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Lipid metabolism in women

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Differences in whole-body lipid metabolism between men and women are indicated by lower-body fat accumulation in women but more marked accumulation of fat in the intra-abdominal visceral fat depots of men. Circulating blood lipid concentrations also show gender-related differences. These differences are most marked in premenopausal women, in whom total cholesterol, LDL-cholesterol and triacylglycerol concentrations are lower and HDL-cholesterol concentration is higher than in men. Tendency to accumulate body fat in intra-abdominal fat stores is linked to increased risk of CVD, metabolic syndrome, diabetes and other insulin-resistant states. Differential regional regulation of adipose tissue lipolysis and lipogenesis must underlie gender-related differences in the tendency to accumulate fat in specific fat depots. However, empirical data to support current hypotheses remain limited at the present time because of the demanding and specialist nature of the methods used to study adipose tissue metabolism in human subjects. *In vitro* and *in vivo* data show greater lipolytic sensitivity of abdominal subcutaneous fat and lesser lipolytic sensitivity of femoral and gluteal subcutaneous fat in women than in men. These differences appear to be due to fewer inhibitory α adrenergic receptors in abdominal regions and greater α adrenergic receptors in gluteal and femoral regions in women than in men. There do not appear to be major gender-related differences in rates of fatty acid uptake (lipogenesis) in different subcutaneous adipose tissue regions. In visceral fat rates of both lipolysis and lipogenesis appear to be greater in men than in women; higher rates of lipolysis may be due to fewer α adrenergic receptors in this fat depot in men. Fatty acid uptake into this depot in the postprandial period is approximately 7-fold higher in men than in women. Triacylglycerol concentrations appear to be a stronger cardiovascular risk factor in women than in men, with particular implications for cardiovascular risk in diabetic women. The increased triacylglycerol concentrations observed in women taking hormone-replacement therapy (HRT) may explain the paradoxical findings of increased rates of CVD in women taking HRT that have been reported from recent primary and secondary prevention trials of HRT.

Lipid metabolism: Women: Adipose tissue

Marked differences in the amount and distribution of body fat between men and women provide clear evidence of gender-related differences in whole-body lipid metabolism (Bjorntorp, 1985; Ley *et al*. 1992). In women a greater amount of fat is stored in the lower-body gluteal regions, whereas in men most fat is stored in the upper body. In addition, women store greater amounts of fat subcutaneously, whereas in men fat storage occurs around the organs in the abdominal cavity and is referred to as visceral fat (Lemieux *et al*. 1993; Kotani *et al*. 1994). Impacts of gender are also reflected in distinct differences in concentrations of circulating lipids and lipoproteins, with concentrations of total cholesterol, LDL-cholesterol and triacylglycerols lower and that of HDL higher in premenopausal women than in men (Williams, 1997). Differences in body fat distribution and circulating lipids appear to reflect the actions of sex steroids on whole-body lipid metabolism, since after the menopause concentrations of lipoproteins, as well as body fat distribution, shift towards a more male pattern (Ley *et al*. 1992). Greater visceral fat accumulation occurs in both gender groups with age (Kotani *et al*. 1994), but this accumulation of fat within the

Abbreviations: HRT, hormone-replacement therapy; LPL, lipoprotein lipase.

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abdominal cavity is reduced in women receiving hormone-replacement therapy (HRT; Mattiason *et al*. 2002). Since visceral fat accumulation is strongly linked to risk of CVD, insulin resistance and diabetes (Kissebah *et al*. 1982), gender differences in fat distribution and whole-body lipid metabolism are of particular interest. Indeed, the lesser tendency to accumulate fat within the intra-abdominal sites in women may be the primary metabolic difference that underlies their reduced risk of CVD, metabolic syndrome and diabetes. The mechanisms underlying gender-related differences in body fat distribution, as well as the interaction between gender and fat distribution with respect to metabolic risk, remain to be fully determined. The present review will focus on the gender differences in regional adipose tissue lipolysis and lipogenesis and the potential impact of these differences on regional fat distribution and predisposition to the lipid abnormalities of the metabolic syndrome.

