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Sex Differences in the Regulation of Body Weight

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Abstract

Obesity and its associated health disorders and costs are increasing. Males and females differ in terms of how and where body fat is stored, the hormones they secrete in proportion to their fat, and the way their brains respond to signals that regulate body fat. Fat accumulation in the intra-abdominal adipose depot is associated with the risk for developing cardiovascular problems, type-2 diabetes mellitus, certain cancers and other disorders. Men and postmenopausal women accumulate more fat in the intra-abdominal depot than do premenopausal women, and therefore have a greater risk of developing metabolic complications associated with obesity. The goal of this review is to explore what we know about sexual dimorphisms in adipose tissue accrual and deposition. Elucidating the mechanisms by which sex hormones may modulate the way in which fat is accumulated and stored is a critical area of research due to the prevalence of obesity and the metabolic syndrome, and the rapid increase in propensity for these diseases following menopause.

Keywords

Body fat; Sex differences; Estrogens; Androgens; Leptin; Insulin

1. Introduction

Obesity is a leading cause for the development of adverse metabolic effects, including non-insulin dependent diabetes mellitus, dyslipidemia, and cardiovascular disease [1,2]. There are important sex differences in the prevalence of these metabolic diseases. Ovarian hormones appear to be protective against the metabolic syndrome because prior to menopause, women have much fewer obesity-related metabolic disorders, and the prevalence of these metabolic disorders increases dramatically in women after menopause [3].

1.1. Adipose tissue distribution and its relationship to the metabolic syndrome

Health risks due to obesity vary depending on the location / accrual of adipose tissue [4]. Differences in distribution of adipose tissue suggests that not all adipose tissue is created

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equally. Rather, different adipose depots have different properties that can have important consequences on health outcomes. Adipose tissue distributed in the abdominal or visceral region (‘android’ or male-pattern body fat distribution) carries a much greater risk for metabolic disorders, than does adipose tissue distributed subcutaneously [5]. In contrast, subcutaneous (‘gynoid’, or female-pattern) fat distribution is poorly correlated with risk for these metabolic disorders [6]. Whereas we know the health consequences associated with visceral fat deposition, very little is known about the metabolic consequences of subcutaneous fat. Additionally, very little is known about the regulation of fat distribution, or more specifically, how excess nutrients are partitioned/stored into the different adipose tissue depots.

1.2. Intra-abdominal/visceral adipose tissues

Intra-abdominal adipose tissue is metabolically and functionally different from subcutaneous adipose tissue, and is characterized by having relatively more capillaries and efferent sympathetic axons per unit volume than does subcutaneous adipose tissue [5]. Furthermore, intra-abdominal adipose tissue has adipogenic, metabolic, pro-atherogenic, and pro-thrombotic characteristics [7]. There is a higher level of catecholamine-induced free fatty acid and glycerol release from intra-abdominal adipose tissue to the portal venous system in obese men relative to age- and BMI-matched women [8].

Surgical removal of intra-abdominal adipose tissue in humans results in decreased insulin and glucose levels [9]. Additionally, in male rats removal of intra-abdominal adipose tissue prevents the onset of age-dependent insulin resistance and glucose intolerance [10]. Removal of visceral fat improves glucose tolerance in both male and female mice [11], whereas removal of subcutaneous adipose tissue does not improve any aspect of the metabolic syndrome in humans [12] or in rodents [10,11]. Furthermore, in a recent paper by Tran et al. [13], they found transplantation of subcutaneous adipose tissue into intraabdominal adipose tissue improved metabolic parameters.

1.3. Subcutaneous fat

Subcutaneous fat is dispersed within a broad area under the skin, is relatively poorly innervated and vascularized, and has a larger average cell diameter than intra-abdominal adipocytes [5]. Subcutaneous adipose tissue was intended for fatty acid uptake and storage of excess calories in both men and women [14,15] , since lipid deposition provides an evolutionary advantage that allows efficient storage of maximal calories per unit volume of tissue. The capacity to store lipids within the subcutaneous depot is the key to facing famine when there is a limited caloric supply. This is especially important for females who need to utilize the energy stored to augment the caloric demands placed on the body from breast feeding. Therefore one hypothesis is that the deposition of adipose tissue in the subcutaneous depot of females is evolutionarily conserved, and that deposition of fat in this depot protects females from the diseases associated the metabolic syndrome and obesity.

1.4. Sex hormones regulate lipolysis and lipogenesis

The amount of fat stored in adipose tissue is the net difference between the rates of lipogenesis and lipolysis. In situations where metabolic fuels are not sufficient to meet

energy needs, a lipolytic cascade is initiated that results in the breakdown of energy stored in the form of triglycerides into free fatty acids and glycerol via hormone-sensitive lipase. Catecholamines trigger lipolysis via membrane-bound α- and β-adrenoceptors [16]. Specifically, catecholamines stimulate lipolysis via β1-, β2- and β3-adrenoceptors and inhibit lipolysis via α2-adrenoceptors [17]. Lipolysis correlates positively with activation of the sympathetic nervous system [18], which may further enhance free fatty acid release into portal circulation [8]. Female rats have higher lipolytic capacities and a lower α2/β3-adrenoceptor ratio in intra-abdominal adipose tissue than do male rats [19].

In situations where there is a prolonged positive energy balance, adipocytes take up circulating fatty acids, which leads to increases in both adipocyte size and number. This is manifested more generally as an increase in body fat mass [20]. The major pathway of free fatty acid uptake is mediated by lipoprotein lipase, an enzyme that hydrolyses meal-derived triglycerides into chylomicrons and very low density lipoprotein triglycerides at the capillary endothelium. Visceral adipose tissue uptake of triglycerides is greater in men than in women [21].

1.5. Teleological explanation for differences in fat distribution

The underlying reasons that males and females store excess calories in different depots are presumably due to differential evolutionary and sexual selection pressures [22]. Visceral fat can be mobilized rapidly to respond to shorter-term energetic challenges. Consequently, one reason to store fat in the visceral depot is to make it more accessible for specific intermittent activities. If males are more responsible for hunting, gathering, or immediate protection, then it would make sense to store calories in a fat depot with greater lipolytic activity, which would facilitate rapid mobilization.

