Review

Steroid hormones and regional adiposity

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ABSTRACT

Steroid hormones are implicated in the determination and maintenance of regional depots of adipose tissue in humans. This review focuses on the effects of steroids (estrogens, androgens, progestins and glucocorticoids) on fat distribution during growth and maturation. General and specific relationships that link androgens with android (abdominal) adiposity and estrogens with gynoid (gluteofemoral) adiposity are covered as they apply across the lifespan. Supporting relationships on steroid hormones and adipose tissue morphology include: adipogenesis and adipocyte hypertrophy and hyperplasia in puberty; regional adiposity in adults; aging and changes at menopause; regional differences in the cellular and metabolic characteristics of adipocytes, including lipoprotein lipase (LPL) activity and lipolysis, and the effects of steroids on these processes. At least in part, the distribution of adipose tissue in men and women appears to be determined by sex steroids. This generalization does not, however, entirely hold in obesity. This is because the additional adipose mass sequesters and produces steroids by aromatization: steroid metabolism varies throughout the body. In obese women, androgen/estrogen balance can account for adipose tissue distribution: such obesity involves a greater tissue exposure to unbound androgens, notably testosterone and dihydro-testosterone, due to reduced levels of sex hormone binding globulin (SHBG). Although lower in obese relative to non-obese women, SHBG is lower still in android obese than in gynoid obese women, tissue exposure to unbound androgens being greater for android obese women. Androgen/estrogen balance is not reflected by adipose tissue distribution in obese men who, despite a lowered androgen/estrogen ratio, tend to be android. Although many investigators have implied that cortisol is related to the distribution of adipose tissue in men and women, especially in obesity, the literature lends uneven support. If cortisol is related to adipose tissue distribution in normal individuals, it is perhaps through the differentiation of adipocyte precursors during adolescence and the induction of abdominal adipose tissue LPL activity, possibly through interactive effects with progesterone in women. Further investigation of relationships between steroid hormones and regional adiposity will prove invaluable for clarifying the known associations of adipose tissue distribution with disease risk, and documenting changes during normal growth, maturation and aging.

INTRODUCTION

The patterns of adipose tissue distribution vary in different individuals. There are two principle

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patterns: android, or abdominal, in which most of the body's adipose tissue is on or within the abdomen, and gynoid, or gluteofemoral, in which most of the adipose tissue is on the buttocks or thighs. Android obesity is associated with greater health risk than gynoid obesity. Both patterns can occur in either sex. The earliest description of these patterns was provided several decades ago by Vague [1, 2], who also noted that android obesity was more commonly observed in men, and gynoid obesity more often observed in women. Obesity *per se* is not a requirement for the association of android adiposity with increased disease risk, although it can be a contributing factor. The strongest risk factor to emerge from prospective studies is actually the combination of low level of obesity (low body mass index) and android adiposity (high waist-to-hip circumference ratio) [3]. Prospective studies that examined the relationship of fat distribution to mortality and disease in both men and women [4-8] have found android fat distribution to be a potent risk factor, greater than and *independent* of level of obesity, for cardiovascular disease, hypertension, stroke and diabetes.

Numerous other studies support the association of android adiposity with glucose intolerance, hyperinsulinemia, hyperlipidemia [9-16] and hypertension [17, 18]. Abdominally localized adipose tissue is also associated with increased risk and incidence of human breast [19, 20], endometrial and ovarian [21] carcinoma, and anthropometric indicators of android adiposity may be of predictive value for these malignancies. Conversely, gynoid adipose tissue distribution *per se* is not directly associated with any health risks [13, 17, 21, 22].

Given the association of morbidity with adipose tissue distribution, there is a need to understand the mechanisms responsible. How is it that women can be considerably fatter than men, yet experience far less of the morbidity and mortality associated with obesity? Certainly, the high estrogen levels of women in their premenopausal years would appear to provide protection from many diseases, especially cardiovascular disease, and postmenopausal women on estrogen therapy enjoy the same protection [23-27]. An alternative answer is provided by the respective distributions of adipose tissue in men and women. Is it a coincidence that low disease risk, high estrogen levels and gynoid fat distribution are associated with each other in women, while high disease risk, high androgen levels and android fat distribution are associated with each other in men?

Whether android adipose tissue distribution is causative in itself of high disease risk, or whether it is the associated hormonal or other factors that influence morbidity and mortality is not the object of discussion here; those questions have been reviewed elsewhere [3, 28], and remain the object of continued research.

This paper examines the roles of steroid hormones in the determination and maintenance of regional depots of adipose tissue in humans, a topic that to our knowledge has only been briefly reviewed [3, 29-31]. We have reviewed the effects of steroid hormones on fat distribution during normal growth and maturation, separating out the confounding effect of obesity, but have not reviewed obesity in general or the cardiovascular and metabolic complications of obesity, topics that have been covered in detail by others.

Sex- and age-dependent differences in adipose tissue

Childhood and puberty

Adipose tissue develops in the fetus as early as the second trimester of pregnancy [32]. At birth, females have slightly more fat than males [33], but sexual dimorphism of fat patterns is not apparent [32]. Skinfold thicknesses decrease from age 9 months to 7 years, and then rise again, with a sex difference appearing at about 8 years [33]. Puberty results in marked differences between the sexes: skinfold thicknesses decrease in boys but continue to increase in girls [33, 34] (Figure 1). There is a large increase in lean body mass and decrease in body fat in boys through puberty: percent body fat (%BF) (by underwater weighing) declines from about 21% at age 11 years to about 11% at age 18 years [35] while skinfold thicknesses, despite a brief prepubertal peak (Figure 1), show little change [36]. For girls, %BF (about 26%) shows little change over the same age span [35], whereas skinfold thicknesses increase significantly [36].
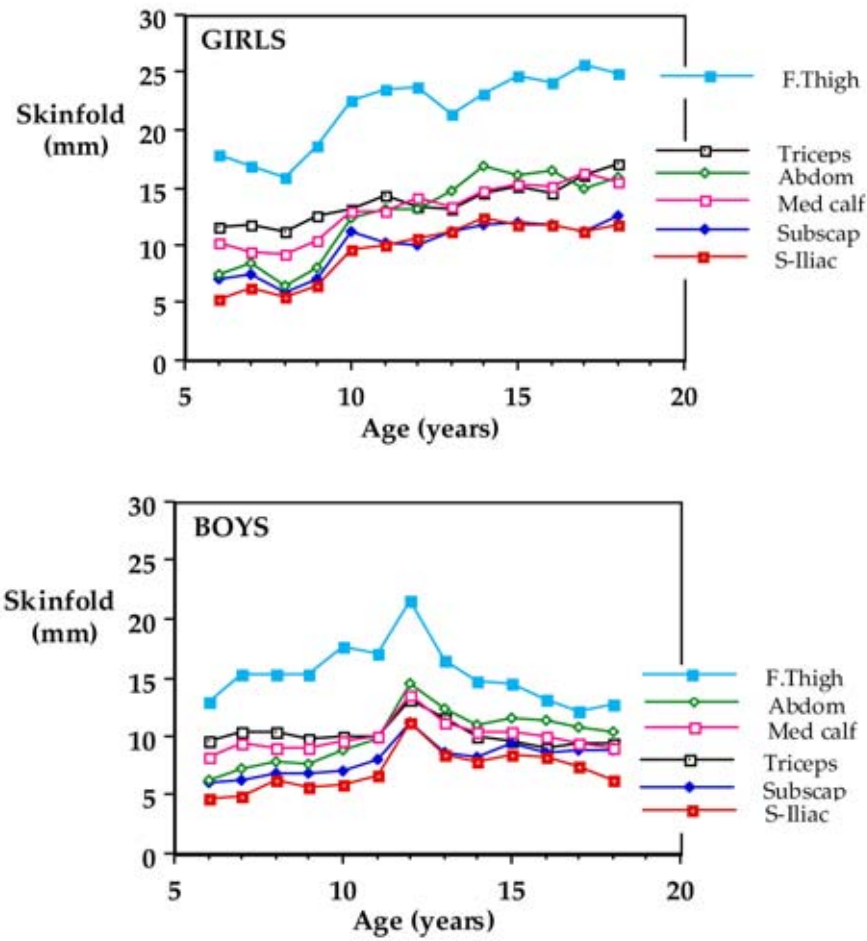
Figure 1. Age changes in skinfold thickness at six sites. (Cross-sectional data, plotted from tabular form [289].)
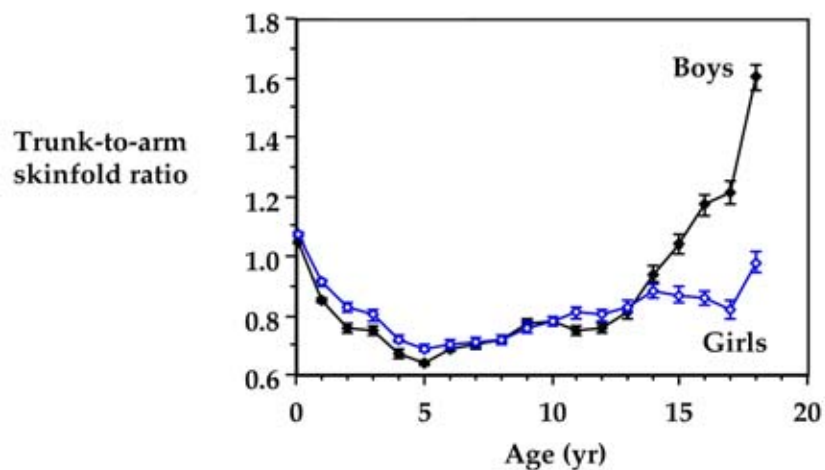

Figure 2. Pubertal changes in body fat distribution. Trunk-to-arm skinfold ratio (subscapular + suprailiac/biceps + triceps) from birth to maturity in boys and girls, showing means and standard errors. (Longitudinal data, plotted from tabular form [37].)