Regulation of fat deposition

The amount of fat deposited at any specific adipose tissue site reflects the balance between rates of lipolysis (fatty acid and glycerol release) and lipogenesis (fatty acid uptake) at that site. In the fasted state and during exercise lipolysis predominates, resulting in increased release of NEFA and glycerol into the circulation. Following meal ingestion insulin secretion results in suppression of lipolysis to basal levels whilst lipogenesis is stimulated. Insulin-mediated activation of lipoprotein lipase (LPL) hydrolyses fatty acids from circulating triacylglycerols in chylomicrons and VLDL, with uptake of the released fatty acids into adipose tissue and their re-esterification into stored triacylglycerol. It follows that regional variations in sensitivity to lipolytic stimulation during fasting and exercise, or variations in insulin-mediated suppression of lipolysis, and stimulation of fatty acid uptake and lipogenesis during the fed state could underlie gender differences in body fat distribution (Jensen, 1997; Blaak, 2001). Recent research has provided an insight into the impact of physiological variation, including gender, on the regulation of lipolysis in human adipose tissue (Arner, 1995, 1999). Much of the relevant information has been derived from *in vitro* studies of lipolysis in adipocytes taken from different body regions. In human subjects only catecholamines (noradrenaline and adrenaline) have acute stimulatory effects on lipolysis. At the cellular level the catecholamines bind to four different adrenoreceptor subtypes, β1, β2, β3 and α2 (Fig. 1). The β receptor subtypes are coupled to stimulatory GTP-sensitive proteins and activate the membrane-bound adenylate cyclase, leading to activation of protein kinase A and phosphorylated activation of hormone-sensitive lipase (HSL). Hormone-sensitive lipase catalyses the breakdown of stored triacylglycerol, releasing NEFA into the circulation. α2 Adrenergic receptors have the opposite effect on lipolysis. They couple to inhibitory GTP-sensitive proteins so that cAMP formation and subsequent activation of protein kinase A, hormone-sensitive lipase and lipolysis are inhibited. The net action of catecholamines on lipolysis will, therefore, depend on the balance between β and α receptors in specific adipose tissue sites. There is some evidence to suggest that this balance differs between regional adipose tissue sites in a gender-specific way, and could be one of the major factors determining whether excess fat is deposited in upper or lower body regions and whether it is stored subcutaneously or intra-abdominally (Wahrenberg *et al*. 1989).

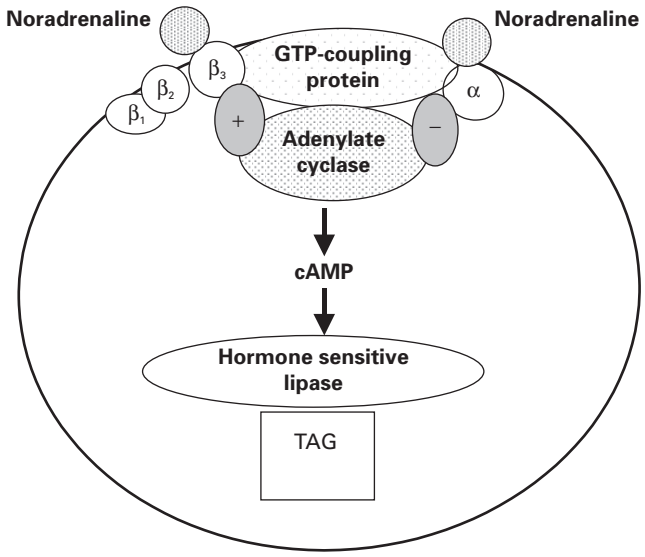

Fig. 1. Adrenergic regulation of adipose tissue lipolysis showing β adrenergic receptors (β1, β2, β3) linked via stimulatory GTP-coupling protein to activation of cAMP and hormone-sensitive lipase. α Adrenergic receptors (α2) are linked via inhibitory GTP-coupling protein to inhibition of cAMP and inhibition of hormone-sensitive lipase. TAG, triacylglycerol.

In the fed state lipolysis is inhibited by insulin-mediated inhibition of hormone-sensitive lipase, whereas LPL is activated by insulin-dependent actions on the release of stored LPL as well as stimulation of LPL gene expression (Merkel *et al*. 2002). Acute activation of LPL occurs via increased translocation of LPL, in its dimer form, from LPL stored in intracellular vesicles to the surface of the adipocyte, and then to the vascular endothelium where LPL is bound by heparan sulfate proteoglycans. Insulin mediates increased transcription of the LPL gene, which maintains intracellular stores of LPL during prolonged postprandial processing of chylomicrons such as that occurring following the ingestion of high-fat meals. Greater density and enhanced postprandial activation of LPL in specific regions could underlie regional differences in fat distribution between men and women. However, direct evidence to support gender-related regional variation in activation, or tissue-specific density of LPL, is rather limited as a result of the small number of studies that have investigated this possibility, especially in the *in vivo* situation. On the other hand, there is evidence to support the possibility that differences in regional adipose tissue blood flow during the postprandial period could contribute to gender-related impacts on body fat distribution (Romanski *et al*. 2000).