In contrast, the lower lipolytic rates in subcutaneous adipose tissue allow for this fat depot to respond to chronic metabolic challenges such as what occurs during gestation and lactation in females. Therefore, the weight gained during pregnancy is disproportionately in subcutaneous adipose tissue, thereby facilitating the female's ability to counteract the metabolic challenge associated with gestation and lactation. These findings support the concept that subcutaneous, but not visceral, adipose tissue is the preferred energy source utilized during late gestation in female rats. Additionally, in women, subcutaneous fat depots are more lipolytically active during lactation than are visceral fat depots; thus subcutaneous adipose tissue is utilized as an important source of energy supply during lactation.

2. Energy balance regulation

Body weight regulation is thought to occur through negative feedback mechanisms which characterize most homeostatic systems [23]. Signals act in the brain to regulate food intake, and ultimately the amount of calories stored in adipose tissue and thereby work to keep overall adiposity levels relatively constant. In addition to paying attention to total body fat, the brain pays attention to where the fat is distributed. Signals such as leptin, insulin and estrogen may play a role in communicate with the brain/CNS the overall level of adiposity fat and body fat distribution.

2.1. Leptin

Leptin provides a powerful catabolic signal to the brain by inhibiting food intake and increasing thermogenesis [24]. Leptin is secreted from adipose tissue in direct proportion to fat content, and it penetrates the blood-brain barrier to interact with leptin receptors in the hypothalamus and brainstem [25]. Direct leptin action on target tissues has previously been demonstrated to stimulate lipolysis and fatty acid oxidation in adipose tissue, skeletal muscle, and the pancreas [26] to decrease triglyceride content and secretion rates in the liver, and suppress insulin expression and secretion from pancreatic β-cells [27,28].

Although there are several splice variants of the leptin receptor, the long form of receptor (termed OB-Rb) is the critical variant for regulating energy balance [29]. OB-Rb are localized in several brain areas including the ventromedial hypothalamic nucleus (VMN) and the arcuate nucleus (ARC) [30] as well as in peripheral tissues including adipose tissues, skeletal muscle, adrenal glands, pancreatic islets, liver, kidney, lymph nodes, and gonads [31]. Animals lacking leptin, leptin receptor, or downstream leptin signaling, exhibit profound obesity [32]. Administration of leptin to leptin-deficient mice, as well as restoration of OBRb in the brain of rats lacking the receptor, ameliorates this obese phenotype (e.g., [33]). In an attempt to assess the role of leptin signaling in the brain vs the periphery, transgenic animal models have been developed. Cohen et al. [34] deleted OB-Rb from neurons (OBRsynKO) and demonstrated that the mice were obese, whereas deletion of the OB-Rb from the liver had no discernable phenotype. Recently, de Luca et al., [35] demonstrated that restoration of OB-Rb in the CNS using synapsin I (Syn1)-Rb reversed the obese phenotype of the Leprdb/db, substantiating a critical role of CNS leptin signaling for the regulation of food intake and body weight.

Leptin controls body weight in part through activation of the sympathetic nervous system (SNS [36]). Functional connections have been established between white adipose tissue (WAT) and/or brown adipose tissue (BAT), via the SNS outflow from hypothalamic regions using the viral transneuronal tract tracer, pseudorabies virus (PRV) [37]. Leptin, via these connections, increases lipolysis, thermogenesis, and energy expenditure and suppresses pancreatic insulin secretion [38]. There is negative feedback between SNS and leptin production in adipose tissue through activation of the β3-adrenergic receptor [39]. Chemical sympathectomy alters CNS leptin-induced body weight regulation [40]. Ob/ob and db/db mice show hyperphagia, hyperinsulinemia and decreased sympathetic outflow leading to obesity [41]. Therefore, a pathway exists by which leptin could initiate a signal mediating SNS outflowto specific adipose depots. This could influence the mobilization of lipid stores in that depot, [42] thus influencing adipose tissue deposition.

In addition to providing information about overall adipose mass, leptin provides information about body fat distribution. Leptin levels have a higher correlation with subcutaneous than with visceral fat levels [43]. Because females have more subcutaneous fat than do males, an important implication is that the “adiposity” message conveyed to the brain differs in males and females, and is correlated with fat distribution [44,45]. Leptin levels are higher in females, even before puberty, compared with males, and this is independent of differences in body composition [46]. After puberty, estrogen and testosterone modulate leptin synthesis and secretion, apparently via sex steroid receptor-dependent transcriptional mechanisms

[47]. One conceptual model of how sex hormones may regulate fat distribution is that estrogen enhances leptin's ability to up-regulate sympathetic activity to stimulate lipolysis specifically in the visceral depot, thereby facilitating fat deposition in the subcutaneous depot.

Leptin levels are inversely correlated with testosterone [48] and exposure of human fat cells to testosterone or dihydrotestosterone inhibits leptin expression [49]. In aging and obese men, there is increased aromatase activity and conversion of androgens to estrogen and this is associated with increased plasma leptin [50]. Testosterone replacement normalizes elevated serum leptin levels in hypogonadal men and in castrated male rats.

In women, leptin fluctuations during the menstrual cycle directly correlate with estrogen, but not with progesterone [51]. Finally, peripheral or central estradiol administered either to ovariectomized females or intact males increases hypothalamic sensitivity to leptin and favors body fat accrual in the subcutaneous over visceral adipose depot [44]. These studies suggest that estrogen regulates energy balance and body fat distribution by interacting with leptin signaling pathways. Consistent with this hypothesis, estrogen deficiency impairs central leptin sensitivity [44,45,52].

2.2. Insulin

Insulin is also considered to be an adiposity signal, despite several important differences with leptin. Leptin is secreted directly from adipocytes in proportion to their metabolic activity, whereas insulin is secreted from pancreatic β cells in response to increases of circulating glucose. Thus, although both the circulating levels of leptin and insulin are directly proportional to the amount of total adiposity, leptin is a more stable signal for two reasons. First, the metabolic activity of adipocytes is more stable than are circulating glucose levels that change with feeding, exercise, and stress. Second, is that the half-life of plasma leptin is approximately 45 min, much longer than that of insulin with a half-life of approximately 2 to 3 min. Consequently, insulin's ability to predict adipose tissue levels is a result of the integrated signal of insulin over time rather than at any particular moment in time.