Thus puberty results in marked sex differences in the amount of adipose tissue and the distribution of body fat as well (Figure 2). A two-decade follow-up study found that a clear sexual difference in body fat distribution appeared in the course of development: 85 out of 86 males (99%) were found to have android fat distribution, and 50 out of 78 females (64%) were found to have gynoid distribution, based on skinfold ratios discriminating central adipose tissue on the trunk from peripheral adipose tissue on the limbs [37]. In support of this observation are earlier reports of a rapid increase in thigh and calf skinfold thicknesses with no concomitant rate of increase at upper body sites in pubertal girls [38], and sex differences in the waist-to-thigh girth ratio (WTR) during development (Figure 3). Several other groups have found an android pattern develops at adolescence in most boys but in few girls [39-42]. When fat patterns were studied across ethnic groups, the only consistent sex difference was the trunk-limb contrast, and it accounted for 34 to 57% of the total variance in subcutaneous adipose tissue distribution [41]. Thus, adolescent females tend to develop a peripheral fat distribution, whereas males tend to store fat centrally.

The waist-to-hip circumference ratio (WHR), by far the most common method of assessing the degree of android/gynoid fat in adults, has not been widely applied to children or adolescents.

This is unfortunate as the WHR is considered by many to be the best and simplest index of android adiposity [13, 43-48] and, consequently, of the health risk imposed by centrally located fat. In adults it is highly correlated with internal-visceral adipose volume determined by computed tomography [49], a valid method for quantifying the size of subcutaneous and visceral fat depots [50-52]. The WHR is also significantly correlated with abdominal fat percentage as determined by photon absorptiometry, another validated *in vivo* method [53]. Cadaver dissection studies have directly validated the WHR as an anthropometric indicator of abdominal adiposity relative to gluteofemoral adiposity [54]. Although circumferences are thought to be more reliable than skinfolds when assessing fat distribution in adults, their validity as measures of such in pre-adults is not known [55]. The waist-to-thigh circumference ratio (WTR) may be more accurate than the WHR for assessing central fat in pre-adults [56].

Neither type of fat distribution is confined solely to one sex or the other; a substantial percentage of females, especially obese females, have the android distribution, and a small percentage of males have the gynoid form [57]. Obese adolescents, in particular, appear not to achieve sexual dimorphism of fat patterning characteristic of the non-obese [58, 59] and it has been found that obesity which originates during or close to
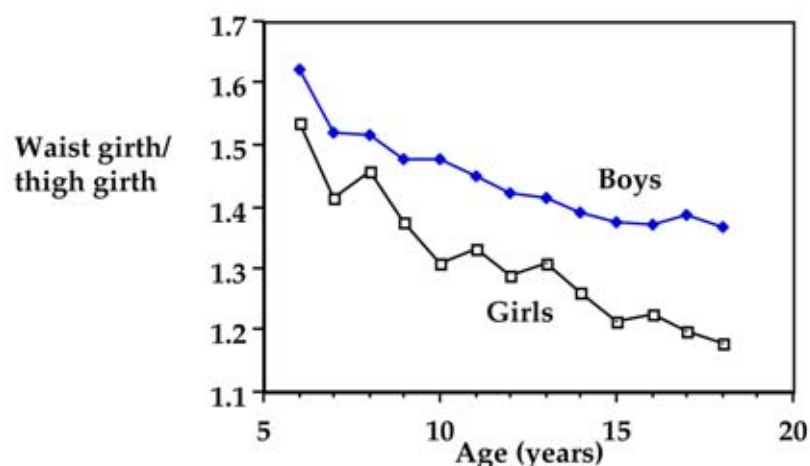

Figure 3. Age changes in waist-to-thigh girth ratio. (Cross-sectional data, plotted from tabular form [289].)

adolescence is usually an android type of obesity for both boys and girls [60].

Aging

In men the degree of android adiposity tends to increase during adulthood, but though women also tend to accumulate fat as they age they still retain the gynoid pattern. However, around menopause women undergo a shift from gynoid to android fat distribution, reducing the degree of sexual dimorphism during middle and old age [2, 61-67]. The shift seems to coincide with the upper limit of reproductive age - just as the lower limit of reproductive age seems to coincide with the onset of gynoid adiposity in girls - but there is a confounding factor. Overall fatness tends to increase with age, and body mass index (BMI) has a positive correlation with WHR (android adiposity) in both men [68] and women [4].

In summary, there are relatively few differences in the pattern of adiposity between males and females until puberty. In girls, puberty results in essentially no change in total fatness (relative to lean body mass), but fat distribution tends to become more gynoid. In boys, total body fat decreases markedly (relative to lean body mass) and fat distribution becomes more android. These aspects of sexual dimorphism are maintained until menopause, when women commonly undergo a shift from gynoid to android fat distribution. As

Vague has pointed out, though fat distribution is very definitely a sex-based characteristic, there is a high degree of overlap between one sex and the other, especially at the two extremes in life [2]. This suggests that hormonal changes coinciding with puberty and menopause are connected to changes in the pattern of adipose tissue distribution in humans.

Steroid hormones in relation to adipose tissue morphology

The steroid hormones considered here are the estrogens, androgens, progestins and glucocorticoids. Pathways of steroid biosynthesis are outlined in Figure 4. The mineralocorticoids will not be discussed, as they are not known to have any direct connection with adipose tissue distribution. That steroid hormones may be involved in the morphology of adipose tissue is suggested by several observations. There is much evidence that adipose tissues are *bona fide* target tissues for steroid hormones. In experimental animals, cytoplasmic estrogen and progesterone receptors have been demonstrated in adipose tissue [69-74], as have glucocorticoid receptors [75, 76]. In *human* adipose tissue, however, although cytoplasmic glucocorticoid binding has been demonstrated [77], different techniques such as gel filtration chromatography, isoelectric focusing and monoclonal antibodies have failed
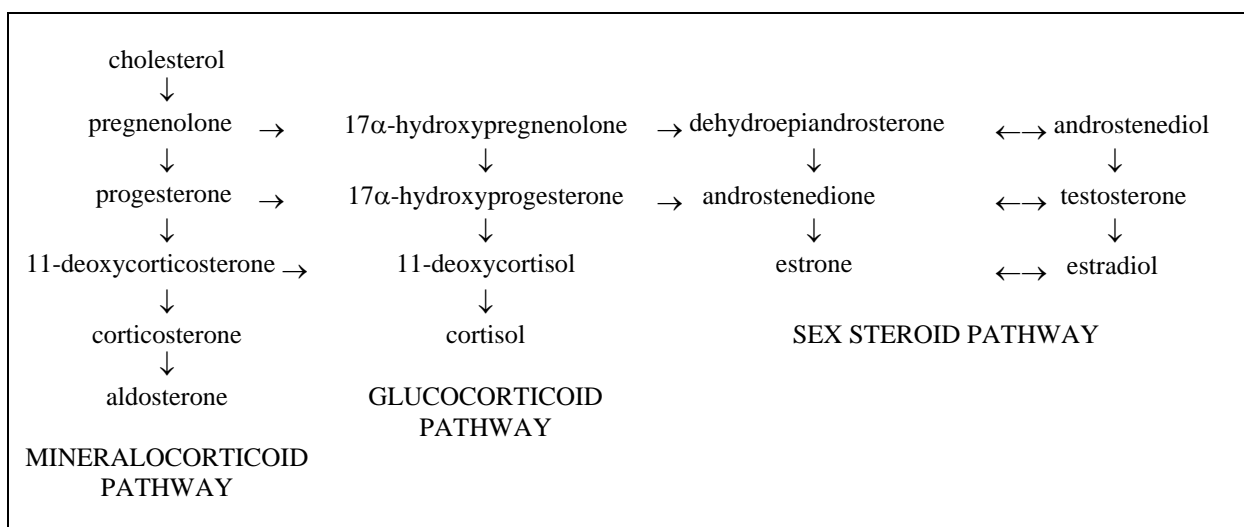
Figure 4. Pathways of steroid biosynthesis. (Adapted from [290]).

to demonstrate any cytoplasmic estrogen or progesterone receptors [30]. Androgen receptors have been identified in human adipose tissue [78].

Adipogenesis in pubertal girls

The effect of sex hormones on adipogenesis, the formation of differentiated adipocytes, is of considerable interest in view of changes in the amount and configuration of adipose tissue in girls at puberty. Adipose tissue mass is dictated not only by the amount of triglyceride in each adipocyte but also by the number of adipocytes with the capacity to store triglyceride. Various studies *in vitro* have established the fact that many mammals, including adult humans, possess adipocyte precursors capable of replication and complete differentiation into mature fat cells [79-82]. This observation has been confirmed *in vivo* [83]. The composition of the adipocyte precursor pool is thought to be an important determinant of the growth of adipose tissue, and appears to explain inter-regional and inter-individual differences [84].

Adipocyte precursors are polyclonal mixtures. Preadipocytes obtained from the fat of experimental animals during tissue culture have been shown to demonstrate marked variation among colonies in the rate at which constituent cells accumulate lipid [84, 85]. An individual could therefore be predisposed to regional adiposity, or obesity in general, because of an unusual proportion of cells programmed for rapid differentiation in the precursor pool [86]. But while genetic susceptibility cannot be discounted in human variation of fat distribution, recent investigations have shown an additive genetic effect of between 20-25% [87] and 24-31% [88] of remaining variance in amount of lower trunk fat and in the relative proportion of lower trunk versus extremity fat. Undoubtedly, other mechanisms are involved; the sex steroids may mediate genetic effects, as well as exerting their own unique influence.

Studies *in vitro* have shown that 17ß-estradiol, at physiological concentrations, can stimulate replication of human omental adipocyte precursors in culture [89, 90], and a similar investigation of rat adipocyte precursors found that administration of both 17ß-estradiol and progesterone stimulated differentiation and consequent new fat cell formation [91]. *In vivo* studies in the mouse have demonstrated that 17ß-estradiol promotes adipocyte hyperplasia [92], while relaxin promotes adipocyte hypertrophy [93]; the effect of 17ß-estradiol and relaxin together on adipocyte precursors is differentiation in which both proliferation and lipid accumulation occur [94]. These studies suggest that in girls at puberty, female sex steroids might regulate adipose tissue storage capacity by means of inducing differentiation of adipocyte precursor cells, thus increasing the number of adipocytes.