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Methods used to study effects of gender on regional fat distribution

The three main approaches used to study the impact of gender on regional fat distribution include (Jensen, 1997; Blaak, 2001): *in vitro* studies of adipose tissue; *in situ* measurements of adipose tissue lipolysis using microdialysis; whole-body studies using isotopic-tracer techniques. Considerable insight has been gained from *in vitro* studies of lipolysis, and to a lesser extent lipogenesis, in adipocytes taken from different regions. In relation to measurement of lipolysis, a number of confounding factors can affect the findings from *in vitro* studies. Local production of adenosine, an anti-lipolytic compound, may affect results, although some authors add adenosine deaminase to overcome this problem. As fat cells in different regions differ in size and surface area, failure to take account of differences in fat cell size or surface area also confounds findings. Microdialysis catheters consisting of very narrow dialysis tubing can be temporarily implanted into adipose tissue *in situ*, allowing sampling for measurement of glycerol concentration as an index of lipolysis. The major drawback to this technique is that regional measurement of blood flow is required to determine whether changes in glycerol concentrations reflect true changes in rates of lipolysis or whether they reflect altered regional blood flow. Many of the published studies in this area suffer the drawback of lack of this information. Since the microdialysis method has been particularly applied to studies of the effects of exercise on lipolysis, the possibility of changes in blood flow are clearly pertinent to the interpretation of the data. The most technically demanding approach for studying regional adipose tissue metabolism in human subjects is an *in vivo* model that employs a combination of isotope dilution, arterio–venous differences and regional body composition measurements to estimate regional fatty acid release relative to regional fat mass. The approach requires simultaneous placement of blood sampling cannulas in the femoral artery and vein and the hepatic vein, the infusion of a fatty acid isotope for dilution measurement and plasma flow measurement using indocyanine green. Regional fat mass is usually assessed using dual-energy x-ray absorptiometry or computed tomography. This *in vivo* method allows the measurement of adipose-tissue fatty acid release from the lower body (leg), and from the portal ('visceral') and non-portal ('subcutaneous') upper body regions. A number of the assumptions made in order to apply this model, e.g. that splanchnic fatty acid release reflects visceral adipose tissue release, are clearly not valid under certain circumstances and limit the strength that can be placed on the interpretation of the findings. This kinetic approach has further limitations when applied in non-steady-state conditions, e.g. postprandially. Under postprandial conditions meals are given in small frequent amounts to enable steady-state kinetics to be applied. However, it cannot be assumed that hormonal regulation of substrate disposition and utilisation under these circumstances are the same as those that apply when food is administered as a single 'acute' meal.

Upper-body *v.* lower-body fat deposition in men and women

It has been shown that abdominal subcutaneous adipocytes are more sensitive to adrenergic stimulation than gluteal adipose tissues in both men and women (Wahrenberg *et al*. 1989). Differences between abdominal and gluteal adipocyte adrenergic sensitivity appear to be greater in women than in men, and this difference may be due to women having greater numbers of adrenergic receptors in the gluteal region or fewer and less-sensitive adrenergic receptors in the abdominal subcutaneous fat (Richelsen, 1986). Thus, in women the overall effect would be a reduced tendency to mobilise fat from the gluteal region in response to adrenergic stimuli. This different pattern of adrenergic receptor distribution in men than women is supported by evidence that during exercise mobilisation of fat from subcutaneous abdominal adipose tissue is much more marked in women than in men (Arner *et al*. 1990; Hellstrom *et al*. 1996). Using the *in situ* microdialysis model, the concentrations achieved for glycerol and fatty acid were 2-fold higher in women than in men exercising at the same relative work loads (50% V_{O_2max}). Use of a specific β adrenergic inhibitor (propanolol) suppressed lipolysis to the same extent in men and women, whereas a selective α antagonist (phentolamine) caused a further increase in lipolysis in men but not in women (Hellstrom *et al*. 1996). These data support the view that the greater lipolytic sensitivity to exercise in women than in men is a result of fewer, or lesser sensitivity of, α adrenergic receptors in this region in women. Measurement of regional fatty acid release in normal-weight men and women in response to adrenaline or following meal ingestion are generally in line with this model (Jensen *et al*. 1996). Leg fatty acid release was shown to double during adrenaline infusion in men, but no change was observed in women, indicating blunted lipolytic response to adrenaline in lower-body fat in women compared with men. However, a more recent microdialysis study showed no major difference in catecholamine-mediated glycerol response in femoral (leg) and abdominal adipose tissue and no difference between men and women (Millet *et al*. 1998).