While both leptin and insulin cross into the brain via dedicated transport processes to act on specific receptors to regulate energy balance and elicit net catabolic responses, there are important differences in their actions in males as compared to females [44,45,53]. Male rats are relatively more sensitive to the catabolic action of insulin delivered into the CNS, whereas female rats are relatively more sensitive to the catabolic action of leptin delivered into the CNS [44,45]. A comparable phenomenon has been reported in a recent human study showing that men, but not women, lose body weight, body fat and waist circumference following intranasal insulin administration [53]. This approach increases insulin concentration in the cerebrospinal fluid and thereby alters brain functions [54]. Therefore, sex differences in sensitivity to the catabolic effects of insulin exists in rodents and humans.

2.3. Estrogens

Estrogens comprise a group of structurally related, hormonally active molecules that regulate critical cellular signaling pathways and, by doing so, control cell proliferation,

differentiation and homeostasis. Estrogens constitute one major group of female sex hormones [55]. The natural forms of estrogens are 17β-estradiol, estrone, and estriol. Estradiol circulates in high levels and potently activates estrogen receptor (ER) mediated transcriptional activity to a greater extent than estrone or estriol. Estradiol is involved in many physiological functions including development, growth, energy homeostasis, and reproductive physiology. Estradiol secretion is under the control of the hypothalamic-pituitary-gonadal axis (HPG axis) and following secretion, reversibly binds to sex hormone binding globulin and, with lower affinity, to albumin.

Estrogen-action is mediated by ER's which are ligand-inducible nuclear transcription factors and they regulate the expression of target genes by binding to specific response elements (EREs) on DNA. [56]. ERs are localized predominantly in the nucleus ER (nER) [57–59] and binding to the nER is thought to be responsible for the genomic actions of estrogens. The “classical” nuclear ERwas cloned in 1985 [60] and renamed ERα when a second nuclear ER, ERβ, was discovered ten years later [61]. ERα is necessary for estradiol's genomic actions with respect to body weight regulation [62], whereas ERβ functions more as a modulator of estrogen actions [63]. ERα and ERβ, are products of two different genes located on separate chromosomes [64–68]. There are several ER mRNA splice variants which have been described [69]; however, their biological functions are not yet known.

Estradiol is able to evoke a ‘fast’ non-genomic response in many tissues, through a plasma membrane associated ER (mER) [70–76] and/or ERα [77]. The rapid signaling cascades induced by estrogens include activation of ion channels, the MAPK pathway; the CREB pathway, the phophatidylinositol 3-kinase (PI3 K)/Akt pathways; the G-protein coupled receptor (cAMP and intracellular calcium); and the nitric oxide pathway [74–76,78]. The rapid non-genomic ER pathway appears to involve mechanisms associated with neuroprotection and aging [79,80], reproduction [76,81], and body weight regulation [82–86]. However, dissociating the genomic vs non-genomic pathways is still a subject for ongoing research.

2.4. Regulation of body weight by estrogen

Food intake and body weight regulation is potently influenced by estradiol in adult females of many species. In female rats during estrus there is a phasic decrease in food intake [87–91]. Changes in food intake directly related to the cycling of estrogen in women have been difficult to characterize due to small differences in consumption over the days of the cycle. However, progressive decreases in eating through the follicular phase have been reported in old-world monkeys, which have gradual increases in estrogen throughout the follicular phase comparable to those of humans [92,93]. Over the 10 to18-day duration of this phase of the menstrual cycle, the difference in intake is sufficient to affect energy balance and adiposity. There are some reports of an increase in energy expenditure during the luteal phase in women; however, this increase is small and unlikely to compensate for changes in intake [94–96].

Ovariectomy (OVX), bilateral removal of the ovaries, results in reductions in circulating estrogen and increases daily food intake and promotes weight gain in rodents [44,97]. However, food intake and energy homeostasis following ovariectomy in women (usually

referred to as oophorectomy) have not been extensively studied. There is one report suggesting that lack of estrogen abolishes the cyclicity of food intake [98–100]. In women who displayed intermittent anovulatory cycles, food diaries reflected changes in intake present during cycles in which ovulation occurred, but not during cycles when ovulation did not occur [101,102]. Thus although these findings are suggestive, specific documentation of estrogen's role in modulating food intake across the cycle in women remain uncertain.

The transition to menopause provides an experimental environment to begin to address the questions about estrogen's role on food intake and body weight in women. However because menopause is a long, gradual process and estrogen secretion does not cease abruptly following the last menses, collection and interpretation of these data are complicated [46,103,104].

The most direct evidence that estradiol controls feeding is that a cyclic regimen of estradiol treatment to OVX rats, designed to mimic the changes in plasma estradiol levels across the estrus cycle, normalizes meal size, food intake, and body weight gain to the levels observed in gonadally intact rats [97]. More specifically, administration of estradiol to an OVX rodent in the middle of the light phase increases plasma estradiol levels in the first night after the injection, which corresponds to the increase of plasma estradiol during the proestrus phase of an intact rodent [97]. Rats eat less the second night after the estrogen injection, which corresponds to the decrease in food intake during the night of estrus in intact animals [97]. Thus in OVX rats, estradiol is sufficient to restore eating behavior and to maintain normal body weight [97].

As previously indicated, leptin and insulin are considered adiposity signals and transduce hormonal input into neurobiological responses to make compensatory adjustments by regulating food intake and energy expenditure, and consequently regulate total body fat stores [25]. Estrogen also fulfills these criteria and thus can be considered another potential ‘adiposity signal’. Specifically, it is released from the ovaries, crosses the blood-brain barrier, binds to ERs located in key hypothalamic nuclei, and reduces food intake and body weight. Additionally, when delivered directly into the ventricular system, it decreases food intake possibly through its actions on the same neurons that are responsible for leptin's anorectic responses (for review: [105]).