Estrogen may induce the production of mitogenic proteins in pubertal girls [95]. MCF-7 mammary carcinoma cells release mitogenic polypeptides when cultures are treated with estrogens [96, 97]. Furthermore, results of *in vivo* experiments have shown that human preadipocytes release mitogenic proteins, and preadipocytes from massively obese persons release substances with higher mitogenic activity than cells from lean persons [98]. Using preadipocytes from massively obese women, it has been shown that cells grown in the presence of 17ß-estradiol are characterized by significantly higher mitogenic activity, whereas 17ß-estradiol is not effective in promoting cell multiplication; these observations suggest that estrogens exert their mitogenic effect on preadipocytes through local factors, presumably via paracrine mechanisms [95]. In this manner, estrogens likely initiate the synthesis of mitogenic proteins by activating pertinent genes [99, 100].

Evidence for the role of ovarian steroids in influencing regionally specific preadipocyte differentiation and conversion to adipocytes at puberty has been obtained utilizing a highly sensitive procedure to quantify differentiated and undifferentiated preadipocytes in normal and ovariectomized rats [101]. Results indicated that in normal female rats at puberty there was: (a) an increase in differentiated preadipocytes and in fat cell number; (b) enlargement of specific regional "female" depots, including the femoral; and (c) a concomitant decline in the percentage of undifferentiated preadipocytes in all but the femoral depot. Ovariectomized animals were found to have reduced pubertal adipose growth in the femoral and parametrial depots, and an

unpreserved femoral undifferentiated preadipocyte pool. It was concluded that the association between ovarian hormones and body fat topography could be accounted for, in the female rat, by the finding that the femoral depot contains an ovarian-dependent infinite pool of fat cell precursors, and that sex steroids may determine the amount and recruitment rate of preadipocytes and, consequently, regional adipose tissue mass [101].

It is reasonable to expect that similar events occur in humans, and several observations support this hypothesis. In a group of pre-menarcheal girls maturation-matched for Tanner's breast stage M2, total serum levels of estrone, estradiol, and testosterone, and the non-SHBG-bound fractions of estradiol and testosterone varied significantly with WHR [102]. Except for obese subjects, serum concentrations of estrone and estradiol, and the non-SHBG bound fraction of estradiol decreased with increasing WHR. Obese girls were characterized by the greatest WHR, and a significantly greater percentage of non-SHBG bound testosterone than leaner girls. The authors concluded that lower WHR (a more gynoid form) is representative of pubertal endocrine activity in girls, and that this type of fat distribution is likely a result of ovarian activity [102]. The extent to which the development of gynoid adiposity reflects increases in adipocyte *number* versus increases in adipocyte *size* in the gluteofemoral region remains to be investigated in pubertal girls. However, gynoid women consistently have greater number [103-105] and size [106, 107] of gluteal and femoral adipocytes relative to fat cells located in other regions, supporting an inferred effect of estradiol in regionally-specific adipogenesis.

The pubertal changes in girls' body fat topography via adipogenesis may not be entirely dependent upon ovarian hormone production. It is possible that development of regional fat depots is facilitated by peripheral estrogen production - secondary to ovarian-estrogen-dependent adipogenesis. Peripheral aromatization of androgens to estrogens by adipose tissue could result in the newly formed estrogens acting upon their own cell of origin and on neighboring adipocytes by autocrine and paracrine mechanisms,

inducing the production of mitogenic proteins, and consequently increasing the number of preadipocytes. This process may occur in adult obesity [95]. Steroid metabolism is *not* uniform throughout the body. The activity of adipose tissue aromatase varies by site [108-110], and gynoid women (in whom there is a greater number of gluteofemoral adipocytes) demonstrate significantly greater rates of peripheral aromatization of androgens to estrogens than do android women [111]. Though only estradiol - not estrone - has been demonstrated to effect adipogenesis, interconversion of estrone to estradiol [112] and extragonadal conversion of testosterone to estradiol [113] could provide sufficient estradiol to effect adipogenesis at the local level, even given the low relative yield of these pathways. Adipose tissue represents a hormone pool in which total steroid expression can be much greater than that in serum [114-116].

Androgens do not induce growth or replication of human adipocyte precursors [90], but rather are inhibitory to these processes [29]. Given that dehydroepiandrosterone sulfate (DHEA-S) may act as a precursor for ovarian testosterone production in women [117], observations of high serum levels of DHEA-S in association with android fat distribution in adolescent girls [118, 119] and female primates [120] suggest that gluteofemoral adipogenesis might be inhibited in androgenic girls at puberty by consequent testosterone formation, thus partly explaining their tendency towards an android rather than gynoid distribution of body fat. Serum DHEA levels have been shown to decrease in peripubertal girls following weight loss [121], but unfortunately, associated changes in regional adiposity were not considered in this study.

In summary, the peri-menarcheal increase in estrogen production is related to an increase in overall adiposity, as well as to the development of a gynoid fat distribution in girls at puberty. These events appear to be due to an increase in both the number and size of gluteofemoral adipocytes in response to increased estrogen concentrations. Both ovarian and peripheral mechanisms of estrogen production are implicated in adipogenesis, which appears to involve an estrogen-induced mitogenic effect on preadipocytes,

mediated by locally-produced autocrine or paracrine factors. Androgens do not induce preadipocyte differentiation or replication, but probably inhibit gluteofemoral adipogenesis when dominant in pubertal girls.

Pubertal boys

The onset of increased testosterone secretion in the pubertal male or administration of exogenous testosterone to the hypogonadal male is accompanied by a decrease in %BF and a change toward android fat distribution [65, 122, 123]. Subcutaneous adiposity decreases in the arms and especially the thighs; fat becomes localized at the abdomen, shoulders and neck. Testosterone is also known to reduce adiposity in animals [124]. Regionally specific testosterone-dependent decreases in adipose tissue mass in humans appear to involve significant decreases in adipocyte number mainly in the trochanteric but also deltoid and femoral regions; these changes are accentuated by secondary decreases in adipocyte volume at these sites [65, 125]. It should be noted, however, that the methodology and assumptions required to determine change in regional adipocyte number are difficult to validate. Regardless, it is clear that in both humans and animals, the degree of sexual maturation in males (dependent upon testosterone production) is inversely related to body fatness [126]. Estradiol levels are positively related to overweight in adolescent boys for any given level of testosterone [127].

Whereas gonadarche results in decreases in overall adiposity and development of an android fat distribution in males, effects of adrenarche are not as clear. Dehydroepiandrosterone sulfate (DHEA-S) concentrations are inversely associated with fatness in male primates [120], but positively associated with high levels of body fat in boys *throughout* puberty [128]. However, pubertal boys in the latter study [128] also demonstrated an association between high levels of DHEA-S and advanced skeletal age, independent of the association between advanced skeletal age and testosterone, the latter relationship implying that fatness should be low. It is possible that effects of DHEA-S on fatness in early puberty are confounded by concomitant cortisol secretion, but increased adrenal androgen production at adrenarche is not accompanied by a parallel rise in glucocorticoid secretion [129, 130]. In humans the association between DHEA-S, high levels of body fat and advanced skeletal age in boys throughout puberty could be explained by the hypothesis that excess prepubertal fatness may potentiate elevated secretion of adrenal androgens and precipitate earlier sexual maturation [128]. Longitudinal studies have yet to confirm this hypothesis, but excess adiposity [131], particularly the android form [66], is associated with early sexual maturation. It is tempting to speculate that in relatively lean boys in whom DHEA-S is unrelated to fatness, testicular conversion of DHEA-S to testosterone in a manner similar to ovarian production of testosterone from DHEA-S [117] could indirectly promote android adiposity, but there are no reports of any direct association of adrenal androgens with adipose tissue distribution in non-obese pubertal boys.

Glucocorticoid hormones could also be involved in the development of android adiposity at puberty, inducing preadipocyte differentiation and promotion of abdominal adipocyte hyperplasia specifically. Corticosteroids bind to human adipose tissue with regional specificity [77], and comparatively high concentrations of cortisol have been found in abdominal adipose tissue [132]. In both *in vivo* [133] and *in vitro* [134] investigations, differentiation of human adipocyte precursors (from normal weight subjects) into mature adipocytes has been shown to be triggered by a combination of cortisol and insulin, and there is a highly significant inverse correlation ($r = -0.78$) between the frequency of adipose differentiation and the age of subjects (age range 20 to 83 years) [134]. But most importantly, adipose differentiation is greater in cells from the abdominal in contrast to cells from the femoral region [135]. Thus, there could be regional differences in the capacity of adipose tissue depots to form mature adipocytes under the influence of cortisol and insulin *in vivo*. As the effects of cortisol are independent of sex steroids but dependent upon insulin [134], it is relevant that insulin responsiveness and sensitivity in the abdominal region are greater in men than in women, with both sexes having greater responsiveness and sensitivity in the abdominal, than in the gluteofemoral, region [136]. However, the catabolic effects of glucocorticoids on body

protein during a period when lean body mass is generally increasing relative to adipose mass, suggest that any substantial effect of cortisol on adipogenesis is limited to obese adolescents in whom there is accelerated adrenocortical function or excess caloric intake leading to hyperinsulinemia.

In summary, the development of android adiposity in boys at puberty appears mainly due to regional decreases in adipose tissue mass via effects of testosterone and perhaps adrenal steroids, which might act as precursors for gonadal testosterone production. Whereas in girls the onset of estradiol production results in increases in the number and size of gluteofemoral adipocytes, the onset of increased testosterone secretion in pubertal boys appears to be followed by decreases in the size and number of peripheral adipocytes, and increases in the size and number of abdominal adipocytes. Android adiposity in adult men is characterized by a larger size of abdominal adipocytes than those located elsewhere [43, 103, 136], and the majority of this android fat is located internally, not subcutaneously [51, 137]. As subcutaneous abdominal adipocytes are larger than intra-abdominal adipocytes in both men and women [138] the high internal proportion of android fat reflects a greater proportion of intra-abdominal adipocytes. Thus, intra-abdominal adipocyte hyperplasia could be a factor in android adiposity, but only cortisol, not testosterone, is effective in inducing preadipocyte differentiation. The capacity of cortisol to induce preadipocyte differentiation is much greater in cells from the abdominal region than in those from the femoral region, and is independent of sex steroids, but further investigation is required to implicate any role for cortisol in the development of android adiposity during adolescence.