Regional differences in adipose tissue deposition between men and women may also reflect greater or lesser tendency for specific depots to undergo suppression of adipose tissue lipolysis in the fed state. Using the *in vivo* isotope-dilution model described earlier to study regional differences in fatty acid release, Jensen (1995) showed an overall greater suppression of whole-body lipolysis in women than in men, but release of fatty acid from leg adipose tissue was equally suppressed in both groups. The major difference between men and women in this study was less postprandial suppression of fatty acid release in upper body 'non-portal' (subcutaneous) adipose tissue in men than in women. Less inhibition would tend to indicate a lower predisposition for the upper-body subcutaneous region to accumulate fat in men compared with women. This explanation is consistent with observed measurements, since although men have larger amounts of upper-body fat, most of this fat is in the visceral rather than subcutaneous compartment. Overall, these data of Jensen (1995) suggest

that reduced sensitivity to the anti-lipolytic actions of insulin in men leads to sustained fatty acid output from this region, even under fed conditions. There are no *in vitro* data for regional rates of lipolysis in response to insulin in adipose tissue from men and women, so it is not known whether the lesser suppression of lipolysis in upper-body adipose tissue compared with leg adipose tissue seen in the *in vivo* studies, is also observed *in vitro*.

Regional variations in rates of fatty acid uptake into adipose tissue triacylglycerol are clearly the other main determinant of net fat deposition at individual sites. However, very few studies have been able to measure regional differences in adipose tissue lipogenesis, particularly in the *in vivo* situation. Rates of whole-body adipose tissue fatty acid uptake into subcutaneous adipose tissue, measured over hours and days following consumption of labelled fats in fat-containing meals, have been conducted in a small number of subjects. Overall, these data illustrate greater net fat deposition in women than in men (Romanski *et al*. 2000), although absolute rates of uptake (per g) of adipose tissue did not differ. More meal fatty acid uptake occurred in abdominal fat than leg fat in both genders, and there were no differences in uptake between men and women in the abdomen, thigh or leg. However, regional blood flow was markedly higher in the leg region in women during the period following food ingestion, which could support greater rates of net fat deposition in this region. A further notable difference in postprandial utilisation of administered fat between men and women observed in this study was the greater percentage of administered fat that was not accounted for by uptake into subcutaneous fat or by fat oxidation in the men. This percentage of the administered dose amounted to 45 in men but only 30 in women. Since this *in vivo* study clearly could not measure uptake of fatty acids into visceral intra-abdominal sites, the authors suggested that the 'missing fat' could reflect greater rates of uptake of fatty acids into intra-abdominal fat depots in men. This explanation supports the concept that in men there is greater diversion of fat stores into upper-body visceral fat stores in the fed state. This concept is further developed in the next section, which specifically focuses on a gender comparison of visceral *v*. subcutaneous fat metabolism.

In summary (Table 1) the greater tendency for women to accumulate fat in lower body regions appears to be a result of a lesser sensitivity to lipolytic stimulation in lower-body fat and a greater sensitivity to lipolytic stimuli in upper abdominal fat in women than in men. With respect to subcutaneous fat there appear to be no regional differences in the rates of adipose tissue lipogenesis between men and women, with both genders showing greater fatty acid uptake into abdominal body fat than lower-body fat during the fed state.

