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Nutrition. 1997 Sep;13(9):795-803.

Body fat distribution, insulin resistance, and metabolic diseases.

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Obesity has now developed into a world-wide epidemic and is associated with large economic costs and prevalent diseases, particularly with central body fat distribution. Insulin resistance almost invariably occurs, and might be a major trigger for disease-generating mechanisms either directly or via generation of other disease precursors ("risk factors"). The hypothalamo-pituitary-adrenal (HPA) axis seems to be hypersensitive in abdominal obesity, a statement supported by increased responses to challenges from the adrenals to central regulatory centers. Furthermore, the feedback control by central glucocorticoid receptors, probably a secondary, functional consequence of an elevated HPA axis activity, because the receptor gene appears normal. Secretion of sex steroid and growth hormones is diminished, which might be consequence of elevated HPA axis activity. Hyperandrogenicity in women is probably of adrenal origin and another consequence of the sensitivity of the HPA axis. The endocrine abnormalities thus are periodically elevated cortisol and androgen (women) concentrations, as well as low secretions of gender-specific steroid and growth hormones. Since elevated cortisol, and low sex-steroid and growth hormone secretions, probably direct storage fat to visceral depots, the multiple endocrine abnormalities probably cause enlargement of these depots. Furthermore, these hormonal abnormalities most likely at least contribute to the creation of insulin resistance with additional effects of elevated fatty acids from central fat depots, which are sensitive to lipid mobilization agents. This chain of events indicates the central role of the hypersensitive HPA axis. Known causes of sensitization of this axis have been identified in subjects with abdominal obesity, including depression, anxiety, alcohol, and smoking. A common cause of HPA axis activation is perceived stress, with a depressive, defeatist, or "helplessness" reaction. In subjects with abdominal preponderance of body fat stores a number of psychosocial and socioeconomics handicaps have been identified, hypothetically predisposing to such reactions. In a primate model (monkeys), mild psychosocial stress is followed by identical psychological, endocrine, anthropometric, and metabolic abnormalities as in humans with abdominal preponderance of body fat stores, including early signs of diabetes and cardiovascular disease. These findings strongly support the interpretation that a stress reaction activating the HPA axis is involved also in the human syndrome. Interventions with normalization of the endocrine perturbations are followed by clear improvements of the multiple abnormalities in both clinical, experimental, cellular and molecular studies, suggesting that the pathogenesis of abdominal preponderance of body fat and its endocrine, anthropometric and metabolic abnormalities are indeed consequences of the endocrine abnormalities identified.

Obes Rev. 2001 May;2(2):73-86.

Do stress reactions cause abdominal obesity and comorbidities?

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'Stress' embraces the reaction to a multitude of poorly defined factors that disturb homeostasis or allostasis. In this overview, the activation of the hypothalamic- pituitary-adrenal (HPA) axis and the sympathetic nervous system have been utilized as objective measurements of stress reactions. Although long-term activation of the sympathetic nervous system is followed by primary hypertension, consequences of similar activation of the HPA axis have not been clearly defined. The focus of this overview is to examine whether or not repeated activation of these two stress centres may be involved in the pathogenesis of abdominal obesity and its comorbidities. In population studies adrenal hormones show strong statistical associations to centralization of body fat as well as to obesity. There is considerable evidence from clinical to cellular and molecular studies that elevated cortisol, particularly when combined with secondary inhibition of sex steroids and growth hormone secretions, is causing accumulation of fat in visceral adipose tissues as well as metabolic abnormalities (The Metabolic

Syndrome). Hypertension is probably due to a parallel activation of the central sympathetic nervous system. Depression and 'the small baby syndrome' as well as stress exposure in men and non-human primates are followed with time by similar central and peripheral abnormalities. Glucocorticoid exposure is also followed by increased food intake and 'leptin resistant' obesity, perhaps disrupting the balance between leptin and neuropeptide Y to the advantage of the latter. The consequence might be 'stress-eating', which, however, is a poorly defined entity. Factors activating the stress centres in humans include psychosocial and socioeconomic handicaps, depressive and anxiety traits, alcohol and smoking, with some differences in profile between personalities and genders. Polymorphisms have been defined in several genes associated with the cascade of events along the stress axes. Based on this evidence it is suggested that environmental, perinatal and genetic factors induce neuroendocrine perturbations followed by abdominal obesity with its associated comorbidities.

Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S80-5.

Neuroendocrine abnormalities in visceral obesity.

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Central obesity is the subfraction which carries most of the risks for comorbidities. In this overview we suggest that this is due to neuroendocrine perturbations, where the hypothalamic-pituitary-adrenal (HPA) axis assumes a central role. The HPA axis is stimulated by central factors, which are often called stress. This is followed by discrete, periodical elevations of cortisol secretion during every day conditions. Such observations require diurnal measurements under undisturbed conditions. Saliva cortisol is useful for such purposes. It seems likely, based on cross-sectional observations in men and longitudinal studies in animals that a prolonged period of HPA axis stimulation is followed by a continuous degradation of the regulatory mechanisms. An end stage is a rigid cortisol secretion with low morning values. In parallel with this is a diminished function of the feed-back control as well as an inhibition of growth and sex steroid hormones. Evidence also suggests that the sympathetic nervous centers become activated in parallel. The net effects of this cascade of neuroendocrine- endocrine pertubations will be insulin resistance as well as visceral accumulation of body fat. These are effects of cortisol in combination with the diminished secretion of growth and sex steroid secretions, which in normal concentrations antagonize the cortisol effects. Blood pressure will also be elevated, which might be a consequence of central stimulation of the sympathetic nervous system, with added effects of insulin. What has developed is a hypothalamic arousal with the Metabolic Syndrome as a consequence. The feed-back regulation of the HPA axis has a key position in this chain of events. This control is mediated via glucocorticoid receptors in the lower parts of the brain. The gene for this receptor has shown polymorphisms which are associated with poorly regulated cortisol secretion, central obesity, insulin resistance and hypertension.

Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S47-9.

Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes.

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Subjects with abdominal obesity are characterized by hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to a condition of 'functional hypercortisolism'. This appears to be the result of two distinct mechanisms. The first, which appears to be central in origin, is characterized by altered ACTH pulsatile secretory dynamics and by hyper-responsiveness of the HPA axis to different

neuropeptides and acute or chronic stress events and, possibly, to selected dietary factors. The other appears to be located in the periphery, specifically the liver and visceral adipose tissue, and is characterized by supranormal cortisol production, whose paracrine and systemic effects remain unclear. It is suggested that increased exposure to cortisol of the body may play a fundamental role not only in the development of increased fat in abdominal/visceral depots, but also in determining all metabolic abnormalities closely related to the abdominal obesity phenotype.

Br J Nutr. 2000 Mar;83 Suppl 1:S49-57.

The metabolic syndrome--a neuroendocrine disorder?

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Central obesity is a powerful predictor for disease. By utilizing salivary cortisol measurements throughout the day, it has now been possible to show on a population basis that perceived stress-related cortisol secretion frequently is elevated in this condition. This is followed by insulin resistance, central accumulation of body fat, dyslipidaemia and hypertension (the metabolic syndrome). Socio-economic and psychosocial handicaps are probably central inducers of hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis. Alcohol, smoking and traits of psychiatric disease are also involved. In a minor part of the population a dysregulated, depressed function of the HPA axis is present, associated with low secretion of sex steroid and growth hormones, and increased activity of the sympathetic nervous system. This condition is followed by consistent abnormalities indicating the metabolic syndrome. Such 'burned-out' function of the HPA axis has previously been seen in subjects exposed to environmental stress of long duration. The feedback control of the HPA axis by central glucocorticoid receptors (GR) seems inefficient, associated with a polymorphism in the 5' end of the GR gene locus. Homozygotes constitute about 14% of Swedish men (women to be examined). Such men have a poorly controlled cortisol secretion, abdominal obesity, insulin resistance and hypertension. Furthermore, polymorphisms have been identified in the regulatory domain of the GR gene that are associated with elevated cortisol secretion; polymorphisms in dopamine and leptin receptor genes are associated with sympathetic nervous system activity, with elevated and low blood pressure, respectively. These results suggest a complex neuroendocrine background to the metabolic syndrome, where the kinetics of the regulation of the HPA axis play a central role

Nutrition. 2000 Oct;16(10):924-36.

Obesity and cortisol.