Adulthood

Given the effects of steroid hormones on growth and differentiation of adipose tissue at puberty, certain relationships should hold in adulthood. For example, serum estradiol concentrations and %BF are significantly correlated in active, non-obese young women [139] and in postmenopausal women [140]; in men, BMI is significantly and inversely correlated with testosterone [141]. In terms of regional fat distribution, numerous observations support associations of android

adiposity with androgens and gynoid adiposity with estrogens. In non-obese and obese adult women, android adiposity (high WHR and/or high WTR) is positively correlated with total serum testosterone [111, 142, 143], free testosterone [44, 144-146], free testosterone to total testosterone ratio [147], the production rates of testosterone and dihydrotestosterone [111], the production rate and metabolic clearance rate of androstenedione and the metabolic clearance rate of DHEA [148]. In young adult women, total serum testosterone and the ratio total serum testosterone to total serum estradiol explain significant portions of the variance in WHR and waist girth [149]. Women with android adiposity have significantly larger abdominal adipocytes than women with gynoid adiposity [18, 44, 103, 105]; abdominal adipocyte hypertrophy is a characteristic of men and android women [3, 104]. Not surprisingly, the more masculine hormonal profile of android women is also frequently associated with masculine characteristics of muscle mass and morphology [3, 150], as well as hirsutism and virilism [143, 145, 151]. Clearly illustrating this are women with the polycystic ovary syndrome, in whom hyperandrogenism is associated with android fat distribution irrespective of obesity level [145], oligo-ovulation or hirsutism [152]. Men predominantly have android adiposity, but in the few who have gynoid fat distribution, plasma estradiol concentrations are elevated [153]. In hypogonadotropic men, there is a major reduction in testosterone production [154] in association with elevated estrogen production rates and predominantly gynoid distribution of adipose tissue.

Sex hormone-binding globulin (SHBG) concentrations are inversely related to WHR [44, 102, 111, 143, 155, 156] and abdominal adipocyte size [44]; estrogen levels are inversely related, and androgen concentrations are positively related, to android adiposity. Such observations suggest that body fat topography is a function of relative androgenic/estrogenic balance, an hypothesis put forward by many [28, 44, 142, 144, 157]. Specifically, it appears that in both men and women, adipose tissue distribution is android when androgens dominate and gynoid when estrogens dominate. The theoretical concept that androgen/estrogen balance can account for the

distribution of adipose tissue has been empirically demonstrated: in women aged 20-35, the ratio total serum testosterone to total serum estradiol accounted for more of the variance in WHR than either total serum testosterone or total serum estradiol alone [149].

Effects of exogenous hormonal intervention also support the concept that body fat distribution is regulated, at least in part, by the androgenic/estrogenic activity ratio. Shifts toward gynoid fat topography occur in males undergoing estrogen therapy [158]. Male-to-female transsexuals given estrogens have female SHBG levels [159] and gynoid adiposity [125]. Conversely, female-to-male transsexuals given androgens develop android adiposity [125]. Indeed, one of the many goals of endocrine therapy for sex changes is to provide feminization or masculinization of body shape, and this is usually achieved [160].

The concept of androgenic/estrogenic balance is important. In considering a theoretical ratio of total or free levels of androgens to estrogens, small differences in either the denominator or numerator could have a large effect on the ratio of androgenic to estrogenic activity or vice versa. Thus, in empirical comparisons of groups or individuals, total amounts of either androgens or estrogens may not be as important as their relative activity. Regional adiposity that is clearly opposite to that which would be expected based upon sex is probably most often not associated with absolute dominance of androgens over estrogens or vice versa, but rather on *relative* dominance of one over the other. A useful way to illustrate this thesis is by way of changes that occur at menopause.

Menopause

Menopause is accompanied by a shift in the hormone balance from estrogen dominant toward more androgen effect. Ovarian estrogen production ceases almost completely, but androgens continue to be produced by the ovaries [161, 162]. Testosterone production is only slightly decreased in comparison with the premenopausal years, but postmenopausal ovaries continue to secrete minor amounts of androstenedione and DHEA [130]. Menopausal levels of plasma estradiol and estrone are lower than those observed in the follicular

phase of the normal ovarian cycle in young women [163], and the estrone to estradiol ratio is greater than two [161, 163, 164], as it is in men [163] (this ratio is close to unity in the follicular phase of normal young women [163, 165]). SHBG decreases to values similar to those of adult men [166, 167], and thereafter serum levels of both estrone and estradiol stay relatively constant with increasing age [140].

The observed shift from gynoid to android adiposity around menopause is thus consistent with the transition toward a more masculine hormonal profile, but no prospective studies of hormones and adipose tissue distribution have been performed. Regardless, gynoid adiposity appears to be estrogen-dependent; with the decrease of estrogens and alteration in androgen/estrogen balance at menopause, the previous difference in size between gluteofemoral and abdominal adipocytes disappears [106, 136]. Contributing to this convergent morphology of the sexes in middle age is the age-associated decline of testosterone and associated increase of SHBG in men [168, 169], indicating increased estrogenic relative to androgenic activity.

Postmenopausal women undergoing estrogen replacement therapy decrease in fat mass [170], particularly android fat [171]. Furthermore, postmenopausal women reporting estrogen treatment at any point during their menopausal years have a lower WHR than women who report never using replacement estrogens [172]. These observations suggest that estrogens counteract the menopause-associated change to android adiposity by shifting androgen/estrogen balance back towards premenopausal levels.

Obesity

Human obesity is associated with several abnormalities of androgen and estrogen metabolism such that the relationship of sex steroids with regional adiposity is not clearly understood. Furthermore, as the abdominal region is the most responsive to changes in weight [173], obesity tends to be associated with increased abdominal adiposity. Large population studies have reported moderate positive correlations between obesity and WHR in both men [68] and women [4]. Although the most common form of

obesity is indeed the android type, to characterize all obesity as the same is to ignore the relationship of steroid hormones with adipose tissue.

Both plasma levels and metabolism of estrogens are elevated in obesity. These observations are explained in part by close relationships between excessive body weight and the metabolic transformation of androstenedione to estrone [174]. This pathway of metabolism becomes more active in the obese due to the increased fat mass available for aromatization [174-178]. Thus, the aromatization rates of androstenedione to estrone and testosterone to estradiol correlate with adiposity in postmenopausal women [113, 140, 164, 179]. Serum levels of estrone and estradiol are mildly correlated with the degree of obesity and fat mass in obese postmenopausal women [164, 180-182], and total and free plasma estradiol levels correlate with body size in postmenopausal women with and without endometrial cancer [183, 184]. These data suggest that the circulating levels of estrone and total or free estradiol are higher in obese postmenopausal women, primarily due to their additional fat mass.

In premenopausal obese women estrone production rates increase with body weight and the peripheral aromatization of androstenedione to estrone increases as a function of obesity [185]. However, no difference in the total circulating serum levels of estrone or estradiol has been demonstrated as assessed by single assays of plasma [186, 187], or the mean 24 hour serum concentration of these hormones [188]. Any contribution of peripheral estrogen production to total estrogen levels in obese premenopausal women thus appears overwhelmed by ovarian estrogen production. However, for reasons explained below, free estradiol *is* elevated in obese premenopausal women [189], as in obese postmenopausal women [183, 184]. Obese men are characterized by elevated plasma estradiol and estrone levels [188, 190-192], elevated estradiol and estrone production, and elevated rates of aromatization of androstenedione to estrone and testosterone to estradiol [190].

As the android type is the most commonly observed form of human obesity, and as estrogens are typically related to gynoid adiposity, increased production rates and levels of estrogens in obese men and women appear to present a paradox. This apparent paradox, however, is explained in part by the well-known inverse relationship of obesity with SHBG concentrations [184, 193-197]. Major changes in the metabolism, action and ultimate impact of sex steroids normally bound to SHBG are a consequence of low SHBG levels.

In obese women, free estradiol and the free fraction of testosterone are elevated as a consequence of subnormal levels of SHBG [189]. Proportionately equal elevations in the production rate and metabolic clearance rate of both testosterone and dihydrotestosterone have been reported [196, 198], and blood conversion rates of testosterone to dihydrotestosterone are positively correlated with the free fraction of testosterone independent of total plasma testosterone in obese women [198]. These data indicate that in response to depressed SHBG, there is increased exposure to potent androgens (free testosterone and dihydrotestosterone) in female obesity, which probably explains associations with android adiposity, notwithstanding the increased free estradiol milieu. It has long been known that obese women have accelerated testosterone metabolism [199], and recent epidemiological investigations have related android obesity specifically to increased tissue exposure to unbound testosterone [146].

At extremes of obesity and hormone metabolism, any biological effect of elevated free estradiol on the distribution of adipose tissue is probably overshadowed by elevated free testosterone and accelerated metabolism of testosterone to dihydrotestosterone. Thus in obese women android obesity is characterized by elevated levels of free testosterone *and* free estradiol. But this does not imply that increased levels of free estradiol in obesity are necessarily without consequence. As discussed, estradiol is probably responsible for adipogenesis in extreme obesity [95], whereby adipocyte numbers are increased by autocrine or paracrine mechanisms. High serum levels of free estradiol [200, 201] and low levels of SHBG [202] are also implicated in the pathogenesis of human breast and endometrial carcinoma, and the action of estradiol in inducing the release of mitogenic polypeptides from cancerous cells [96, 97] parallels the estradiol-dependent release

of mitogenic proteins from preadipocytes during adipogenesis [95]. Despite relationships between estradiol and breast and endometrial carcinoma, these cancers are strongly associated with android obesity [19-21], and it has been reported that serum testosterone levels are elevated in women with breast cancer [203, 204]. The nature of these inter-relationships between estrogen-dependent cancers, android obesity, elevated estradiol and testosterone, have not been clarified. However, the predominantly android distribution of adipose tissue in female obesity primarily reflects increased tissue exposure to free testosterone, whereas the mass of adipose tissue (i.e. in terms of adipocyte number), and the risk and incidence of certain carcinomas, may reflect increased tissue exposure to free estradiol.