Visceral *v*. subcutaneous fat deposition

Men have a marked tendency to accumulate fat in the intra-abdominal visceral fat depots. Initially, therefore, it is surprising that one of the major, and most consistently observed, differences in adipose tissue metabolism between men and women is the greater rates of visceral tissue lipolysis reported in men. Rebuffé-Scrive *et al*. (1989) compared basal and noradrenaline (β and α adrenergic agonist)- and isoprenaline (β-agonist)-stimulated rates of lipolysis in visceral tissue and in non-visceral adipose tissue in men and premenopausal women. They showed that in men catecholamine-stimulated rates of lipolysis in visceral fat were approximately 1·5- and 2-fold higher in response to noradrenaline and isoprenaline respectively than those in women. This data supports the idea of greater β and lesser α adrenergic sensitivity in visceral fat in men than in women, opposite to the effects of gender on adrenergic sensitivity within subcutaneous adipose tissue. These *in vitro* findings are supported by estimates of regional fatty acid turnover in men and women following the administration of adrenaline (Jensen *et al*. 1996). In this study adrenaline stimulated a 2-fold increase in splanchnic fatty acid release in men, but there was no corresponding increase in women.

An explanation for this apparently contradictory situation, in which greater rates of visceral lipolysis in men are associated with larger visceral fat stores, may lie in the fact that rates of fatty acid uptake into visceral or splanchnic areas also appear to be considerably higher in men compared with women. Most of the available *in vivo* data, whilst sparse, support the view that the greater tendency for fat deposition in visceral adipose tissue in men is a result of higher rates of postprandial fatty acid uptake into this depot in the fed state. Although whole-body uptake of meal fatty acids into storage fat is markedly higher during the postprandial state in women than in men (Romanski

Table 1. Mechanisms underlying the greater tendency to body fat accumulation in the lower body in women than in men

	Site	Women *v*. men	Cause
Rates of fatty acid release (lipolysis)	Abdominal adipose tissue	Higher in women than men	Greater β adrenergic or lesser α adrenergic sensitivity in abdominal adipose tissue
	Gluteal or femoral adipose tissue	Lower in women than men	Lesser α adrenergic sensitivity in lower-body-fat adipose tissue
Rates of suppression of fatty acid release in the fed state (anti-lipolysis)	Abdominal adipose tissue	Higher in women than men	Less sensitivity to anti-lipolytic action insulin
	Leg adipose tissue	Similar	
Rates of uptake of fatty acids in the fed state (lipogenesis)	Abdominal	Similar	
	Femoral, gluteal	Similar	

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et al. 2000), it would appear that in men a greater proportion of meal fatty acids is deposited in visceral fat. Using tracer techniques and serial biopsy of subcutaneous adipose tissue for 24 h after meal consumption, Romanski *et al*. (2000) showed fatty acid uptake to be greater in the upper-body fat than in the lower-body fat in both men and women. However, in women uptake into subcutaneous adipose tissue accounted for 38 % of the total meal fatty acids, whereas in men only 24 % of the meal fatty acids appeared in adipose tissue within 24 h. Since fat oxidation did not differ between the two groups (approximately 26 % for both genders), the other main difference was in the percentage of the meal fatty acid not accounted for, which was 45 in men and 30 in women. The authors showed a significant correlation between the percentage 'missing' meal fatty acid and the visceral fat mass (r 0·58; $P < 0·005$) and suggested that the missing fatty acid may be deposited in visceral fat. This explanation is supported by the findings of Marin *et al*. (1995), who showed avid uptake of meal fatty acids into intra-abdominal fat deposits in men, as well as marked effects of androgens on uptake in this region (Marin *et al*. 1996). Nguyen *et al*. (1996) measured splanchnic uptake of fatty acids in the postprandial state and showed that the percentage of the meal triacylglycerols removed from the splanchnic region was >70 for men, but <10 for women. This finding supports the view that in women meal fatty acid uptake occurs into subcutaneous fat, and more in the abdominal region than in lower body region. However, in men meal fatty acids largely appear to enter the visceral fat compartment during the postprandial period.

Support for the view that there are gender differences in the regulation of visceral fat is provided by recent reports of a gender-specific impact of gene polymorphisms in adrenergic receptors on risk of abdominal obesity. Common polymorphisms in the β2 and β3 adrenergic receptor have been studied in relation to risk of obesity. Some studies show greater risk of abdominal obesity for the β2 adrenergic receptor gene variant (Gln27Glu; Large *et al*. 1997), while other investigators do not (Kortner *et al*. 1999; Oberkofler *et al*. 2000). Contradictory findings in relation to the impact on the prevalence of obesity have also been revealed for the common β3 polymorphism (Trp64Arg; cited by Kawamura *et al*. 2001). These contradictory findings may relate to the fact that there appears to be a strong gender–gene interaction for these polymorphisms. In a Japanese-American population the presence of the variant β3 gene and a BMI of >24·2 kg/m^2 was linked with increased visceral fat accumulation and with insulin resistance in men but not in women (Kawamura *et al*. 2001). Similarly, the β2 Gln27Glu polymorphism was associated with a 10-fold higher risk of abdominal obesity in men, but there was no effect of the polymorphism on risk of abdominal obesity in women (Corbalán *et al*. 2002). Since these variant forms are linked with reduced functional activity of the adrenergic receptor, these data would suggest that the lack of normal adrenergic sensitivity in visceral adipose tissue predisposes men, but not women, to visceral accumulation of fat in situations of positive energy balance.

