Sexual Dimorphism in Human Lipid Metabolism

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ABSTRACT The existing work demonstrates that striking differences exist between men and women in lipid kinetics. These differences cannot be explained simply by the presence and action of sex hormones and are not always due to secondary, phenotypic traits that characterize men and women (e.g., body composition, regional fat distribution). In fact, some of these secondary traits may even be the result of sexual dimorphism in metabolism, and being of female or male genotype also determines intermediary metabolism. This review provides an overview of the currently available information regarding sexual dimorphism in human lipid metabolism but does not provide an in-depth account of current knowledge (due to limited space); it will be a broad introduction to those interested in the field and will, hopefully, stimulate further efforts to unravel the secrets of male and female metabolism. What has been discovered so far regarding differences in lipid metabolism between men and women is likely only the tip of the iceberg; clearly, more work is necessary to fully understand human substrate metabolism and the implications the presence of sexual dimorphism in the control of substrate kinetics has on the prevention and treatment of disease. J. Nutr. 135: 681–686, 2005.

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Within the past decade, a great deal of effort has been dedicated to uncovering the relevant physiologic differences between the sexes that may affect the prevention, diagnosis, and treatment of disease. For example, there are differences between the sexes in the lipid profile that may have clinical implications. In women, high plasma triglyceride (TG) concentrations are independent and better predictors of cardiovascular disease risk than total or LDL cholesterol (1,2). Treatment of hypertriglyceridemia may, therefore, be of greater importance in women than in men. Also, differences in hepatic handling of fatty acids between men and women are likely responsible for the greater susceptibility of women to fatty liver disease and the more severe liver injury as a result of it (3). A better understanding of the control of lipid metabolism by a person’s sex will therefore not only increase our knowledge of human intermediary and macronutrient metabolism, but may also be useful for the development of novel approaches for the treatment and prevention of disease.

There are 2 general approaches when evaluating differences in metabolism between the sexes. One (clinically probably the most relevant) is to accept the differences in phenotype between men and women (e.g., body composition, regional fat distribution, aerobic fitness, all of which affect substrate metabolism in persons of the same sex) and acknowledge that the observed differences in lipid metabolism may be secondary to those characteristics. The other strives to eliminate as many potential confounding variables as practically feasible to determine whether sex per se represents an underlying factor in the control of metabolism.

A simple view concerning the underlying cause for sexual dimorphism in metabolism would be to blame it on the presence and known action of the sex hormones. However, we are now starting to discover that many genes are actually expressed in a sexually dimorphic manner, and there is evidence for differences in post-translational changes in men and women (although the mechanisms are mostly unknown); this will almost certainly result in different enzyme activities, abundance of cellular signal transduction elements, and consequently, in substrate kinetics. Furthermore, the association of many gene polymorphisms [e.g., (4–6)], associated with risk factors for disease and substrate kinetics is also often sex specific (Fig. 1).

The aim of this article is to review the major findings on differences of human fatty acid and TG metabolism between men and women in the basal, overnight fasted state and during those characteristics. The other strives to eliminate as many potential confounding variables as practically feasible to determine whether sex per se represents an underlying factor in the control of metabolism.

Fatty acid kinetics

Circulating fatty acids, derived from the breakdown of endogenous TG that are stored in adipose tissue and muscle, are an important source of fuel. Insulin is the major regulator of basal and postprandial lipolytic rates (7), whereas cat-

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3 Abbreviations used: LPL, lipoprotein lipase; Ra, rate of appearance; TG, triglyceride.
Echolamines are important for stimulating lipolysis during metabolic stress. The release of fatty acids into the bloodstream is stimulated during conditions of "glucose-shortage" (e.g., fasting, exercise) to meet the increased demand and inhibited when glucose is available to cover fuel requirements (Fig. 2). An imbalance between the release and utilization of fatty acids leads to elevated plasma fatty acid concentrations, which is associated with increased plasma TG concentrations and insulin resistance and, most likely as a result of that, an increased risk for the development of cardiovascular disease (8). The following sections will provide an overview of our current knowledge concerning differences between men and women in fatty acid kinetics during basal, postabsorptive conditions, and the major physiologic conditions that inhibit (meal intake/hyperinsulinemia) and stimulate (exercise and fasting) lipolysis. The amount of information available for each of these topics varies greatly, with exercise clearly being the most extensively studied field.