Given that the adrenal androgens, androstenedione, DHEA and DHEA-S are poorly bound by SHBG, the obesity-related reduction in SHBG concentration has little effect on their levels and metabolism. However, adipose tissue serves as an important steroid hormone reservoir [116], and steroid sequestration by adipose tissue may serve to increase the clearance and metabolism of adrenal androgens. It has been reported that despite normal circulating levels [44, 148, 205], the production rate and metabolic clearance rate of DHEA, androstenedione and DHEA-S are elevated in obese women [148, 206]. Presumably the increased production rate of adrenal androgens occurs to compensate for an increased metabolic clearance rate, the latter a function of adipose mass [148]. However, the ratio DHEA/ testosterone is significantly lower in obese women [189], which could indicate increased tissue activity of 3ß-hydroxysteroid dehydrogenase as well as 17-ß-hydroxysteroid-dehydrogenase. The abdominal region specifically contains a large pool of tissue-bound DHEA in obese women [206, 207]. Therefore, beyond the enhanced metabolic clearance rate of bound androgens, the greater propensity of abdominal adipose tissue to sequester steroids in obesity may elevate the clearance and metabolism of androgens, especially those not significantly bound to SHBG.

An increase in the production rate of adrenal androgens can lead to increased production of their metabolites. Δ_5-androstenediol (Δ_5-adiol), a 17-ß-hydroxysteroid-dehydrogenated metabolite of DHEA, has unique properties in relation to estrogen. It can compete for the estrogen receptor, inhibit estradiol metabolism, and increase the free fraction of estradiol by displacing it from SHBG [208]. Interestingly, DHEA and DHEA-S have also been observed to have a modulating effect on estrogen metabolism, noncompetitively inhibiting the conversion of estrone to estradiol at near-physiological concentrations, particularly in omental as opposed to subcutaneous abdominal adipose tissue [116]. Given that significant correlations of Δ_5-androstenediol with DHEA have been observed in omental and subcutaneous abdominal tissue [116], it appears that adrenal androgens may influence peripheral estrogen metabolism, further promoting androgenic versus estrogenic effects and, consequently, the android form of obesity.

In obese men, depressed serum SHBG levels are associated with subnormal serum levels of total [190, 191, 193, 209-211] *and* free testosterone [141, 189, 193, 212]. It has been argued that free testosterone is relatively normal due to low SHBG levels [190], except perhaps in morbid obesity [209], but such controversy appears resolved with the report that serum levels of total, non-SHBG-bound and free testosterone are all highly correlated inversely with total body fat over a broad range of values [141]. Levels of free and non-SHBG-bound testosterone thus decrease in proportion to degree of obesity, as does the total serum testosterone level. Serum levels of androstenedione are normal or slightly low in obese men, but the metabolic clearance rate and production rate of androstenedione are elevated [190, 213, 214].

Why then, given a diminished androgen/estrogen ratio, do obese men generally have the android form? This observation is discordant with documented relationships between androgens and android adiposity, and estrogens and gynoid adiposity in both men and women. It could be contended that as the abdominal region is the most responsive to changes in weight [173], the greater proportion of excess fat in extreme obesity is deposited in the subcutaneous abdominal and intra-abdominal adipose depots irrespective of pre-existing biological mechanisms concerning

the bodily distribution of adipose tissue. However, this is not necessarily the case: high BMI is associated with elevated abdominal *and* peripheral adiposity in men, whereas high WHR is associated with increased abdominal adiposity (especially visceral fat) only [215]. Thus despite correlations between BMI and WHR, WHR is not dependent on BMI. Perhaps BMI is better related to low androgen levels and high estrogen levels than high WHR; such a relationship would implicate estrogen-dependent adipogenesis as the mechanism by which peripheral adiposity is increased in addition to abdominal adiposity. The effect of obesity on serum levels of androgens and estrogens in men may vary with the distribution of adipose tissue, and suggest application of the android-gynoid dichotomy in further investigations of obese men, an approach not yet attempted. Such an approach has had tremendous utility in the study of obese women, where the hormonal milieu of gynoid obesity has been found to be considerably different from that of android obesity [111].

Few studies have examined the endocrine environment of women with differing forms of obesity. Women with android obesity have higher levels of free and total serum estradiol and testosterone, but similar serum concentrations of androstenedione, estrone, dihydrotestosterone, DHEAS and cortisol when compared to those with gynoid obesity [111]. The metabolic clearance rates of testosterone and dihydrotestosterone were greater in the android obese women, and the blood production rate of testosterone was higher. Gynoid obese women had higher serum concentrations of SHBG, greater rates of peripheral conversion of androstenedione to estrone, and greater urinary excretion rates of estrone [111]. Other studies have shown that android obesity, again specifically in comparison to gynoid obesity, is characterized by elevated secretion of testosterone, androstenedione and cortisol after stimulation by adrenocorticotropin (ACTH) [3].

The significant differences in androgen and estrogen levels, metabolism and excretion rates between android and gynoid obesities, provide clear evidence that obesity in women is not a homogeneous entity. Women with android obesity have increased tissue exposure to testosterone and

dihydrotestosterone as a result of lower concentrations of SHBG. The effect of elevated levels of free estradiol in android obese women appears minimal in terms of the distribution of adipose tissue, although free estradiol is implicated in influencing the amount of adipose tissue via adipogenesis, and also in the pathogenesis of certain cancers. The ability of fatty tissue to sequester steroids probably increases the clearance of androgens, leading to an extremely large pool of steroids and enhanced androgen metabolism in the obese. Adrenal androgens, not bound significantly by SHBG, might thus contribute substantially to the distribution of adipose tissue via local effects. But perhaps the most important difference between the android and gynoid forms of obesity is the extent to which SHBG is decreased. Though always lower in the obese relative to the non-obese, SHBG is lower in android obesity than in gynoid obesity, and the degree of tissue exposure to unbound androgens is correspondingly greater in android versus gynoid obesity. As in normal growth and maturation, relative androgen/estrogen balance affects adipose tissue distribution in obese women.

In obese men, despite the fact that total serum estrogen levels are elevated and that free and total serum levels of testosterone are subnormal, it is possible that differences in androgen/estrogen ratios and metabolism exist in relation to the relative distribution of adipose tissue, as in obese women. This hypothesis requires investigation; male obesity may be no more a homogeneous entity than is female obesity. But the elucidation of relative differences in sex steroid levels and metabolism, even if such differences did vary with the distribution of the adipose mass, would not likely account for the tendency of abdominal adipose mass to increase with increasing weight when there is absolute dominance of estrogens over androgens. Though increases in overall adiposity might be attributed to estrogen-induced adipogenesis in both abdominal and peripheral regions, it is probable that other factors are involved. Genetic influences cannot be overlooked, nor can dietary factors or other hormones, particularly peptide hormones, be disregarded. For example, elevated plasma insulin concentrations

in extreme obesity and inter-relationships between insulin and steroid hormones influence adipocyte metabolism and size [45, 103, 216, 217]. High insulin levels are implicated in the suppression of SHBG [218, 219], which is also suppressed by above-average consumption of dietary lipids [220, 221]. Not excluding other relevant factors, rigorous investigations of steroid hormones and their relationship with the distribution of adipose tissue are required in obese men.

Cortisol and android obesity

Several early reports suggested that android obesity was associated with a minor degree of hypercortisolism. Relationships were noted between cortisol production rates and masculine characteristics of fat distribution [222-224], but these early reports were not followed by rigorous studies. Elevated cortisol production was thought to be due to an increased sensitivity of the adrenal to ACTH in android obese subjects, as suggested by greater plasma cortisol after intravenous injection of $ß^{1-24}$ corticotropin [225]. The report that Cushing's syndrome was associated with hyperandrogenism [226] seemed to support the hypothesis that elevated adrenocortical function, with increased production of cortisol and androgens, was related to android obesity [57]. However, it is currently accepted that plasma levels of cortisol, its circadian secretion, and the response of cortisol to metyrapone or ACTH are not altered in obesity [205, 227-232].

Normal plasma levels of cortisol are maintained in obesity and, despite early claims of accelerated production rates [228, 233, 234], it is clear that the production rate of cortisol is not altered in obesity. In both obese and non-obese individuals, cortisol production rate has been shown to be closely correlated with lean body mass [235, 236], and it has been demonstrated that the production rate of cortisol is weight-invariant when corrected for lean body mass by expressing it per gram urinary creatinine [237]. Therefore relative to lean persons, obese persons do not have accelerated adrenocortical function, nor are the obese exposed to a greater impact of cortisol.

Notwithstanding that plasma cortisol levels, production and excretion rates are not affected in obesity, there is circumstantial evidence that pure hypercortisolemia favours the android form of obesity. It has been observed that high doses of cortisol, when administered for therapeutic use, increased android adiposity independently of the degree of obesity in subjects ranging from non-obese to more than twice their ideal body weight [57]. In an unrelated study, subjects on extended glucocorticoid therapy were observed to have larger mediastinal fat areas in comparison to normal subjects [238]. Relatively high concentrations of cortisol have been observed in abdominal adipose tissue [132], and mid-morning plasma cortisol levels (0900 hrs) have been found to correlate weakly (r = 0.29) with WHR in obese women with and without hirsutism [143]. Glucocorticoid receptor density is higher in intra-abdominal relative to subcutaneous abdominal tissue, but there are no differences in receptor affinities between these two sites [77]. However, regarding the expression of glucocorticoid receptors in regional fat depots, mRNA concentration is highest in omental fat tissue, and lower in subcutaneous abdominal and femoral fat depots [239].