Estrogen and leptin have overlapping target nuclei. Hypothalamic cells that are immunoreactive for ERs also express leptin receptors [106]. There is extensive hypothalamic co-localization of the long form of the leptin receptor and ERs, Ob-Rb and ERα, in the critical brain regions that modulate energy homeostasis, including ARC, VMN and parvicellular portion of the paraventricular nucleus (PVN). This colocalization suggests a closely coupled interaction between these peripheral signals and the regulation of behavioral and neuroendocrine mechanisms of energy homeostasis [106]. In addition to anatomic overlapping of their receptors, estrogen influences leptin receptor expression. Estrogen treatment of intact female rats downregulates the long form or signaling form of the leptin receptor in the hypothalamus [107]. Estrogen levels during the estrus cycle also appear to regulate the expression of the leptin receptors, such as Leptin receptor expression levels in the choroid plexus is lowest during proestrus, the stage of the estrus cycle with the

highest levels of estradiol [107]. Although circulating leptin does not change during the estrus cycle, ARC Ob-Rb expression is highest during estrus and metestrus [107], providing a potential mechanism for cyclic variations in energy intake and activity seen in females. Consistent with this idea, peripheral or central administration of 17 β-estradiol to ovariectomized female rats restores central leptin sensitivity [44]. In addition, administration of 17 β-estradiol increases sensitivity to central leptin, and decreases sensitivity to central insulin in male rats [44]. These findings suggest that gonadal steroids interact with the adiposity message conveyed to the brain by leptin and insulin, resulting in differential sensitivity to these signals in males and females [44].

2.5. Estrogen regulates adiposity

Visceral fat varies inversely with estrogen levels [108]. Visceral fat accumulation occurs in females when estrogen levels become sufficiently low. This is possibly due to direct effects of estrogen, as sex steroid hormone receptors (including progesterone and androgen receptors [PR and AR] as well as ER) are expressed in adipose tissues [109]. Subcutaneous adipose tissue has higher concentrations of ER and PR; however, visceral adipose tissue has higher concentrations of AR [110]. Furthermore, subcutaneous adipose tissue has few androgen receptors, and estrogen down-regulates AR expression in subcutaneous fat [111]. In accordance with the negative regulation between estrogen and AR in the adipose tissue, adipose tissue-specific AR knockout mice have increased intra-adipose estradiol levels, which further leads to subcutaneous obesity and hyperleptinemia with enhanced leptin sensitivity [112].

Ovariectomized female rats gain fat, specifically visceral fat with no change of subcutaneous fat [44]. Peripheral or central administration of 17 β-estradiol to ovariectomized females and changes their body fat distribution to mirror that of intact females. Additionally, altering the sex hormone milieu in males with 17 β-estradiol administration increases subcutaneous fat deposition [44]. An important implication from these findings is that estrogen regulates body fat distribution.

Heine et al. [113] reported that male and female mice with a targeted deletion in the ERα subunit (αERKO) have increased adiposity, consistent with other evidence linking estrogen with body weight regulation and adipocyte function. Recently, site-specific deletion of ERα in the VMH, a brain region critical for body weight regulation, demonstrated the role of estrogen activation of ERα in the regulation of body weight [62]. Specifically, lack of estrogen activation of ERα results in obesity due to an anabolic process, with changes in energy expenditure primarily mediating the weight gain [62]. These data are consistent to a previous finding in the ERα total body knockout mice are obese primarily due to changes in energy expenditure, rather than to changes in food intake [113,114]. Together, these data suggest that estrogen signaling within critical hypothalamic nuclei is responsible for the regulation of body weight via modulating energy expenditure.

Abnormal adiposity has been associated with the XbaI polymorphism of the human ERα gene, in which guanidine is substituted for adenine in exon one of the gene [115–117]. In a cross-sectional epidemiological sample of over two thousand middle-aged, premenopausal Japanese women who have the polymorphism, there is increased fat mass and increased

waist-hip ratios, an index of visceral adiposity, compared to pre-menopausal women with the normal genotype [115,117]. The polymorphism does not affect adiposity in postmenopausal women or in men. Thus, polymorphisms of the human ERα gene may impair estrogen signaling and lead to increased visceral adiposity and its attendant health risks.

2.6. Androgens and adipose tissue

We would be remiss if we did not mention the potential role for androgens in regulating body adiposity; however, data on the role of androgens and body fat distribution appear to be contradictory. On one hand, abdominal obesity is associated with reduced testosterone in plasma; on the other hand, androgens directly promote lipid mobilization and inhibit lipid uptake in adipocytes. There are reports which suggest androgens facilitate intra-abdominal fat deposition - as demonstrated by observations that high doses of androgens to female-to-male transsexuals leads to a change in adipose tissue deposition to resemble more android body fat accrual [118]. However, other reports suggest low levels of androgens facilitate deposition of fat in the intra-abdominal depot [119]. Regardless of its direct role in facilitating adipose distribution into one depot or the other, androgens have been shown to enhance the lipolytic capacity of cultured male rat adipose precursor cells by increasing the number of β-adrenoreceptors and the activity of adenylate cyclase [120]. An increase in fatty acid turnover has been observed in human males treated with testosterone, and in these studies they found that testosterone treatment inhibited the activity of adipose tissue LPL [121]. Evidence of a direct action of androgens in adipose tissue also comes from studies that have demonstrated the presence of androgen receptors [122] and androgen binding [123] in both human and rodent adipose tissue. At the adipocyte level, androgens directly modulate lipid mobilization and lipid uptake, presumably by binding to androgen receptors expressed in adipose tissue.

3. Summary

Sex specific distribution of body fat has important implications for how obesity influences a wide variety of co-morbid conditions. Evidence links differences in body fat distribution to gonadal steroids which have important effects on the regulation of energy balance. As a result, males and females also appear to have important differences in the systems that regulate energy balance and body weight. Females store energy in the subcutaneous depot when energy is surfeit and utilize subcutaneous fat under energy challenging conditions. The more global implication is that much of the underlying health risk of obesity is conferred by intra-abdominal rather than total body fat. Therefore, elucidating the role of gonadal hormones in mediating body fat distribution may provide novel strategies for therapeutic targets. Further, understanding how intra-abdominal fat is regulated may provide other opportunities to lower intra-abdominal fat levels in the general population and thereby lower many of the co-morbidities associated with growing rates of obesity. It is our contention that much more research must be done to understand how males and females differ with respect to metabolism, and how approaches to weight loss can be tailored to each sex.