In summary (Table 2), an increased tendency to accumulate visceral fat in men compared with women appears to be a result of markedly higher rates of fatty acid uptake (6–7-fold) into this region during the fed state in men. Rates of lipolysis are also higher in men than in women (1·5–3-fold), and this gender difference appears to be a result of fewer α adrenergic receptors in visceral fat adipose tissue in men.

Implications of differences in adipose tissue metabolism and body fat distribution on circulating lipids and risk of chronic disease

The role of visceral fat metabolism, in particular enhanced rates of visceral fat lipolysis, in mediating some of the adverse effects of upper abdominal obesity has been suggested for some time (Arner, 1995). The effects appear to be related to the overproduction and increased delivery of fatty acids to the liver. Unlike other fat depots visceral fat has direct access to the liver via the portal system. Here elevated concentrations of fatty acids can interfere with normal hepatic metabolism, leading to reduced insulin clearance, increased triacylglycerol and VLDL synthesis, as well as stimulation of hepatic gluconeogenesis. Systemically, at increased concentrations fatty acids compete with glucose for uptake into peripheral tissues via the Randle's glucose–fatty acid cycle. Thus, it is clear that visceral fatty acid release can contribute to the metabolic disturbances associated with abdominal obesity; notably glucose intolerance, hypertriacylglycerolaemia and ultimately the dyslipidaemia of the metabolic syndrome. Couillard *et al*. (1999), in a comparison of postprandial lipoprotein metabolism in men and women, concluded that much of the excess lipidaemia observed in men compared with women was a direct consequence of increased visceral fat mass and associated elevated postprandial fatty

Table 2. Mechanisms underlying the greater tendency for fat accumulation in visceral adipose tissue in men than women

	Site	Men *v*. women	Cause
Rates of fatty acid release (lipolysis)	Visceral adipose tissue	Higher in men than women	Lesser α adrenergic sensitivity in men
Rates of suppression of fatty acid release in the fed state (anti-lipolysis)	Visceral adipose tissue	Similar?	
Rates of uptake of fatty acids in the fed state (lipogenesis)	Visceral	Higher in men than women	Greater sensitivity to insulin?

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acid concentrations. In this study, although men and women were matched for total body fat mass, men had 50% more visceral fat than women. Fasting triacylglycerols and postprandial triacylglycerol responses to fat-containing meals were also approximately 50% higher in men than in women. The biggest difference between the two groups was in the area under the postprandial fatty acid response curve, which was 3-fold higher in men than in women, with a particularly marked difference in the 4–8 h postprandial period. When male and female subjects were matched for visceral fat mass, differences in fasting triacylglycerols disappeared and much of the difference in postprandial lipidaemia between the genders was also removed. However, the postprandial response of the small triacylglycerol-rich lipoproteins remained higher in males than in females matched for visceral fat mass. Overall, the data are supportive of the view that visceral fat mass and accelerated fatty acid delivery to the liver drives increased synthesis of VLDL, leading to elevated triacylglycerols in the fasted state. Prolonged elevation in fasting triacylglycerols contributes to increased competition between VLDL and chylomicrons following fat ingestion, leading to an elevated postprandial triacylglycerol response. Elevated fasting and postprandial triacylglycerols can then drive the transfer of triacylglycerols onto cholesterol-containing lipoproteins (LDL- and HDL-cholesterol) via neutral lipid transport catalysed by cholesteryl ester transfer protein. Removal of excess triacylglycerol from LDL and HDL by the action of hepatic lipase leads to the formation of small dense LDL and HDL (Williams, 1997). The latter is rapidly catabolised, leading to low HDL concentrations. Small dense LDL has a prolonged circulation time and greater penetration of the endothelium because of its smaller particle diameter. It can therefore be seen that greater visceral fat mass is at least a major contributor to the dyslipidaemia of the metabolic syndrome and other insulin-resistant states. This dyslipidaemia, termed the atherogenic lipoprotein phenotype, consists of a combination of elevated fasting and postprandial triacylglycerols, low HDL and raised small dense LDL, and is associated with a 3–4-fold higher risk of CVD.