Hypercortisolism present in Cushing's syndrome is associated with enlargement of the abdominal but not gluteofemoral fat depots in women [240]. Subjects with true Cushing's Disease, studied by computed tomography have higher levels of subcutaneous abdominal fat by a factor of two and greater levels of intra-abdominal fat by a factor of five in comparison to normal subjects [241]. The administration of glucocorticoid antagonists (acting at the receptor level) ameliorates the central adiposity of Cushing's syndrome [242]. These data support the previously noted early reports suggesting an association between cortisol and android adiposity. However, the extent to which glucocorticoids influence adipose tissue distribution has not been thoroughly investigated, and rigorous longitudinal studies of individuals with android and gynoid obesity are required to elucidate the relationship further [243]. It currently appears that android adiposity is related to cortisol only in situations where there is pure hypercortisolemia; i.e. sustained exposure to high levels of exogenous corticoids, or elevated endogenous levels of cortisol as in Cushing's Disease.

Cellular and metabolic characteristics of adipocytes

Not only do steroid hormones affect differentiation and growth, they also affect the adaptation of cells to new metabolic demands. Thus, the influence of steroid hormones on adipocyte metabolism is important in view of effects upon adipocyte size, particularly in adulthood. It is suggested that inter-regional differences in the number of adipocytes reflect, in general, steroid hormone-mediated events that occur in adolescence and early adulthood. This, however, does not rule out the possibility of steroid hormone-mediated adipogenesis in adulthood, in which estrogen [90], progesterone [91], and cortisol [134] have all been implicated. For example, a moderate increase of body fat in adulthood is associated with enlargement of existing adipocytes, but additional weight gain is followed by increases in the number of adipocytes [13, 244].

Adipocyte metabolism

The main function of adipose tissue is to store triglyceride during periods of nutrient sufficiency and to release the stored lipid as fatty acids when energy is needed. Uptake of triglyceride (triacylglycerol) into adipose tissue is controlled by the rate-limiting enzyme lipoprotein lipase (LPL). This enzyme hydrolyzes the triacylglycerol transported in very low density lipoproteins and chylomicrons, making triacylglycerol fatty acids available for uptake in adipose and other tissues. Specifically, LPL hydrolyzes triacylglycerol to diacylglycerol to monoacylglycerol and then into free fatty acids and glycerol. Uptake into adipose tissue is accomplished by esterification. The release and efflux of fatty acids from adipose tissue (lipolysis) is accomplished by action of hormone-sensitive lipase; this is the key enzyme responsible for hydrolysis of triacylglycerol in adipose tissue to free fatty acids and glycerol. Lipolysis and LPL activity have sex hormone-related and regional differences. Aspects of adipocyte metabolism as well as the direct effect of steroid hormones on these processes have been studied.

Lipolysis

Human adipocytes possess both ß- and α_2-adrenoreceptors coupled respectively in a positive and negative fashion to plasma membrane adenylate cyclase. Adenylate cyclase has a central role in controlling the lipolytic activity of adipocytes (via cyclic-AMP production) through protein-kinase and hormone-sensitive lipase activation. Catecholamines are the major lipolysis-promoting hormones in adult human adipocytes, and this effect is mediated by ß-adrenoreceptors [245]. In human adipocytes, however, unlike in fat cells from other species, catecholamines also have antilipolytic properties that are mediated by α_2-adrenoreceptors [246].

There are marked regional variations in catecholamine-induced lipolysis. In men and women, epinephrine and norepinephrine are both more lipolytic in abdominal than in gluteofemoral adipocytes [12, 103, 246-252]. The enhanced lipolytic effect of catecholamines in abdominal adipocytes appears to reflect a greater number of ß-adrenoreceptors (with normal affinity and normal coupling to plasma membrane adenylate cyclase) in abdominal adipocytes relative to adipocytes in other regions [253, 254]. The lower lipolytic response of femoral adipocytes to catecholamines could reflect either a greater number of α_2-adrenoreceptors or inhibition of ß-adrenoreceptor-induced lipolysis [12, 247, 248, 255]. Variation in the ratio of ß- to α_2- adrenoreceptors [246] via differences in the expression of genes encoding for adrenoreceptor types [254] could provide a molecular mechanism for regional differences in the lipolytic response of adipose depots to catecholamines, but also may relate to the influence of circulating steroids on adrenoreceptor activity.

Free testosterone concentrations are significantly correlated with abdominal adipocyte volume [44], which suggests that testosterone may enhance abdominal α_2-adrenoreceptor activity. This finding is apparent in castrated male hamsters: testosterone treatment *in vivo* promotes α_2-adrenoreceptor-mediated antilipolysis to a greater extent than it increases the ß-adrenergic lipolytic effect of catecholamines [256]. This action of testosterone could explain why men and androgenic women accumulate adipose tissue in the abdominal region. However, an *in vitro* study of adipose precursor cells from male rats suggests that testosterone stimulates lipolysis at the ß-adrenoreceptor level and that both testosterone

and dihydrotestosterone increase adenylate cyclase activity [257]. As the authors of this latter study claim that the α_2-adrenergic action of testosterone is weak and perhaps nonexistent, caution must be taken in extrapolating these findings to humans. Little α_2-adrenergic control of lipolysis occurs in rats and the validity of a rat model is questionable. The hamster model much better approximates human ß/α_2-adrenergic control of lipolysis, and it is not surprising that the results of the hamster study [256] are incongruent with those of the rat study [257].

In middle-aged men, testosterone has been found to stimulate norepinephrine-induced abdominal lipolysis [258], supporting an effect of testosterone on ß-adrenoreceptor-mediated lipolysis. It is unknown to what extent, if any, that α_2-adrenoreceptors were stimulated in this study. Furthermore, if testosterone does indeed preferentially stimulate ß-adrenoreceptor-mediated lipolysis in abdominal adipocytes, an inverse relationship between abdominal adipocyte size and testosterone could be postulated. These variables, however, have been shown positively rather than inversely correlated [44]. Although an inverse relationship has been demonstrated between free testosterone concentration and the amount of intra-abdominal fat [259], such a relationship is confounded by various lifestyle factors and the previously noted decrease in total and free serum testosterone that occurs with increasing obesity and chronological age. Given discrepancies in the data reported to-date, the precise effects of testosterone in ß/α_2 control of lipolysis remain to be elucidated.

Cortisol may affect adipocyte responses to adrenoreceptor agonists [260]. For example, norepinephrine-stimulated lipolysis is low in the abdominal region in women with Cushing's syndrome [240], and in women exposed to exogenous corticosteroids there is a decrease in gluteal adipocyte size and in gluteal skinfold thickness [261]. These observations are consistent with the commonly observed peripheral to central redistribution of fat seen with elevated levels of adrenal glucocorticoids. Analogous findings have been reported in the rat [262, 263].

In rats, estrogens increase *in vitro* catecholamine-stimulated lipolysis in adipocytes by enhancing hormone-sensitive lipase activity [74]. As in humans, the strong regulatory effects of estradiol on enzyme activities in rat adipose tissue are mediated by cyclic-AMP [264]. Estrogens likely promote lipolysis in rat fat cells by this mechanism [265]. Treatment of rats with 17ß-estradiol alone or in combination with progesterone has been shown to facilitate lipolysis with regional variation in response, but administration of progesterone alone has no effect [266]. In humans, it appears that estradiol is especially lipolytic in the abdominal region [30].

To summarize the above data, it is clear that adipose tissue lipolysis is normally much greater in the abdominal region than in the gluteofemoral region in both men and women. This phenomenon appears to relate to the effect of steroids on lipolytic sensitivity, and the relative number of α_2- versus ß-adrenoreceptors within these adipose depots. In the rat, 17ß-estradiol increases lipolytic sensitivity to catecholamines, with regional variation in response, and it appears that in humans, estradiol promotes lipolysis specifically in the abdominal region. Extrapolation of these observations to humans suggests that given their estrogenic dominance, young women would be leaner about the waist than men, androgenic and postmenopausal women, consistent with gross relationships between androgen/estrogen activity ratio and android relative to gynoid adiposity. The effects of cortisol and testosterone on adipocyte metabolism have not been researched adequately. In women, excess cortisol production is associated with a decrease in gluteal adipocyte size in association with low rates of lipolysis in the abdominal region, and similar findings in the rat also suggest that cortisol influences adrenoreceptor response to lipolytic agents with the potential to promote android (or central) adiposity. Again, this notion is consistent with descriptive data. Data about the role of testosterone in ß/α_2-adrenergic control of lipolysis are contradictory, but given significant regional changes in adipocyte size concomitant with testosterone therapy, it is probable that testosterone exerts regionally specific metabolic effects, though such effects are likely inter-dependent on other factors not yet known.

Lipoprotein lipase (LPL) activity

Steroid hormones also account for sex and regional differences in LPL regulation of

adipocyte size by influencing the uptake of fatty acids. In the rat, LPL activity is highest in gonadal regions and lowest in subcutaneous sites [267, 268]. There is also regional variation of LPL activity in humans. In non-obese premenopausal women with normal ovarian and adrenal function, LPL activity is greater in the gluteofemoral region than in the abdominal region [250]. Moderately obese women have higher activities of LPL in the gluteal and femoral regions than in the abdominal or triceps region, in parallel with the cell size differences [269, 270]. A study of morbidly obese men and women also found that fat cell size and LPL activity were greater in the femoral region than in the subcutaneous abdominal region in women, with men showing less marked regional variation [107]. Other studies have reported higher adipose tissue LPL activity in the gluteal region of females compared to males [271-273]; however, these latter investigations did not contrast regional differences in LPL activity between the sexes. Men generally have low adipocyte LPL activity in the femoral region, even lower than in postmenopausal women; LPL activity is greater in abdominal than in femoral adipocytes in men [136]. Postmenopausal women have lower femoral LPL activity than premenopausal women [251]. Furthermore, no difference in LPL activity or lipolytic response between femoral and abdominal adipocytes is found in postmenopausal women [251]. These data indicate the presence of mechanisms serving to emphasize gynoid adiposity in premenopausal women via enhanced gluteofemoral LPL activity, whereas android adiposity is promoted in men and postmenopausal women.

Glucocorticoids may promote LPL activity in certain adipose depots. Young women with Cushing's syndrome demonstrate considerably greater LPL activity in the abdominal region in comparison to control subjects [240]. This observation explains in part the large abdominal adipocytes by which Cushing's syndrome is characterized, and is consistent with descriptive data associating abnormally high levels of glucocorticoids with android adiposity. In rats, although regional effects of corticosteroids on LPL activity are not definite [274, 275], glucocorticoids do mediate regionally specific effects upon glucose uptake [263].