References

1. Cummings DE, Schwartz MW. Genetics and pathophysiology of human obesity. Annu Rev Med. 2003; 54:453–71. [PubMed: 12414915]
2. Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases Working Group on the Pathophysiology of Obesity-Associated Cardiovascular Disease. Circulation. 2002; 105:2923–8. [PubMed: 12070124]
3. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care. 2005; 28:1769–78. [PubMed: 15983333]
4. Bjorntorp P. Body fat distribution, insulin reistance, and metabolic diseases. Nutrition. 1997; 13:795–803. [PubMed: 9290093]
5. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev. 2000; 21:697–738. [PubMed: 11133069]
6. Bjorntorp P. The android woman-a risky condition. J Intern Med. 1996; 239:105–10. [PubMed: 8568477]
7. Trayhurn P. Adipose tissue in obesity-an inflammatory issue. Endocrinology. 2005; 146:1003–5. [PubMed: 15713941]
8. Lonnqvist F, Thorne A, Large V, Arner P. Sex differences in visceral fat lipolysis and metabolic complications of obesity. Arterioscler Thromb Vasc Biol. 1997; 17:1472–80. [PubMed: 9261282]
9. Thorne A, Lonnqvist F, Apelman J, Hellers G, Arner P. A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. Int J Obes Relat Metab Disord. 2002; 26:193–9. [PubMed: 11850750]
10. Gabriely I, Ma XH, Yang XM, Atzmon G, Rajala MW, Berg AH, et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: an adipokine-mediated process? Diabetes. 2002; 51:2951–8. [PubMed: 12351432]
11. Shi H, Strader AD, Woods SC, Seeley RJ. The effect of fat removal on glucose tolerance is depot specific in male and female mice. Am J Physiol Endocrinol Metab. 2007; 293:E1012–20. [PubMed: 17652151]
12. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med. 2004; 350:2549–57. [PubMed: 15201411]
13. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab. 2008; 7:410–20. [PubMed: 18460332]
14. Michailidou Z, Jensen MD, Dumesic DA, Chapman KE, Seckl JR, Walker BR, et al. Omental 11beta-hydroxysteroid dehydrogenase 1 correlates with fat cell size independently of obesity. Obesity (Silver Spring). 2007; 15:1155–63. [PubMed: 17495191]
15. Shadid S, Koutsari C, Jensen MD. Direct free fatty acid uptake into human adipocytes in vivo: relation to body fat distribution. Diabetes. 2007; 56:1369–75. [PubMed: 17287467]
16. Carpene C, Bousquet-Melou A, Galitzky J, Berlan M, Lafontan M. Lipolytic effects of beta 1-, beta 2-, and beta 3-adrenergic agonists in white adipose tissue of mammals. Ann N Y Acad Sci. 1998; 839:186–9. [PubMed: 9629148]
17. Lafontan M, Langin D. Cellular aspects of fuel mobilization and selection in white adipocytes. Proc Nutr Soc. 1995; 54:49–63. [PubMed: 7568265]
18. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activation in visceral obesity. Circulation. 2002; 106:2533–6. [PubMed: 12427647]
19. Llado I, Rodriguez-Cuenca S, Pujol E, Monjo M, Estrany ME, Roca P, et al. Gender effects on adrenergic receptor expression and lipolysis in white adipose tissue of rats. Obes Res. 2002; 10:296–305. [PubMed: 11943840]
20. Faust IM. Role of the fat cell in energy balance physiology. Res Publ Assoc Res Nerv Ment Dis. 1984; 62:97–107. [PubMed: 6364276]

21. Nguyen TT, Mijares AH, Johnson CM, Jensen MD. Postprandial leg and splanchnic fatty acid metabolism in nonobese men and women. Am J Physiol. 1996; 271:E965–72. [PubMed: 8997213]
22. Hoyenga KB, Hoyenga KT. Gender and energy balance: sex differences in adaptations for feast and famine. Physiol Behav. 1982; 28:545–63. [PubMed: 7043508]
23. Woods SC, Seeley RJ, Porte DJ, Schwartz MW. Signals that regulate food intake and energy homeostasis. Science. 1998; 280:1378–83. [PubMed: 9603721]
24. Seeley RJ, Woods SC. Monitoring of stored and available fuel by the CNS: implications for obesity. Nat Rev Neurosci. 2003; 4:901–9. [PubMed: 14595401]
25. Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000; 404:661–71. [PubMed: 10766253]
26. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Muller C, Carling D. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature. 2002; 415:339–43. [PubMed: 11797013]
27. Kulkarni RN, Wang ZL, Wang RM, Hurley JD, Smith DM, Ghatei MA, et al. Leptin rapidly suppresses insulin release from insulinoma cells, rat and human islets and, in vivo, in mice. J Clin Invest. 1997; 100:2729–36. [PubMed: 9389736]
28. Emilsson V, Liu YL, Cawthorne MA, Morton NM, Davenport M. Expression of the functional leptin receptor mRNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion. Diabetes. 1997; 46:313–6. [PubMed: 9000710]
29. Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ, et al. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell. 1996; 84:491–5. [PubMed: 8608603]
30. Elmquist JK, Bjorbaek C, Ahima RS, Flier JS, Saper CB. Distributions of leptin receptor mRNA isoforms in the rat brain. J Comp Neurol. 1998; 395:535–47. [PubMed: 9619505]
31. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell. 1995; 83:1263–71. [PubMed: 8548812]
32. Munzberg H, Bjornholm M, Bates SH, Myers MG Jr. Leptin receptor action and mechanisms of leptin resistance. Cell Mol Life Sci. 2005; 62:642–52. [PubMed: 15770417]
33. Morton GJ, Niswender KD, Rhodes CJ, Myers MG Jr, Blevins JE, Baskin DG, et al. Arcuate nucleus-specific leptin receptor gene therapy attenuates the obesity phenotype of Koletsky (fa(k)/fa(k)) rats. Endocrinology. 2003; 144:2016–24. [PubMed: 12697710]
34. Cohen P, Zhao C, Cai X, Montez JM, Rohani SC, Feinstein P, et al. Selective deletion of leptin receptor in neurons leads to obesity. J Clin Invest. 2001; 108:1113–21. [PubMed: 11602618]
35. de Luca C, Kowalski TJ, Zhang Y, Elmquist JK, Lee C, Kilimann MW, et al. Complete rescue of obesity, diabetes, and infertility in db/db mice by neuron-specific LEPRB transgenes. J Clin Invest. 2005; 115:3484–93. [PubMed: 16284652]
36. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science. 1995; 269:546–9. [PubMed: 7624778]
37. Bartness TJ, Bamshad M. Innervation of mammalian white adipose tissue: implications for the regulation of total body fat. AmJ Physiol. 1998; 275:R1399–411. [PubMed: 9791054]
38. Shimazu T. Neuronal regulation of hepatic glucose metabolism in mammals. Diabetes Metab Rev. 1987; 3:185–206. [PubMed: 3568978]
39. Mantzoros CS, Qu D, Frederich RC, Susulic VS, Lowell BB, Maratos-Flier E, et al. Activation of beta(3) adrenergic receptors suppresses leptin expression and mediates a leptin-independent inhibition of food intake in mice. Diabetes. 1996; 45:909–14. [PubMed: 8666142]
40. Dobbins RL, Szczepaniak LS, Zhang W, McGarry JD. Chemical sympathectomy alters regulation of body weight during prolonged ICV leptin infusion. Am J Physiol Endocrinol Metab. 2003; 284:E778–87. [PubMed: 12626326]
41. Elmquist JK, Maratos-Flier E, Saper CB, Flier JS. Unraveling the central nervous system pathways underlying responses to leptin. Nat Neurosci. 1998; 1:445–50. [PubMed: 10196541]
42. Bartness TJ, Kay Song C, Shi H, Bowers RR, Foster MT. Brain-adipose tissue cross talk. Proc Nutr Soc. 2005; 64:53–64. [PubMed: 15877923]