**Basal, postabsorptive state**

Early studies that used isotope tracer methods found that the basal rate of appearance (Ra) of fatty acids in the bloodstream is stimulated during conditions of "glucose-shortage" (e.g., fasting, exercise) to meet the increased demand and inhibited when glucose is available to cover fuel requirements (Fig. 2). An imbalance between the release and utilization of fatty acids leads to elevated plasma fatty acid concentrations, which is associated with increased plasma TG concentrations and insulin resistance and, most likely as a result of that, an increased risk for the development of cardiovascular disease (8). The following sections will provide an overview of our current knowledge concerning differences between men and women in fatty acid kinetics during basal, postabsorptive conditions, and the major physiologic conditions that inhibit (meal intake/hyperinsulinemia) and stimulate (exercise and fasting) lipolysis. The amount of information available for each of these topics varies greatly, with exercise clearly being the most extensively studied field.

**Food intake/hyperinsulinemia**

Insulin stimulates glucose uptake by tissues in response to food intake and is the major regulator of lipolysis (14–16). No study has compared the inhibitory effect of insulin on adipose tissue lipolytic activity in men and women, but it appears that women are more sensitive to its effects. The suppression of plasma fatty acid concentrations during an oral glucose tolerance test (17) and suppression of oleate Ra (18) after a standard meal were greater in women than in men, predominantly because of the resistance of men's upper-body subcutaneous adipose tissue to insulin (18). These findings are particularly striking because women in those studies were fatter than men and increased body fat mass is associated with a reduced sensitivity of adipose tissue to the effects of insulin (19). The greater sensitivity of women to the antilipolytic effect of insulin probably compensates, at least in part, for the higher basal fatty acid flux and helps maintain overall fatty acid homeostasis. In addition to the differences between men and women in the response of the endogenous release of fatty acids during hyperinsulinemia/meal intake, there are also differences in the handling of meal TG-bound fatty acids. Compared with women, men take up a considerably greater proportion of exogenous fatty acids in splanchnic tissues (20), whereas women store a greater percentage (~40% vs. 25%) of dietary fatty acids in subcutaneous adipose tissue (21). This phenomenon likely contributes to the greater fat storage in visceral adipose tissue in men (22). The reasons for the sex-dependent regional channeling of dietary fatty acids are unknown; we can, however, rule out testosterone as one of the possible causes because administration of testosterone, which caused a
doubling of its concentration in plasma, reduced the storage of dietary fatty acids in visceral and retroperitoneal adipose tissue and increased the storage in subcutaneous adipose tissue (23). The effects of female sex hormones (or lack thereof) on regional fatty acid storage have not been studied to date.

Exercise

Evaluating lipid kinetics in men and women during exercise is particularly difficult because it is affected by body composition, aerobic fitness, and training status, age, menstrual cycle phase (during high-intensity exercise), and possible other less explored factors such as muscle fiber-type composition (24,25). This may explain in part the often controversial results in the literature. For example, several studies found that the rate of fat oxidation was higher in both untrained and trained women than men, whereas others found that women use more fat and less carbohydrate than men; still others were unable to report differences between the sexes (25). To avoid those confounding influences, we recently examined lipid metabolism during moderate-intensity endurance exercise in young adult men and women who were matched for fatness, aerobic fitness, and age (26). We found that fatty acid Ra [and rate of disappearance (Rd)] during exercise was greater in women than in men, but that the rate of total fatty acid oxidation did not differ between the 2 groups. Compared with men, however, women oxidized more plasma free fatty acids, derived primarily from adipose tissue TG, and less nonplasma fatty acids, presumably derived primarily from intramuscular TG and possibly VLDL-TG. The greater reliance on plasma free fatty acids as a fuel in women than in men was likely a result of greater availability of those fatty acids in women than in men. Contradicting those findings, studies performed at the August Krogh Institute in Copenhagen (27,28) suggested that intramuscular TG use during exercise, determined by evaluating fat content in muscle biopsies, is actually greater in women than men, who were matched for aerobic fitness but not body composition. Limitations in using intramuscular TG content as a measure of intramuscular TG oxidation during exercise and differences in matching men and women on body composition may be responsible for the discrepancy between studies. The mechanism(s) responsible for the differences between the sexes in lipolysis of adipose tissue TG observed in our subjects during exercise is not entirely understood but is partly related to differences in lipolytic sensitivity to \( \beta \)-adrenergic stimulation and \( \alpha \)-adrenergic receptor activity [see (24,25)]. Most of the increase in lipolytic activity that occurs during exercise is mediated through catecholamine stimulation of adipose tissue \( \beta \)-adrenergic receptors; although \( \alpha \)-adrenergic receptor activity was also shown to inhibit lipolysis during exercise, thereby counteracting the \( \beta \)-adrenergic effect in men, it is not involved in the regulation of lipolysis during exercise in women.