Available data regarding direct sex steroid effects on adipose tissue and plasma LPL activity in humans are contradictory. However, endogenous sex steroid levels have only been measured in a few investigations; most studies have utilized exogenous sex steroids and have looked specifically at their effect on postheparin plasma LPL activity. A recent investigation of endogenous sex steroid levels and their relationship with LPL activity in obese pre- and post-menopausal women found estradiol to be a major negative regulator of fasting adipose tissue LPL activity, independent of degree of obesity [276]. Estradiol reduces LPL activity in both intact and gonadectomized animals of a variety of species [71, 74, 277-280]. Estradiol also affects hormone-sensitive lipase activity [101] whereas progesterone, only affecting adipose tissue in females [71], counteracts the negative estrogen effects on LPL activity [71, 279]. Androgens also appear to inhibit LPL activity [258], but it has been suggested that under *in vivo* conditions, androgen inhibition of adipose tissue LPL is indirect via aromatization to estradiol [281]. The inhibition by estradiol of adipose tissue LPL activity might be related to its function in promoting regionally specific lipolysis, but the potential of estradiol to inhibit LPL activity with regional specificity has not been studied. It is possible that in women estradiol selectively inhibits abdominal adipocyte LPL activity concomitant with the promotion of abdominal adipocyte lipolysis. Any inhibitory effect of estradiol on gluteofemoral adipocyte LPL activity may be marginal, thus partially explaining gynoid distribution of adipose tissue in premenopausal women and postmenopausal women on estrogen replacement therapy.

Progesterone effectively competes with glucocorticoids present in human adipose tissue [77]. This may explain how progesterone counteracts estrogen effects on LPL activity. Interestingly, progesterone alone has no effect on LPL induction in *in vitro* experiments, but addition of cortisol to the progesterone-containing culture medium increases the cortisol effect on LPL activity [282]. However, a directly anabolic role for progesterone in adipose tissue lipogenesis, independent of cortisol, has been suggested on the basis of rat experiments [283]. Progesterone reverses the adiposity-reducing actions of estradiol

in rats, but in hamsters the action of estradiol and progesterone together is weight loss [284]; weight loss also occurs in postmenopausal women undergoing therapy with estrogen and progestins [170], and the majority of this weight is lost from the abdominal region [171]. These data suggest synergistic effects of estrogen and progestins in adipose tissue LPL induction. The data also suggest that in humans the respective positive and negative effects of progesterone and estrogen on adipose tissue LPL activity are regionally specific.

In premenopausal women, progesterone appears to increase femoral LPL activity under *in vivo* conditions [285], and this observation is consistent with the large femoral adipocytes in these women. Thus, a lack of progesterone in postmenopausal women and greater levels of testosterone in men might explain the smaller size of femoral adipocytes in these groups [30]. This thesis also has implications for fat distribution in women with anovulation and amenorrhea. Low progesterone production could result in less fat being accumulated in the typical gluteofemoral depots and more fat being accumulated abdominally, especially as the lipolytic effect of estrogen on abdominal adipocytes would be diminished if estrogen levels were low. Importantly, when progesterone levels are low, such as in women with the polycystic ovary syndrome, there are no differences in LPL activity between abdominal and femoral fat depots [286]. Nor are there any differences in LPL activity between the subcutaneous abdominal and femoral regions in postmenopausal women [136], but administration of estrogen and progestin to postmenopausal women significantly enhances LPL activity in femoral relative to abdominal adipocytes [136].

Estrogen appears to be required for the progesterone effect on femoral LPL activity; the formation of specific progesterone receptors for translocation of the hormone to the nucleus requires estrogen [70, 287]. Furthermore, in the ovariectomized rat uterus, estradiol and non-steroidal anti-estrogens (tamoxifen and mono-hydroxytamoxifen) increase progesterone receptor content [288]. Progesterone has been implicated in the control of peripheral aromatase activity in humans [132]; it is possible that progesterone promotes production of the estrogens required for formation of its own receptors.

In summary, these data suggest that female sex steroids stimulate lipoprotein lipase activity specifically in gluteofemoral adipocytes. In premenopausal women characterized by varying degrees of adiposity, gluteofemoral LPL activity is always greater than abdominal LPL activity. Gluteofemoral LPL activity is much greater in premenopausal women than in men. LPL activity decreases in the gluteofemoral region in women at menopause, and the previous difference between gluteofemoral and abdominal LPL activity disappears. Human and animal studies implicate progesterone as the most important female steroid for induction of LPL activity; in contrast, estradiol appears to reduce LPL activity, which probably relates to its pro-lipolytic effect. However, estradiol appears necessary for the effect of progesterone in promoting LPL activity. Although testosterone seems to inhibit LPL activity, it is possible that this effect of testosterone is indirect and mediated by aromatization to estradiol. The possibility that cortisol promotes LPL activity specifically in the abdominal region is suggested by findings in women with Cushing's syndrome. The promotion of LPL activity by progesterone may reflect effective competition with cortisol for glucocorticoid receptors. However, more data are required to clarify the precise role of cortisol in the regional induction of adipose tissue LPL activity.

Summary

The distribution of adipose tissue clearly varies with degree of reproductive maturation and by gender. Body fat distribution is similar in males and females throughout childhood, but changes at puberty. Sexual dimorphism in both the amount and the distribution of body fat then becomes apparent. Males decrease in relative fatness and take on an android (abdominal) fat distribution, while females have essentially no change in relative fatness but take on a gynoid (gluteofemoral) fat distribution. Whereas the android pattern of adipose tissue distribution dominates in males throughout adulthood, the gynoid pattern of women changes at middle age. Menopause is associated with a shift from gynoid to android

body fat topography, and fat distribution between sexes becomes similar again later in life. On the basis that changes in serum concentrations and rates of synthesis of steroid hormones at puberty and menopause occur concomitant with shifts of body fat topography, steroid hormones are implicated in mediating these changes in the distribution of adipose tissue.

In pubertal males, the development of android adiposity seems mainly due to decreases in gluteofemoral adipose mass via the effects of testosterone and perhaps adrenal steroids that could act as precursors for gonadal testosterone production. Increased testosterone secretion decreases the size and number of peripheral adipocytes, accentuating the size and number of abdominal adipocytes, although a direct effect of testosterone in mediating increases in abdominal adipocyte size cannot be excluded. Android adiposity in adult men is characterized by a larger size of abdominal adipocytes compared to those located elsewhere. The majority of this android fat is located intra-abdominally, not subcutaneously. This greater proportion of intra-abdominal fat reflects a greater number of internal adipocytes, and thus intra-abdominal adipocyte hyperplasia could be a factor in android adiposity. However, only cortisol, not testosterone, is effective in inducing preadipocyte differentiation. The capacity of cortisol to induce preadipocyte differentiation is much greater in cells from the abdominal compared with the femoral region. The implications of regional specificity are unclear. A small proportion of men have gynoid adiposity; this is associated with elevated estradiol levels or production rates and/or with hypogonadism.

The onset of estrogen production in girls during the peri-menarcheal period is followed by an increase in absolute adiposity and development of a gynoid distribution. These events appear due to an increase in both the number and size of gluteofemoral adipocytes in response to increased estradiol concentrations. Both ovarian and peripheral mechanisms of estrogen production are implicated in adipogenesis, in which estrogens act by paracrine or autocrine mechanisms to induce the production of mitogenic proteins by preadipocytes, leading to an increased number of adipocytes. As androgens seem to inhibit the differentiation and replication of preadipocytes, gluteofemoral adipogenesis is probably inhibited in androgen-dominant pubertal girls. In adult women, android adiposity is positively related to total and free levels of androgens and their production rates, and women with android adiposity have larger abdominal adipocytes than women with gynoid adiposity. Abdominal adipocyte hypertrophy thus is a characteristic of men and android women, and reflects androgen dominance.

As adipose tissue distribution is android when androgens dominate, and gynoid when estrogens dominate, many investigators believe that body fat topography is a function of relative androgen/estrogen balance. The concept that body fat distribution is regulated in part by androgenic/estrogenic activity ratio is supported by topographical shifts in body fat distribution that occur with therapeutic administration of sex steroid hormones. In both males and females, estrogen therapy effects changes toward gynoid adiposity, whereas administration of androgens effects changes toward android adiposity. Furthermore, in women at menopause, it appears that the disproportionate decrease in estrogen and progesterone levels relative to continued androgen production effects the shift from gynoid to android adiposity; abdominal adipocytes hypertrophy, and the previous difference in size between gluteofemoral and abdominal adipocytes disappears.

The concept that androgen/estrogen balance explains adipose tissue distribution applies to female, but not male, obesity (Table 1). In women, obesity is clearly not a homogeneous entity; significant differences have been observed in androgen/estrogen levels, metabolism and excretion rates between women who have android obesity, and those who have gynoid obesity. Obesity in females is characterized by increased tissue exposure to unbound androgens, most notably testosterone and dihydrotestosterone, as a consequence of reduced levels of SHBG. The ability of fatty tissue to sequester steroids as a function of adipose mass could also increase androgen clearance, leading to an extremely large pool of steroids and enhanced androgen metabolism. The difference between the android

Table 1. Relationships between steroid hormones, obesity and abdominal fat distribution in men and women*†.