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Cortisol in obesity is a much-studied problem. Previous information indicates that cortisol secretion is elevated but that circulatory concentrations are normal or low, suggesting that peripheral disappearance rate is elevated. These studies have usually not taken into account the difference between central and peripheral types of obesity. Recent studies using saliva cortisol have indicated that the problem is complex with both high and low secretion of cortisol, perhaps depending on the status of the function of the hypothalamic-pituitary-adrenal gland axis. A significant background factor seems to be environmental stress. The results also suggest that the pattern of cortisol secretion may be important. Other neuroendocrine pathways are also involved, including the central sympathetic nervous system, the gonadal and growth hormone axes, and the leptin system. In concert, these abnormalities seem to be responsible for the abnormal metabolism often seen in central obesity. Several associated polymorphisms of candidate genes may provide a genetic background. Cortisol conversion to inactive

metabolites may be a factor increasing central signals to secretion and may add to the increased secretion of cortisol induced by centrally acting factors. Perinatal factors have been found to be involved in the pathogenesis of obesity and its complications. The mechanism involved is not known, but available information suggests that programming of the hypothalamic-pituitary-adrenal axis may be responsible.

Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S50-5.

The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes.

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The stress system coordinates the adaptive response of the organism to real or perceived stressors. The main components of the stress system are the corticotropin-releasing hormone (CRH) and locus ceruleus-norepinephrine/ autonomic (LC/NE) systems and their peripheral effectors, the hypothalamic-pituitary-adrenal (HPA) axis, and the limbs of the autonomic system. Activation of the stress system leads to behavioral and peripheral changes that improve the ability of the organism to adjust homeostasis and increase its chances for survival. Thus, CRH and the LC/NE system stimulate arousal and attention, as well as the mesocorticolimbic dopaminergic system, which is involved in anticipatory and reward phenomena, and the amygdala, which are responsible for the generation of fear. Hypothalamic CRH plays an important role in inhibiting gonadotropin- releasing hormone secretion during stress, while via somatostatin it also inhibits growth hormone, thyrotropin-releasing hormone and thyrotropin secretion, suppressing thus reproduction, growth and thyroid function. Glucocorticoids directly inhibit pituitary gonadotropin, growth hormone and thyrotropin secretion and make the target tissues of sex steroids and growth factors resistant to these substances. In addition, glucocorticoids stimulate hepatic gluconeogenesis, and inhibit or potentiate insulin actions on skeletal muscle and adipose tissue respectively, ultimately promoting visceral adiposity and the metabolic syndrome. Glucocorticoids also have direct effects on the bone, inhibiting osteoblastic activity and causing osteoporosis. Obese subjects with psychiatric manifestations ranging from those of melancholic depression to anxiety with perception of 'uncontrollable' stress, frequently have mild hypercortisolism, while carefully screened obese subjects with no such manifestations are eucortisolemic. The former may have stress-induced glucocorticoid-mediated visceral obesity and metabolic syndrome manifestations, which in the extreme may be called a pseudo-Cushing state that needs to be differentiated from frank Cushing syndrome. Stress-induced hypercortisolism and visceral obesity and their cardiovascular and other sequelae increase the all-cause mortality risk of affected subjects by 2-3-fold and curtail their life expectancy by several years.

Panminerva Med. 2003 Sep;45(3):189-95.

Is visceral obesity a physiological adaptation to stress?

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Visceral obesity represents an important risk factor associated with hypertension, diabetes and cardiovascular diseases. Since this condition is associated with a disruption of the functioning of the HPA axis, stress-induced HPA axis activation has been identified to play an important role in this preferential body fat accumulation. HPA axis activation increases cortisol (corticosterone) production which has been shown to exert hyperphagic and antithermogenic effects. Since abdominal adipose tissue has more cells per mass units, higher blood flow and more glucocorticoid receptors, glucocorticoids affect abdominal fat to a greater extent than subcutaneous adipose tissue. Cushing's

syndrome in humans is the best evidence showing a link between hypercortisolemia and accumulation of central fat. The Hervey's hypothesis which suggests that fat cells take up and catabolize glucocorticoids is one of the possible regulatory effect that supports the adaptive role of visceral fat in response to stress. This is also supported by other evidence showing that abdominal obesity is associated with an increased cortisol clearance. Hormonal and enzymatic changes have been implicated in this preferential body fat accumulation in response to stress. Specific genetic background may also accentuate this visceral fat accumulation in some individuals exposed to stress. Alternatively, obesity could also be a source of stress promoting the visceral fat accumulation since visceral fat is able to release cytokines which stimulate the HPA axis. Even if the available literature does not permit to establish clearly which comes first, it suggests that visceral obesity could represent a non optimal physiological adaptation to stress. In this context, visceral obesity treatment should focus on stress management and weight loss strategies in order to stop this vicious circle.