43. Dua A, Hennes MI, Hoffman RG, Maas DL, Krakower GR, Sonnenberg GE, et al. Leptin: A significant indicator of total body fat but not of visceral fat and insulin insensitivity in African-American women. Diabetes. 1996; 45:1635–7. [PubMed: 8866572]
44. Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to central leptin and insulin. Diabetes. 2006; 55:978–87. [PubMed: 16567519]
45. Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. Differential sensitivity to central leptin and insulin in male and female rats. Diabetes. 2003; 52:682–7. [PubMed: 12606509]
46. Demerath EW, Towne B, Wisemandle W, Blangero J, Chumlea WC, Siervogel RM. Serum leptin concentration, body composition, and gonadal hormones during puberty. Int J Obes Relat Metab Disord. 1999; 23:678–85. [PubMed: 10454100]
47. Machinal F, Dieudonne MN, Leneveu MC, Pecquery R, Giudicelli Y. In vivo and in vitro ob gene expression and leptin secretion in rat adipocytes: evidence for a regional specific regulation by sex steroid hormones. Endocrinology. 1999; 140:1567–74. [PubMed: 10098489]
48. Kristensen K, Pedersen SB, Richelsen B. Regulation of leptin by steroid hormones in rat adipose tissue. Biochem Biophys Res Commun. 1999; 259:624–30. [PubMed: 10364468]
49. Wabitsch M, Blum WF, Muche R, Braun M, Hube F, Rascher W, et al. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. J Clin Invest. 1997; 100:808–13. [PubMed: 9259579]
50. Morley JE, Perry HM III. Androgen deficiency in aging men: role of testosterone replacement therapy. J Lab Clin Med. 2000; 135:370–8. [PubMed: 10811051]
51. Quinton ND, Smith RF, Clayton PE, Gill MS, Shalet S, Justice SK, et al. Leptin binding activity changes with age: the link between leptin and puberty. J Clin Endocrinol Metab. 1999; 84:2336–41. [PubMed: 10404799]
52. Ainslie DA, Morris MJ, Wittert G, Turnbull H, Proietto J, Thorburn AW. Estrogen deficiency causes central leptin insensitivity and increased hypothalamic neuropeptide Y. Int J Obes Relat Metab Disord. 2001; 25:1680–8. [PubMed: 11753591]
53. Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. Diabetes. 2004; 53:3024–9. [PubMed: 15504987]
54. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci. 2002; 5:514–6. [PubMed: 11992114]
55. Blaustein JD. An estrogen by any other name. Endocrinology. 2008; 149:2697–8. [PubMed: 18493023]
56. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med. 2002; 346:340–52. [PubMed: 11821512]
57. Greene GL, Sobel NB, King WJ, Jensen EV. Immunochemical studies of estrogen receptors. J Steroid Biochem. 1984; 20:51–6. [PubMed: 6200700]
58. King WJ, Greene GL. Monoclonal antibodies localize oestrogen receptor in the nuclei of target cells. Nature. 1984; 307:745–7. [PubMed: 6700704]
59. Welshons WV, Lieberman ME, Gorski J. Nuclear localization of unoccupied oestrogen receptors. Nature. 1984; 307:747–9. [PubMed: 6700705]
60. Matelski H, Greene R, Huberman M, Lokich J, Zipoli T. Randomized trial of estrogen vs. tamoxifen therapy for advanced breast cancer. Am J Clin Oncol. 1985; 8:128–33. [PubMed: 3914839]
61. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci U S A. 1996; 93:5925–30. [PubMed: 8650195]
62. Musatov S, Chen W, Pfaff DW, Mobbs CV, Yang XJ, Clegg DJ, et al. Silencing of estrogen receptor {alpha} in the ventromedial nucleus of hypothalamus leads to metabolic syndrome. Proc Natl Acad Sci U S A. 2007; 104:2501–6. [PubMed: 17284595]
63. Schomberg DW, Couse JF, Mukherjee A, Lubahn DB, Sar M, Mayo KE, et al. Targeted disruption of the estrogen receptor-alpha gene in female mice: characterization of ovarian responses and phenotype in the adult. Endocrinology. 1999; 140:2733–44. [PubMed: 10342864]