Steroid	Measure	Men	Women
Cortisol	total serum concentration		$+_{afd}$ (weak)
	production rate	weight-invariant	weight-invariant
Testosterone	total serum concentration	$-_{o}, \downarrow_{o}$	$+_{afd}, \uparrow_{ao}$
	free and non-SHBG-bound	$-_{o}, \downarrow_{o}$	$\uparrow_{o}, +_{afd}, \uparrow_{ao}$
	production rate		$\uparrow_{o}, +_{afd}$
	metabolic clearance rate		$\uparrow_{o}, \uparrow_{ao}$
Dihydrotestosterone	production rate		$\uparrow_{o}, +_{afd}$
	metabolic clearance rate		$\uparrow_{o}, \uparrow_{ao}$
Dehydroepiandrosterone	production rate		$\uparrow_{o}$
	metabolic clearance rate		$\uparrow_{o}, +_{afd}$
DHEA-S‡	total serum concentration	$+_{o}$	$\uparrow_{o}$
	production rate		$\uparrow_{o}$
	metabolic clearance rate		$\uparrow_{o}$
Androstenedione	production rate	$\uparrow_{o}$	$\uparrow_{o}, +_{afd}$
	metabolic clearance rate	$\uparrow_{o}$	$\uparrow_{o}, +_{afd}$
Estrone	total serum concentration	$\uparrow_{o}$	$+_{o}$
	aromatization rate from androstenedione	$\uparrow_{o}$	$+_{o}, \downarrow_{ao}$
Estradiol	total serum concentration	$\uparrow_{o}$	$+_{o}, \uparrow_{ao}$
	free and non-SHBG-bound		$+_{o}, \uparrow_{o}, \uparrow_{ao}$
	aromatization rate from testosterone	$\uparrow_{o}$	$+_{o}$
SHBG§	total serum concentration	$\downarrow_{o}$	$\downarrow_{o}, -_{afd}, \downarrow_{ao}$

* +/- symbols denote the nature of statistically significant correlations with obesity ($+_{o}/-_{o}$) or android fat distribution specifically ($+_{afd}/-_{afd}$).

† $\uparrow/\downarrow$ symbols indicate the nature of statistically significant differences either for obese relative to non-obese persons ($\uparrow_{o}/\downarrow_{o}$) or for android obese persons relative to gynoid obese persons specifically ($\uparrow_{ao}/\downarrow_{ao}$).

‡ DHEA-S denotes dehydroepiandrosterone sulfate.

§ SHBG denotes sex hormone-binding globulin.

and gynoid forms of obesity appears to reflect the extent to which SHBG is decreased. Though always lower in obese relative to non-obese women, SHBG is lower in android obesity than in gynoid obesity, and the degree of tissue exposure to unbound androgens is correspondingly greater in android versus gynoid obesity. Tissue exposure to free estradiol is also greater as a result of low SHBG, but the biological effect is better related to adipogenesis and the pathogenesis of certain carcinomas than to adipose tissue distribution. Relative androgen/estrogen balance is therefore reflected by adipose tissue distribution in female obesity.

In men, obesity is probably no more a homogeneous entity than in women, but definitive conclusions cannot yet be drawn. The relative distribution of adipose tissue in obese men could reflect variability in the serum levels and metabolism of androgens and estrogens, but such an

investigation has never been reported. Despite a decreased androgen/estrogen ratio, most obese men are nevertheless android. Factors other than sex steroids are therefore implicated in determining the predominant distribution of adipose tissue in obese men, be they genetic, endocrine or dietary. Males may lack gluteofemoral adipocyte precursors. Insulin may directly or indirectly interact with sex steroids or glucocorticoids in effects on abdominal adipocyte metabolism, size, or number. Investigations of such factors and inter-relationships with specific adipose depots (e.g. subcutaneous abdominal, intra-abdominal, gluteofemoral) in obese men classified on the basis of their gross anatomical distribution of adipose tissue would help to resolve the discordance between android obesity and low androgen/estrogen ratio.

It is of interest that pure hypercortisolemia seems to favour an android fat distribution. The therapeutic administration of high doses of cortisol has been observed to increase android adiposity independent of the level of obesity. Individuals on extended glucocorticoid therapy have increased amounts of intra-abdominal fat. Relatively high concentrations of cortisol have been observed in abdominal adipose tissue, and cortisol concentrations have been found to correlate weakly with android adiposity. These associations may reflect high glucocorticoid receptor density in intra-abdominal adipose tissue. In individuals with Cushing's syndrome, the gluteofemoral fat depot is normal, but the subcutaneous abdominal and intra-abdominal fat depots are much larger than in normal individuals. Administration of glucocorticoid antagonists ameliorates this android fat distribution of Cushing's syndrome. It appears that android adiposity is related to cortisol only in situations where there is true hypercortisolemia. When corrected for lean body mass, the circadian secretion, production and metabolic clearance of cortisol in obese people is weight-invariant. Obese persons thus do not have accelerated adrenocortical function, nor are they exposed to a greater impact of cortisol.

The concept that body fat distribution is regulated in part by androgenic/estrogenic balance requires that steroids be capable of effecting regional changes in adipocyte metabolism, and therefore in the size of adipocytes. Much descriptive data suggest that female sex steroids specifically stimulate lipid uptake by gluteofemoral adipocytes (Table 2). In women, gluteofemoral LPL activity is greater than abdominal LPL activity, and gluteofemoral LPL activity is much greater in women than in men. LPL activity decreases in the gluteofemoral region in women at menopause, and the difference between gluteofemoral and abdominal LPL activity disappears. Human and animal studies implicate progesterone in the induction of LPL activity; in contrast, estradiol appears to reduce LPL activity, which probably reflects its pro-lipolytic effect. Estradiol, however, appears necessary for the effect of progesterone on LPL activity. Testosterone can inhibit LPL activity, but this effect may be indirect via aromatization to estradiol. Cortisol may promote LPL activity specifically in the abdominal region, and it has been speculated that the promotion of LPL activity by progesterone reflects effective competition of progesterone with cortisol for glucocorticoid receptors. More data are required to clarify cortisol's role in the regional induction of adipose tissue LPL activity.

Table 2. Adipocyte metabolism by region in women and men.

Region	Pre-menopause	Post-menopause	Men
Relative lipolytic enzyme activity according to adipocyte region			
Abdominal	moderate	high	high
Gluteal-femoral	low	high	moderate
Relative lipoprotein lipase (LPL) activity according to adipocyte region			
Abdominal	low	moderate	moderate
Gluteal-femoral	high	low	low

Lipid mobilization also appears to be regulated by steroid hormones, but the role of steroids in lipolysis is poorly understood. Adipose tissue lipolysis is much greater in the abdominal region than in the gluteofemoral region in humans. This phenomenon appears to relate to the effect of steroids on lipolytic sensitivity, and the relative number of α_2- versus ß-adrenoreceptors within these adipose depots. In the rat, 17ß-estradiol increases lipolytic sensitivity to catecholamines with regional variation in response. However, in humans, estradiol promotes lipolysis in the abdominal region specifically. Given estrogenic dominance, this could explain why premenopausal women are leaner about the waist than men and postmenopausal women. The effects of cortisol and testosterone on lipolysis remain to be fully elucidated. In women, excess cortisol production seems to correspond to a decrease in gluteal adipocyte size in association with low rates of lipolysis in the abdominal region. Similar findings

in the rat suggest that cortisol influences adrenoreceptor response to lipolytic agents. Data regarding the role of testosterone in ß/α_2-adrenergic control of lipolysis are inconsistent, but it seems probable that testosterone exerts regionally specific metabolic effects.

CONCLUSION

The distribution of adipose tissue in humans appears to be determined and maintained, at least in part, by the relative effects of androgens versus estrogens (Table 3). General and specific relationships between androgens and android adiposity, and estrogens and gynoid adiposity apply throughout the lifespan, and in all states of biological importance. An exception is male, but not female obesity, in which total and free testosterone levels are suppressed in response to hyperestrogenemia brought about by increased serum levels of estrogens produced peripherally in direct proportion to the surplus adipose mass.

Table 3. Summary of steroid hormone effects on adipocyte formation, metabolism and adipocyte size by region in men and women.

Steroid	Effect on new adipocyte formation	Effect on adipocyte size	Effect on adipocyte metabolism
Abdominal adipose tissue			
Cortisol	promotes*	increases	promotes lipoprotein lipase activity; inhibits lipolysis
Testosterone	inhibits	decreases	inhibits lipoprotein lipase activity; promotes lipolysis†
Estradiol	no	decreases	inhibits lipoprotein lipase activity; promotes lipolysis
Progesterone	no	no	not clear
Gluteofemoral adipose tissue			
Cortisol	no	decreases	inhibits lipoprotein lipase activity; promotes lipolysis
Testosterone	inhibits	decreases	inhibits lipoprotein lipase activity‡; promotes lipolysis
Estradiol	promotes	no	pro-lipolytic effect inhibited by progesterone
Progesterone	no	increases	promotes lipoprotein lipase activity; inhibits pro-lipolytic effect of estradiol

* dependent on insulin, independent of sex steroids.
† precise effects on ß/α_2 control of lipolysis are unclear.
‡ possibly indirect via aromatization to estradiol in women.

Several routes of study have been proposed to elucidate the factors responsible for this discordance. Nonetheless, in separating out the confounding effect of male obesity, the magnitude and complexity of inter-relationships between steroid hormones and the distribution of the adipose mass become more evident. It is clear that total serum levels of sex steroids are not as important as their free fractions and degree of tissue exposure. Measurement of free and/or non-SHBG-bound proportions of steroids, and their production rates and metabolic clearance rates are therefore crucial in assessing the relative impact of androgens and estrogens upon regional adiposity.

Though many authors have implied that cortisol concentrations are related to the distribution of adipose tissue in men and women, especially in obesity, the literature lends little support to this hypothesis. If cortisol levels are related at all to adipose tissue distribution in normal individuals, it is perhaps involved in the differentiation of adipocyte precursors during adolescence and in the induction of abdominal adipose tissue LPL activity, possibly via interactive effects with progesterone in women. There is much evidence associating cortisol with android obesity in individuals treated with exogenous cortisol and in individuals with Cushing's Disease, but it is physiologically inappropriate to infer that similar relationships might exist in healthy persons. More relevant in terms of the distribution of adipose tissue, therefore, are sex steroids, not glucocorticoids. As discussed, genetic factors are implicated in the determination of body fat distribution, but genetic factors do not account for all variation in the distribution in adipose tissue. Further investigation of relationships between steroid hormones and regional adiposity will prove invaluable for clarifying the known associations of adipose tissue distribution with disease risk, and documenting changes during normal growth, maturation and aging.

ACKNOWLEDGEMENTS

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