Horm Res. 1993;39 Suppl 3:81-5.

Endocrine-metabolic pattern and adipose tissue distribution.

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The associations between cardiovascular disease (CVD), non-insulin-dependent diabetes mellitus (NIDDM) and abdominal fat distribution are well established. The most important adipose tissue depot in this context is probably the mass of intra-abdominal adipose tissue which has been found to be associated with CVD, NIDDM and their established metabolic risk factors. This type of adipose tissue distribution is also associated with multiple endocrine aberrations, probably comprising an increased responsiveness of the hypothalamo-adrenal axis and a parallel or secondary decreased activity of the hypothalamic-gonadal axis. Epidemiological studies in both men and women indicate that this may be a consequence of psychological stress. Recently, indirect evidence for decreased production of growth hormone in this condition has also been recognized. These multiple and interrelated abnormalities comprise a syndrome where the primary disturbance could be localized to the hypothalamus and the main peripheral consequences would be metabolic effects on the mass and function of intra- abdominal adipose tissue. This in turn, probably by the effects of elevated concentrations of portal free fatty acid levels on the liver, could result in insulin resistance and other metabolic risk factors known to be strongly associated with CVD and NIDDM.

Diabetes Care. 1991 Dec;14(12):1132-43.

Metabolic implications of body fat distribution.

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Insulin resistance is the cornerstone for the development of non-insulin-dependent diabetes mellitus (NIDDM). Free fatty acids (FFAs) cause insulin resistance in muscle and liver and increase hepatic gluconeogenesis and lipoprotein production and perhaps decrease hepatic clearance of insulin. It is suggested that the depressing effect of insulin on circulating FFA concentration is dependent on the fraction derived from visceral adipocytes, which have a low responsiveness to the antilipolytic effect of insulin. Elevated secretion of cortisol and/or testosterone induces insulin resistance in muscle. This also seems to be the case for low testosterone concentrations in men. In addition, cortisol increases hepatic gluconeogenesis. Cortisol and testosterone have "permissive" effect on adipose lipolysis and therefore amplify lipolytic stimulation; FFA, cortisol, and testosterone thus have powerful combined effects, resulting in insulin resistance and increased hepatic gluconeogenesis. All these factors promoting insulin resistance are active in abdominal visceral obesity, which is closely associated with insulin resistance, NIDDM, and the "metabolic syndrome." In addition, the endocrine aberrations may provide a cause for

visceral fat accumulation, probably due to regional differences in steroid-hormone-receptor density. In addition to the increased activity along the adrenocorticosteroid axis, there also seem to be signs of increased activity from the central sympathetic nervous system. These are the established endocrine consequences of hypothalamic arousal in the defeat and defense reactions. There is some evidence that suggests an increased prevalence of psychosocial stress factors is associated with visceral distribution of body fat. Therefore, it is hypothesized that such factors might provide a background not only to a defense reaction and primary hypertension, suggested previously, but also to a defeat reaction, which contributes to an endocrine aberration leading to metabolic aberrations and visceral fat accumulation, which in turn leads to disease.

J Endocrinol Invest. 1999;22(5 Suppl):41-6.

Growth hormone and the metabolic syndrome.