64. Greenberg C, Kukreja SC, Bowser EN, Hargis GK, Henderson WJ, Williams GA. Effects of estradiol and progesterone on calcitonin secretion. Endocrinology. 1986; 118:2594–8. [PubMed: 3698924]

65. Greenberg LH. Regulation of brain adrenergic receptors during aging. Fed Proc. 1986; 45:55–9. [PubMed: 3000836]

66. Enmark E, Pelto-Huikko M, Grandien K, Lagercrantz S, Lagercrantz J, Fried G, et al. Human estrogen receptor beta-gene structure, chromosomal localization, and expression pattern. J Clin Endocrinol Metab. 1997; 82:4258–65. [PubMed: 9398750]

67. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, et al. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology. 1997; 138:863–70. [PubMed: 9048584]

68. Menasce LP, White GR, Harrison CJ, Boyle JM. Localization of the estrogen receptor locus (ESR) to chromosome 6q25, 1 by FISH and a simple post-FISH banding technique. Genomics. 1993; 17:263–5. [PubMed: 8406468]

69. Hirata S, Shoda T, Kato J, Hoshi K. Isoform/variant mRNAs for sex steroid hormone receptors in humans. Trends Endocrinol Metab. 2003; 14:124–9. [PubMed: 12670738]

70. Pedram A, Razandi M, Levin ER. Nature of functional estrogen receptors at the plasma membrane. Mol Endocrinol. 2006; 20:1996–2009. [PubMed: 16645038]

71. Pietras RJ, Marquez-Garban DC. Membrane-associated estrogen receptor signaling pathways in human cancers. Clin Cancer Res. 2007; 13:4672–6. [PubMed: 17699844]

72. Song RX. Membrane-initiated steroid signaling action of estrogen and breast cancer. Semin Reprod Med. 2007; 25:187–97. [PubMed: 17447208]

73. Toran-Allerand CD. Estrogen and the brain: beyond ER-alpha and ER-beta. Exp Gerontol. 2004; 39:1579–86. [PubMed: 15582272]

74. Mendelsohn ME. Nongenomic, ER-mediated activation of endothelial nitric oxide synthase: how does it work? What does it mean? Circ Res. 2000; 87:956–60. [PubMed: 11090536]

75. Ronnekleiv OK, Malyala A, Kelly MJ. Membrane-initiated signaling of estrogen in the brain. Semin Reprod Med. 2007; 25:165–77. [PubMed: 17447206]

76. Vasudevan N, Kow LM, Pfaff D. Integration of steroid hormone initiated membrane action to genomic function in the brain. Steroids. 2005; 70:388–96. [PubMed: 15862822]

77. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev. 1999; 20:279–307. [PubMed: 10368772]

78. Collins P, Webb C. Estrogen hits the surface. Nat Med. 1999; 5:1130–1. [PubMed: 10502813]

79. Behl C. Estrogen can protect neurons: modes of action. J Steroid Biochem Mol Biol. 2002; 83:195–7. [PubMed: 12650716]

80. Mendez P, Cardona-Gomez GP, Garcia-Segura LM. Interactions of insulin-like growth factor-I and estrogen in the brain. Adv Exp Med Biol. 2005; 567:285–303. [PubMed: 16370144]

81. Kow LM, Pfaff DW. The membrane actions of estrogens can potentiate their lordosis behavior-facilitating genomic actions. Proc Natl Acad Sci U S A. 2004; 101:12354–7. [PubMed: 15302933]

82. Asarian L, Geary N. Modulation of appetite by gonadal steroid hormones. Philos Trans R Soc Lond B Biol Sci. 2006; 361:1251–63. [PubMed: 16815802]

83. Johnston M, Graves C, Arbogast PG, Cooper WO. Feeding attitudes of pregnant women with diabetes. Diabetes Care. 2006; 29:1457–8. [PubMed: 16732047]

84. Dagnault A, Richard D. Involvement of the medial preoptic area in the anorectic action of estrogens. Am J Physiol. 1997; 272:R311–7. [PubMed: 9039023]

85. Liang SL, Pan JT. Pretreatment with antisense oligodeoxynucleotide against D(2) or D(3) receptor mRNA diminished dopamine's inhibitory effect on dorsomedial arcuate neurons in brain slices of estrogen-treated ovariectomized rats. Brain Res. 2002; 926:156–64. [PubMed: 11814418]

86. Gao Z, Wang Z, Zhang X, Butler AA, Zuberi A, Gawronska-Kozak B, et al. Inactivation of PKCtheta leads to increased susceptibility to obesity and dietary insulin resistance in mice. Am J Physiol Endocrinol Metab. 2007; 292:E84–91. [PubMed: 16896164]

87. Houpt KA, Coren B, Hintz HF, Hilderbrant JE. Effect of sex and reproductive status on sucrose preference, food intake, and body weight of dogs. J Am Vet Med Assoc. 1979; 174:1083–5. [PubMed: 571424]

88. Friend DW. Self-selection of feeds and water by swine during pregnancy and lactation. J Anim Sci. 1971; 32:658–66. [PubMed: 5571549]

89. Eckel LA, Houpt TA, Geary N. Spontaneous meal patterns in female rats with and without access to running wheels. Physiol Behav. 2000; 70:397–405. [PubMed: 11006440]

90. Czaja JA, Goy RW. Ovarian hormones and food intake in female guinea pigs and rhesus monkeys. Horm Behav. 1975; 6:329–49. [PubMed: 816725]

91. Gong EJ, Garrel D, Calloway DH. Menstrual cycle and voluntary food intake. Am J Clin Nutr. 1989; 49:252–8. [PubMed: 2916445]

92. Czaja JA. Ovarian influences on primate food intake: assessment of progesterone actions. Physiol Behav. 1978; 21:923–8. [PubMed: 552083]

93. Rosenblatt H, Dyrenfurth I, Ferin M, vande Wiele RL. Food intake and the menstrual cycle in rhesus monkeys. Physiol Behav. 1980; 24:447–9. [PubMed: 6769135]

94. Bisdee JT, Garlick PJ, James WP. Metabolic changes during the menstrual cycle. Br J Nutr. 1989; 61:641–50. [PubMed: 2758017]