Female sex hormones, hormone-replacement therapy and CVD

For many years HRT has been recommended as a means of cardio-protection in post-menopausal women. This recommendation has been made on the basis of observed beneficial effects of oestrogen-replacement therapy on circulating LDL, HDL and lipoprotein(a) concentrations, as well as observational data showing lower rates of CVD in women selecting to undertake HRT (Stampfer & Colditz, 1991). However, a series of randomised controlled secondary prevention trials have failed to show the benefit of HRT on major cardiovascular events (cited in Klein & Herrington, 2002). More recently, and contrary to expectations, the Women's Health Initiative, which was the first placebo-controlled trial of HRT in women without previous CVD, demonstrated increased risk for cardiovascular events, stroke and venous thrombo-embolic events (Writing Group for the WHI Investigators, 2002). As a result of the adverse findings one arm of the trial was stopped prematurely. The impact of these data, as well as previous negative outcomes from secondary prevention trials of HRT, have resulted in marked changes in the accepted indications for HRT use in post-menopausal women. It is considered that use of HRT in peri- and post-menopausal women should be advised only for the alleviation of menopausal symptoms and/or prevention of premature osteoporosis. Importantly, for women with a previous history of heart disease HRT is now considered as being contraindicated.

Table 3. Comparison of blood lipids in postmenopausal women and women taking hormone-replacement therapy (HRT)

Plasma lipid	Post-menopausal women	Women on HRT
Total cholesterol	Increased	Decreased
LDL-cholesterol	Increased	Decreased
HDL-cholesterol	Decreased	Increased
Triacylglycerols	Increased	Increased

A major consideration has been the possible mechanisms that could underlie these negative findings, especially in view of the overall positive impact of HRT on circulating lipoprotein concentrations. The explanation may relate to the different effects of natural oestrogens and those used in HRT on circulating triacylglycerols (Table 3; Blum & Cannon, 2001; Ariyo & Villablanca, 2002). Unlike naturally-produced oestrogens, and some of the recently-developed selective oestrogen-receptor modulators, the oestrogens used in most HRT preparations lead to elevated fasting and postprandial triacylglycerols (Table 3). The disparity between the different forms of oestrogen appears to be a result of selectivity of oestrogen receptors (Ray *et al*. 2002) at various tissue sites. The adverse influence of HRT on triacylglycerols does not appear to be a result of the impact on visceral fat mass since, as previously indicated, oestrogen therapy leads to a reduction in visceral fat mass in post-menopausal women (Mattiason *et al*. 2002). The most likely explanation appears to be adverse effects on hepatic VLDL synthesis and fat oxidation, which has been demonstrated in younger women using oral contraceptives (Perseghin *et al*. 2001).

Along with other evidence showing the greater impact of raised triacylglycerol concentrations (e.g. in diabetes) on the risk of CVD in women, these data support the view that triacylglycerols may be a more important blood lipid risk factor in women than in men (Williams, 1997). From a nutritional perspective, this evidence suggests that the debate concerning the relative public health benefits of low-fat diets *v*. moderate-fat diets should take greater account of the possibility that raised triacylglycerols resulting from the effects of high-carbohydrate diets may have a greater adverse impact in women than in men.

Conclusions

Greater tendency to accumulate fat in lower body regions in women appears to be largely a result of lesser sensitivity to lipolytic stimulation in this region, with greater

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sensitivity in upper-body subcutaneous fat. In men accumulation of visceral fat in intra-abdominal sites results from a greater uptake of fatty acids from meal fat during the postprandial state, although rates of lipolysis are also higher in visceral fat stores in men than in women. Exaggerated release of fatty acids from visceral fat and its direct delivery to the liver via the portal vein provides substrate for increased synthesis of VLDL, leading to elevated fasting and postprandial triacylglycerols, which is thought to be the primary metabolic disturbance leading to the development of an atherogenic lipoprotein phenotype. Elevated triacylglycerol concentrations appear to be a stronger cardiovascular risk factor in women than in men, and may underlie the adverse effects of diabetes and HRT on cardiovascular risk in women.

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