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The association of several risk factors, obesity, dyslipoproteinemia, hepatic steatosis, insulin resistance and hypertension with Type 2 (non-insulin-dependent) diabetes mellitus and myocardial infarction has long been known and has been termed the "metabolic syndrome". In 1988 Reaven introduced syndrome X as the link between insulin resistance and hypertension. It has been suggested that a critical factor in the association between obesity, Type 2 diabetes and cardiovascular morbidity is the mass of intraabdominal fat. Striking similarities exist between the metabolic syndrome and untreated growth hormone (GH) deficiency in adults. The central findings in both these syndromes are abdominal/visceral obesity and insulin resistance. Other features common to both conditions are premature atherosclerosis and increased mortality from cardiovascular diseases. These similarities indicate that undetectable and low levels of GH may be of importance in the metabolic aberrations observed in both these conditions. Recent investigations have found that abdominal/visceral distribution of adipose tissue is associated with endocrine disturbances including increased activity of the hypothalamic-pituitary-adrenal axis and a blunted secretion of GH and sex steroids. Theoretically, these endocrine perturbations can be a consequence of obesity, but the endocrine aberrations may have causal effects. We studied moderately obese, middle-aged men with a preponderance of abdominal body fat. As a group, they had slight to moderate metabolic changes known to be associated with abdominal/visceral obesity. Nine months of GH treatment reduced their total body fat and resulted in a specific and a marked decrease in both abdominal subcutaneous and visceral adipose tissue. Moreover, insulin sensitivity improved and serum concentrations of total cholesterol and triglyceride decreased. Diastolic blood pressure also decreased. The finding that GH replacement in men with abdominal obesity can diminish the negative metabolic consequences of visceral obesity suggests that low levels of this hormone are of importance for the metabolic aberrations associated with visceral/abdominal obesity.

Diabete Metab. 1987 Jul;13(3 Pt 2):381-5.

Adipose tissue distribution, plasma insulin, and cardiovascular disease.

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Hyperinsulinaemia is of great importance, being a primary risk factor for cardiovascular disease and non-insulin dependent diabetes (NIDDM). Furthermore, unwanted effects of increased exposure of tissues to insulin are known. Hyperinsulinaemia may, in principle, be caused by primary hypersecretion, or be a secondary consequence of diminished effectiveness of insulin in the periphery. Obesity is the commonest condition characterized by insulin resistance, which is seen most frequently when excess

adipose tissue is localized to the abdominal region. Insulin resistance in obesity is found in several tissues, however, with liver and muscle being quantitative the most important. Muscle insulin sensitivity is regulated by genetic factors, hormonal effects, and the influence of free fatty acids, as well as the state of physical activity. There is evidence for the action of each of these factors in obesity. The pathogenetic mechanisms linking hyperinsulinaemia with cardiovascular disease and NIDDM are unknown. Comparisons between development of NIDDM in experimental animal models and in humans in prospective studies however, provide useful hypotheses for further studies.

Acta Med Scand Suppl. 1988;723:121-34.

The associations between obesity, adipose tissue distribution and disease.

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Recent research has shown the marked differences in association with disease between obesity localized to the abdominal respectively to the gluteal-femoral regions. In this review systematic analyses were performed of the associations between obesity (body mass index, BMI) or abdominal obesity (increased waist- over-hip circumference ratio, WHR) on the one hand, and a number of disease end points, and their risk factors, as well as other factors on the other, WHR was associated with cardiovascular disease, premature death, stroke, non-insulin- dependent diabetes mellitus and female carcinomas. In contrast, BMI tended to be negatively correlated to cardiovascular disease, premature death, and stroke, but positively to diabetes. The established risk factors for these end points were found to correlate to WHR, while this was often not the case with BMI. BMI was positively correlated only to insulin, triglycerides and blood pressure. Together with diabetes mellitus, this seems to constitute a metabolic group of conditions which are thus associated with BMI. Androgens (in women), and perhaps cortisol, seem to be positively, and progesterone negatively correlated to WHR. The WHR was also positively associated with sick leave, several psychological maladjustments, psychosomatic and psychiatric disease. Attempts were made to interpret these findings. In a first alternative an elevation of FFA concentration, produced from abdominal adipose tissue, was considered to be the trigger factor for the pathologic aberrations associated with abdominal distribution of body fat. When obesity is added, the metabolic aberrations may be exaggerated. In a second alternative adrenal cortex hyperactivity was tested as the cause. When combined with the FFA hypothesis, this might explain many but not all of the findings. It seems possible to produce an almost identical syndrome in primates by defined experimental stress. Women with high WHR were found to have a number of symptoms of poor coping to stress. It was therefore suggested that part of the background to this syndrome might be a hypothalamic arousal syndrome developing with stress. It was concluded that obesity and abdominal distribution of adipose tissue constitute two separate entities with different pathogenesis, clinical consequences and probably treatment.