Excess body fat blunts the relative increase in fatty acid Ra induced by endurance exercise in both men and women (29–31). However, the mechanism responsible for the blunted lipolytic response to exercise associated with obesity may differ in men and women. First, we (30) and others (32,33) found that exercise causes a smaller increase in plasma epinephrine concentration in obese than in lean men, whereas the catecholamine response during exercise does not differ in lean and obese women (29,31,34). Furthermore, unlike obese men (35–37), adipose tissue \( \beta \)-adrenergic receptor sensitivity is decreased in obese women (30), whereas \( \alpha \)-adrenergic receptor stimulation during exercise is greater in both obese men and women compared with lean subjects (38). Therefore, the composite of these data suggests that there is sexual dimorphism in the adrenal medullary response to exercise and in adipose tissue lipolytic response to epinephrine stimulation in obese subjects.

Information regarding the metabolic response to exercise training in men and women is controversial. In one study, exercise training caused a greater increase in fat oxidation during exercise in women than in men (39–41). However, these findings were confounded by the fact that the increase in aerobic fitness was also greater in women (25%) than in men (9%). In another study, 12 wk of endurance training in women increased total fat oxidation by \( \approx 25\% \) during exercise performed at the same absolute intensity (15). This response is the same as that reported in men after a similar training-induced increase in fitness (42,43). When plasma free fatty acid oxidation was assessed by isotope tracer methods, and whole-body fat oxidation was assessed simultaneously by indirect calorimetry, it was found that the training-induced increase in fat oxidation was due primarily to an increase in the oxidation of nonplasma fatty acids, presumably intramuscular TG (15). In contrast, Steffensen et al. (28) found no effect of training status on intramuscular TG use between men and women, when TG content was measured in muscle biopsies during moderate intensity exercise, and exercise was performed at the same relative intensity in a cross-sectional study of untrained, moderately, and highly trained subjects. However, total fat oxidation was higher in highly trained than sedentary and moderately trained subjects. The reason for the discrepancy in the source of oxidized TG between studies is not clear but may be related to differences in study design (longitudinal vs. cross-sectional analysis) and the methods used to assess intramuscular TG use (muscle biopsy vs. isotope tracer and indirect calorimetry techniques).

Fasting

The initial response to fasting is characterized by an increase in the mobilization of adipose tissue TG and a decrease in the production and oxidation of glucose. Studies that were performed many years ago showed that the increase in plasma fatty acid and ketone body concentrations (44–46) is greater in women than in men. These findings may at first suggest that the mobilization of fatty acids from adipose tissue is likely greater in women than in men during fasting. However, plasma substrate concentration represents the balance between substrate delivery into plasma and substrate tissue uptake but does not provide information regarding the dynamic metabolic events responsible for the observed concentrations. In fact, contrary to these earlier studies, we found that the relative increase in glycerol Ra during brief fasting was greater in men than in women, most likely because of both higher basal plasma insulin concentrations and a greater increase in epinephrine release during fasting in men (47). The relatively blunted lipolytic response in women may be beneficial by preventing excessive and potentially harmful increases in plasma fatty acid concentrations (48).