95. Bisdee JT, James WP, Shaw MA. Changes in energy expenditure during the menstrual cycle. Br J Nutr. 1989; 61:187–99. [PubMed: 2706224]

96. Tai MM, Castillo TP, Pi-Sunyer FX. Thermic effect of food during each phase of the menstrual cycle. Am J Clin Nutr. 1997; 66:1110–5. [PubMed: 9356527]

97. Asarian L, Geary N. Cyclic estradiol treatment normalizes body weight and restores physiological patterns of spontaneous feeding and sexual receptivity in ovariectomized rats. Horm Behav. 2002; 42:461–71. [PubMed: 12488112]

98. Wade GN. Gonadal hormones and behavioral regulation of body weight. Physiol Behav. 1972; 8:523–34. [PubMed: 4556652]

99. Wade GN. Some effects of ovarian hormones on food intake and body weight in female rats. J Comp Physiol Psychol. 1975; 88:183–93. [PubMed: 1120795]

100. Roy EJ, Wade GN. Role of food intake in estradiol-induced body weight changes in female rats. Horm Behav. 1977; 8:265–74. [PubMed: 881167]

101. Barr SI, Janelle KC, Prior JC. Energy intakes are higher during the luteal phase of ovulatory menstrual cycles. Am J Clin Nutr. 1995; 61:39–43. [PubMed: 7825535]

102. Rock CL, Gorenflo DW, Drewnowski A, Demitrack MA. Nutritional characteristics, eating pathology, and hormonal status in young women. Am J Clin Nutr. 1996; 64:566–71. [PubMed: 8839501]

103. Longcope C. Endocrine function of the postmenopausal ovary. J Soc Gynecol Investig. 2001; 8:S67–8.

104. Poehlman ET. Menopause, energy expenditure, and body composition. Acta Obstet Gynecol Scand. 2002; 81:603–11. [PubMed: 12190834]

105. Gao Q, Horvath TL. Cross-talk between estrogen and leptin signaling in the hypothalamus. Am J Physiol Endocrinol Metab. 2008; 294:E817–26. [PubMed: 18334610]

106. Diano S, Kalra SP, Sakamoto H, Horvath TL. Leptin receptors in estrogen receptorcontaining neurons of the female rat hypothalamus. Brain Res. 1998; 812:256–9. [PubMed: 9813356]

107. Bennett PA, Lindell K, Wilson C, Carlsson LM, Carlsson B, Robinson IC. Cyclical variations in the abundance of leptin receptors, but not in circulating leptin, correlate with NPY expression during the oestrous cycle. Neuroendocrinology. 1999; 69:417–23. [PubMed: 10364693]

108. Bouchard C, Despres JP, Mauriege P. Genetic and nongenetic determinants of regional fat distribution. Endocr Rev. 1993; 14:72–93. [PubMed: 8491156]

109. Crandall DL, Busler DE, Novak TJ, Weber RV, Kral JG. Identification of estrogen receptor beta RNA in human breast and abdominal subcutaneous adipose tissue. Biochem Biophys Res Commun. 1998; 248:523–6. [PubMed: 9703958]

110. Lu SF, McKenna SE, Cologer-Clifford A, Nau EA, Simon NG. Androgen receptor in mouse brain: sex differences and similarities in autoregulation. Endocrinology. 1998; 139:1594–601. [PubMed: 9528939]

111. Bjorntorp P. Hormonal control of regional fat distribution. Hum Reprod. 1997; 12 (Suppl 1):21–5. [PubMed: 9403318]

112. Yu IC, Lin HY, Liu NC, Wang RS, Sparks JD, Yeh S, et al. Hyperleptinemia without obesity in male mice lacking androgen receptor in adipose tissue. Endocrinology. 2008; 149:2361–8. [PubMed: 18276764]

113. Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, Cooke PS. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. Proc Natl Acad Sci U S A. 2000; 97:12729–34. [PubMed: 11070086]

114. Ohlsson C, Hellberg N, Parini P, Vidal O, Bohlooly M, Rudling M, et al. Obesity and disturbed lipoprotein profile in estrogen receptor-alpha-deficient male mice. Biochem Biophys Res Commun. 2000; 278:640–5. [PubMed: 11095962]

115. Okura T, Koda M, Ando F, Niino N, Ohta S, Shimokata H. Association of polymorphisms in the estrogen receptor alpha gene with body fat distribution. Int J Obes Relat Metab Disord. 2003; 27:1020–7. [PubMed: 12917706]

116. Speer G, Cseh K, Fuszek P, Dworak O, Vargha P, Takacs I, et al. The role of estrogen receptor, vitamin D receptor and calcium receptor genotypes in the pathogenesis of colorectal cancer. Orv Hetil. 2001; 142:947–51. [PubMed: 11392075]

117. Yamada Y, Ando F, Niino N, Ohta S, Shimokata H. Association of polymorphisms of the estrogen receptor alpha gene with bone mineral density of the femoral neck in elderly Japanese women. J Mol Med. 2002; 80:452–60. [PubMed: 12110951]

118. Elbers JM, Asscheman H, Seidell JC, Frolich M, Meinders AE, Gooren LJ. Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. J Clin Endocrinol Metab. 1997; 82:3267–70. [PubMed: 9329351]

119. Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, Fabbri R, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism. 1991; 40:101–4. [PubMed: 1984562]

120. Sjogren J, Li M, Bjorntorp P. Androgen hormone binding to adipose tissue in rats. Biochim Biophys Acta. 1995; 1244:117–20. [PubMed: 7766646]

121. Marin P. Testosterone and regional fat distribution. Obes Res. 1995; 3(Suppl 4):609S–12S. [PubMed: 8697064]

122. Dieudonne MN, Pecquery R, Boumediene A, Leneveu MC, Giudicelli Y. Androgen receptors in human preadipocytes and adipocytes: regional specificities and regulation by sex steroids. Am J Physiol. 1998; 274:C1645–52. [PubMed: 9611130]

123. Pedersen SB, Fuglsig S, Sjogren P, Richelsen B. Identification of steroid receptors in human adipose tissue. Eur J Clin Invest. 1996; 26:1051–6. [PubMed: 9013078]