Baillieres Clin Endocrinol Metab. 1998 Oct;12(3):441-51.

Androgens and abdominal obesity.

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Central or visceral obesity is recognized as a main risk factor for cardiovascular disease and type 2 diabetes mellitus. The co-existence of visceral obesity, increased blood lipid levels, hypertension and impaired glucose tolerance defines the metabolic syndrome that today is widely recognized as one of the prime factors behind cardiovascular morbidity and mortality. Endocrine disorders such as insulinoma, hypothyroidism and hypercortisolism are known to cause obesity. However, it is only hypercortisolism that is associated with increased abdominal fat accumulation. Recently, new findings

have shed light on subtle endocrinopathies that are prevalent in individuals presenting with the metabolic syndrome. Such derangements are of borderline character and often fall within the normal reference range. Intervention studies demonstrate that correction of relative hypogonadism in men with visceral obesity and other manifestations of the metabolic syndrome seem to decrease the abdominal fat mass and reverse the glucose intolerance, as well as lipoprotein abnormalities in the serum. Further analysis of the underlying mechanism has also disclosed a regulatory role for testosterone in counteracting visceral fat accumulation. Longitudinal epidemiological data demonstrates that relatively low testosterone levels are a risk factor for development of visceral obesity. The primary event that triggers the initial development of visceral obesity is not known, but it seems plausible that increased activity in the hypothalamus-pituitary-adrenal axis can be of major importance.

Diabetes Metab. 2001 Apr;27(2 Pt 2):209-14.

Fat distribution and metabolism

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It is well known that adipose tissue distribution is an important factor involved in the etiology of type 2 diabetes and cardiovascular diseases. Adipose tissue distribution is obviously different between men and women, men being prone to accumulate their excess of energy in the abdominal region, more specifically in the intra-abdominal depot (visceral) whereas women show a selective deposition of adipose tissue in the gluteo-femoral region. Several studies have demonstrated an association between age and adipose tissue distribution and a selective deposition of visceral adipose tissue has been reported with age, in both men and women. In this regard, the menopause transition also appears to be a factor associated with an accelerated accumulation of abdominal adipose tissue. This increase in visceral adipose tissue has been suggested to play a significant role in the etiology of metabolic complications increasing the risk of type 2 diabetes and cardiovascular diseases. However, a selective mobilization of visceral adipose tissue in response to a weight loss program has been noted among viscerally obese patients, this reduction in visceral adipose tissue being associated with improvements in the lipoprotein-lipid profile and insulin sensitivity. Thus, the distribution of adipose tissue is an important factor to take into account in the evaluation of the patient. Furthermore, the amount of abdominal adipose tissue should also be considered as an important therapeutic target for the optimal management of cardiovascular disease risk.

Acta Med Scand Suppl. 1988;723:205-12.

Physical training and changes in regional adipose tissue distribution.

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Obesity has been associated with numerous metabolic complications, such as changes in the concentration and/or composition of plasma lipoproteins, glucose intolerance and hyperinsulinemia leading to diabetes and hypertension. The relation of obesity to cardiovascular disease has not, however, been consistently reported. Recent prospective studies have clearly indicated that the distribution of adipose tissue was a significant cardiovascular risk factor and numerous studies have shown that metabolic disturbances were more closely associated with the level of abdominal fat than excess adiposity per se. As obese men generally store their energy excess in the abdominal region and women in the peripheral fat depots, the metabolic complications of obesity seem to be more closely related to adiposity in men than in women. It is suggested that the sex dimorphism observed in adipose tissue localization could partly explain the greater cardiovascular risk associated with obesity in men than in women. Indeed, obese women with a "male" (abdominal) distribution of body fat have greater metabolic complications than women with lower body fat. When aerobic exercise-training is used to

induce weight loss, men generally lose more fat than women. In men, the loss of adipose tissue appears to be central, potentially reducing the risk of cardiovascular disease, whereas a relative resistance to fat loss is observed in women compared to men. Although resistance to fat loss is noted in women, those with a "male" distribution of adipose tissue (high waist-to-hip ratio and high intra-abdominal fat deposition) and with associated metabolic complications greatly benefit from aerobic exercise-training.

Diabetes Metab. 2000 Jun;26 Suppl 3:10-2.