Sex hormones

Little information is available regarding the direct effect of sex hormones on human fatty acid metabolism. That is undoubtedly due to the undesirable side effects when administering sex hormones in excess or to the opposite sex, or blocking their action. Surprisingly, the literature does not satisfactorily cover those gaps with data from studies in animals, and studies of postmenopausal women or hypogonadal men. There is evidence that variations in circulating female
sex hormones can affect substrate kinetics during extreme physiologic conditions such as high-intensity exercise (49); however, fatty acid kinetics were the same during the follicular and luteal phases of the menstrual cycle during basal and many other conditions (49–53). Interestingly, administration of estrogen to postmenopausal women increased basal fatty acid Ra (54); however, this was only a ~10–20% increase, probably too small a difference to be detected during normal fluctuations of the menstrual cycle. It is also possible that progesterone may counteract the effects of estrogen, but the effects of progesterone on the control of human lipid metabolism have not been systematically studied. Also, at odds with the findings that basal lipolytic rates are higher in women than men (see above), are the results from studies in which testosterone administered to obese men for 2 mo increased abdominal adipose tissue turnover (23). In adipocytes cultured in vitro (55,56), testosterone had no effect on the basal rate of lipolysis but increased the responsiveness of the adipocytes to isoproterenol and forskolin. The physiologic relevance of those findings is unknown because adipose tissue lipolytic sensitivity is similar in men and women when adipocytes are isolated and exposed to physiologic concentrations of catecholamines (57–60) and in vivo during catecholamine infusion (10,61).

Plasma triglyceride kinetics

Chylomicrons and VLDL contain the greatest amount of TG in the fed and fasted states, respectively. Triglycerides in chylomicrons and VLDL are progressively hydrolyzed by lipoprotein lipase (LPL) present in muscle and adipose tissue capillary endothelia (62), and the resulting fatty acids are taken up by local tissues, where they can be oxidized for fuel or stored as TG. Alterations in lipoprotein metabolism are involved in the pathogenesis of cardiovascular disease. Epidemiologic studies demonstrated a direct relation between both fasting and postprandial plasma TG concentration and the risk for the development of cardiovascular disease, especially in women (1,2,63,64). Moreover, an increase in fasting plasma TG concentration is often associated with a decrease in plasma HDL cholesterol (1), which also contributes to the risk for cardiovascular disease (65) and that more so in men than in women (2). Despite increasing evidence that alterations of the plasma lipid profile that pose a risk for the development of disease and vice versa are associated with certain diseases differ greatly between men and women, few studies have been designed to better understand lipoprotein metabolism in the 2 sexes.

Basal, postabsorptive VLDL-TG kinetics

We demonstrated recently that sex, independent of body fatness, has a substantial effect on basal VLDL-TG kinetics and the relation between VLDL-TG kinetics and plasma TG concentration. We found that VLDL-TG secretion rates were greater in lean women than in lean men, and the rate of VLDL-TG secretion rate increases with increasing amounts of body fat in men but not in women (66). This is probably due to the greater availability of nonsystemic fatty acids for VLDL-TG production in obese men, likely because of greater visceral fat accumulation in obese men compared with obese women (22). Furthermore, the concentration of plasma VLDL-TG concentration was directly related to basal VLDL-TG production in men, but was inversely related to VLDL-TG clearance in women. There is some evidence that adipose tissue and skeletal muscle LPL activity may be affected by both sex and obesity (35–39); the results from different studies, however, are inconsistent. Sex differences appear to also exist in the rate of secretion of VLDL-apolipoprotein B; in this case, however, the secretion rate is higher in men than women (67), which suggests that the VLDL particles secreted in men are smaller than those in women, consistent with data that measured concentrations of different size VLDL particles in the bloodstream (68). Differences in the particle size may contribute to the differences in risk for the development of cardiovascular disease (69) between men and women.

