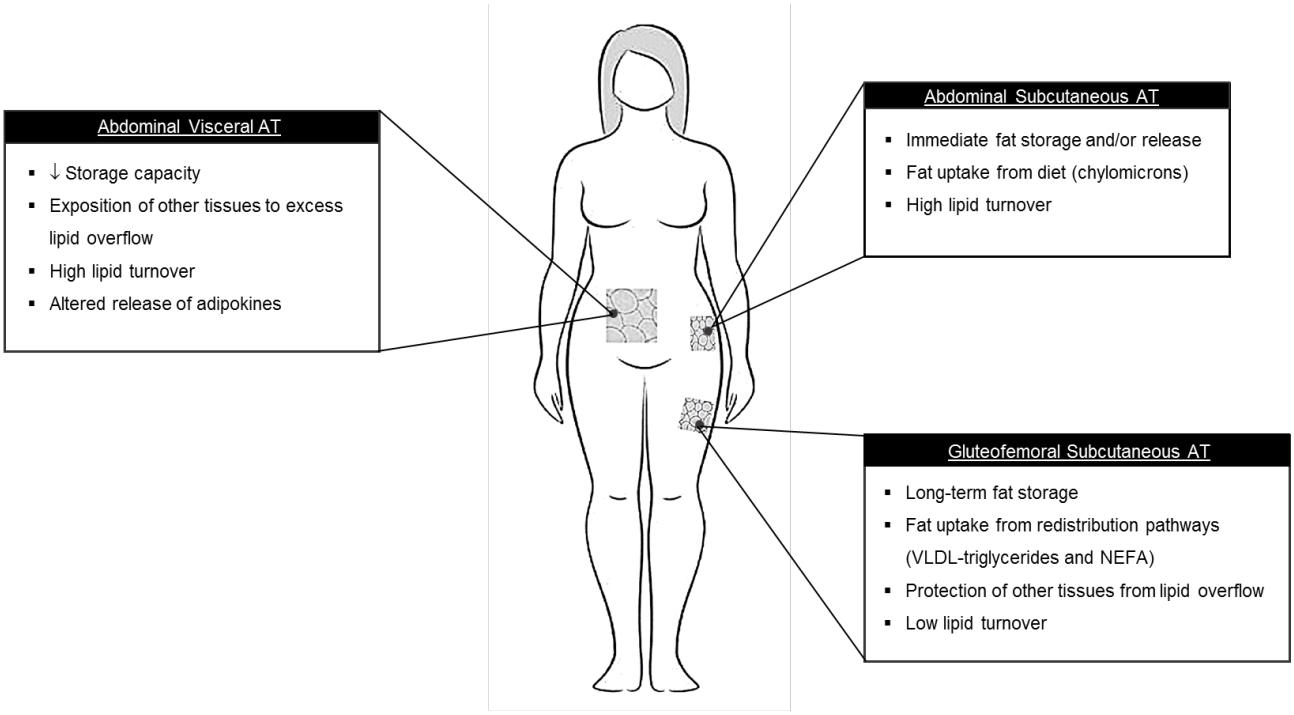

Figure 1 Functional differences between adipose tissue depots

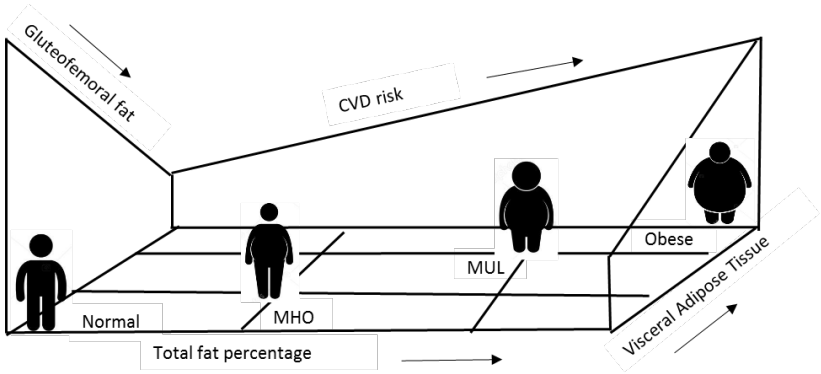

Figure 2. Relationship between body fat depots and obesity phenotypes against cardiovascular risk . Axis represent Total fat percentage (total fat mass/total mass), visceral adipose tissue (VAT) and Gluteofemoral fat (GF). Normal individuals are characterised by ↑GF and ↓VAT; MHO (metabolically healthy obese characterised by ↑↑GF, MUL (metabolically healthy, but lean) characterised by ↑↑VAT and obese phenotype characterised by ↓GF and ↑↑VAT.