VLDL-TG kinetics during hyperglycemia-hyperinsulinemia/meal intake

Decreasing endogenous VLDL-TG production during postprandial conditions is important for regulating whole-body TG flux when dietary TG are entering the systemic circulation via chylomicrons. A suppression of VLDL-TG production during feeding is probably mediated in large part by the glucose-induced stimulation of insulin secretion; a euglycemic-hyperinsulinemic clamp lowered the rate of secretion of VLDL-TG into plasma, in lean and obese women (no data are available in men) with no difference in the magnitude of the effect between the lean and obese. However, this conclusion may not be robust because VLDL-TG production rate was determined by using a tracer method that did not account for hepatic tracer recycling, which can have considerable effects on the calculation of VLDL-TG kinetics (70). We examined the effect of hyperglycemia-hyperinsulinemia induced by glucose infusion (to achieve postprandial plasma glucose and insulin concentrations) on VLDL-TG metabolism in lean and obese men and women. Glucose infusion markedly decreased VLDL-TG production in lean and obese men and lean women, but not in obese women. The blunted response in obese women occurred despite plasma fatty acid concentrations similar to those in the other groups. These data demonstrate that sex and adiposity affect the glucose/insulin-mediated suppression of VLDL-TG production and suggest that plasma fatty acid availability, despite the common belief that it is the main regulator of VLDL-TG production, may not be the primary regulator of VLDL-TG metabolism, at least in obese women. Data from several studies that suggest that VLDL-TG production is controlled largely by hepatic fatty acid availability were obtained under conditions that do not always mimic physiologic conditions (e.g., fatty acid concentrations were raised several fold above the normal range observed throughout a day) or were confounded by the methods used (e.g., heparin, which stimulates lipoprotein lipase activity and likely TG turnover, was given to raise fatty acids). In addition, the availability of fatty acids for VLDL-TG production depends also on fatty acid delivery to the liver from peripheral and intrahepatic and intraportal adipose tissue TG and fatty acids that are newly synthesized. Furthermore, insulin may also inhibit VLDL-TG production by a mechanism that is independent of its effect on fatty acid availability. In fact, it was found that insulin infusion suppressed VLDL-TG production even when the insulin-mediated decrease in fatty acid availability was prevented (71). The mechanism(s) responsible for the impaired suppression of VLDL-TG production during glucose infusion observed in the obese women in our study is not known but our findings are consistent with studies that investigated the effect of insulin on plasma VLDL-TG concentration. Lewis et al. (72) found that plasma VLDL-TG concentration decreased in response to hyperinsulinemia in lean but not in obese women (72), and Bilo et al. (73), who compared a group of obese men and women with lean men only found that the insulin-induced decrease in plasma
VLDL-TG concentration was blunted in the obese compared with the lean.

### Postprandial lipemia

The postprandial lipemic response, which is characterized by the change in total TG and TG-rich lipoprotein concentrations in plasma in response to dietary fat intake, is determined predominantly by the fat content of a meal. However, other factors, such as meal fatty acid composition, body-composition (i.e., total body fat, visceral fat accumulation), insulin-sensitivity, and physical activity, also play a role in the postprandial lipemic response (74–77). Postprandial plasma TG concentrations are lower in women than men (77). The differences can be attributed largely to differences in body-fat distribution (and differences in insulin sensitivity associated with it) because the differences between the sexes disappeared when men and women were matched for visceral adipose tissue accumulation (77), whereas women who had the same amount of total body fat (but likely less visceral adipose tissue than men) also had a smaller response than men (76).

### Exercise

The plasma TG lowering effect of exercise was recognized several decades ago [e.g., (78)]. However, the exact mechanisms responsible for the hypotriglycerideremic effect of exercise, which appears to result predominantly from a decrease in VLDL-TG, both during fasting and fed conditions, are still unknown. Furthermore, most of the studies that investigated the effect of exercise on plasma TG concentrations were performed in lean, frequently trained men, but not in obese persons and women.

In conclusion, having established that women differ from men metabolically, focus should be directed to better understand metabolism in women, not only to complement the knowledge we have obtained in men over many years, but also because of its clinical implications in terms of understanding the metabolic consequences of maintenance of good health and the treatment of disease.

### LITERATURE CITED