Metabolic difference between visceral fat and subcutaneous abdominal fat

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Obesity stands as a public health issue. Obesity prevalence is increasing throughout every industrialized country. Android obesity is linked with an increased cardiovascular mortality and with type 2 diabetes mellitis, thus calling for an early management of this disease. Several studies showed a significant association between an android fat distribution and an increased cortisol secretion, raising the still debated question of a causal relationship between the development of android obesity and hypercorticism. Moreover, android obese subjects exhibit reduced plasma testosterone and growth hormone levels, meaning complex hormonal abnormalities in these subjects. Current hypotheses suggest that android fat distribution depends on the association of these hormonal abnormalities. Android obese patients have supranormal free fatty acid plasma concentrations. Visceral fat tissue, through its portal drainage, could be an important source for free fatty acids that may exert complex metabolic effects: involvement in hepatic lipogenesis, increase in hepatic neoglucogenic flux, reduction in insulin metabolic clearance and involvement in peripheral insulin resistance through a competition mechanism described by Randle. Technics in vitro (isolated adipocytes) and in vivo in human (labelled fatty acid flux) showed that visceral fatty acid flux was increased in obese patients and subcutaneous adipose tissue, as opposed to common opinion, was also involved in free fatty acid pool in obese patients. Thus, visceral obesity and diabetes could be linked through an enhanced fatty acid availability from adipose tissues (visceral and subcutaneous) in otherwise genetically type 2 diabetes-prone individuals.

Int J Obes Relat Metab Disord. 1996 Apr;20(4):291-302.

The regulation of adipose tissue distribution in humans.

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The regulation of adipose tissue distribution is an important problem in view of the close epidemiological and metabolic associations between centralized fat accumulation and disease. With visceral fat accumulation multiple endocrine perturbations are found, including elevated cortisol and androgens in women, as well as low growth hormone (GH) and, in men, testosterone (T) secretion. These abnormalities probably derive from a hypersensitive hypothalamo-pituitary- adrenal axis, with hyperinsulinemia related to a marked insulin resistance as a consequence. These hormonal changes exert profound effects on adipose tissue metabolism and distribution. At the adipocyte level cortisol and insulin promote lipid accumulation by expressing lipoprotein lipase activity, while T, GH and probably estrogens exert opposite effects. The consequences will most likely be more expressed in visceral than subcutaneous adipose tissues because of a higher cellularity, innervation and blood flow. Furthermore, the density of cortisol and androgen receptors seems to be higher in this than other adipose tissue regions. The endocrine perturbations found in visceral obesity with an abundance of the lipid accumulating hormones cortisol and insulin, and a relatively low secretion of the lipid mobilizing sex steroid hormones and GH would therefore be expected to be followed by visceral fat accumulation. The potential significance of local synthesis of steroid hormones in adipose tissue requires more attention.

Although studies in vitro are informative when elucidating detailed mechanisms of hormonal interactions, they might not give a true picture of the regional integrated regulation of adipose tissue lipid storage and mobilization. Such information can be obtained by regional measurements of lipid mobilization by free fatty acid turnover or by microdialysis techniques, both showing lower rates of mobilization in leg than in upper body adipose tissues. More detailed information can be obtained by physiological oral administration of triglycerides, labelled with a small amount of oleic acid, followed by measurements of the regional uptake and turn-over of adipose tissue triglycerides. Such studies show lipid uptake in the order omental = retroperitoneal > subcutaneous abdominal > subcutaneous femoral adipose tissues in men, with a similar rank order for half-life of the triglyceride, indicating also a turn-over of triglycerides in that order. T amplifies these differences in men. In premenopausal women subcutaneous abdominal has a higher turnover than femoral adipose tissue. Results of studies in vitro indicate that this difference is diminished at the menopause, and restored by estrogen substitution, suggesting that the functional effects of estrogens in women are similar to those of T in men. The mechanisms are, however, probably indirect because of the apparent absence of specific estrogen and progesterone receptors in human adipose tissue. This interpretation from the studies referred to above fits well with physiological, and clinical conditions with increased visceral fat mass, where the balance between the lipid accumulating hormone couple (cortisol and insulin) and the hormones which prevent lipid accumulation and instead activate lipid mobilization pathways (sex steroid hormones and GH) is shifted to the advantage of the former. Such conditions include Cushing's syndrome, the polycystic ovary syndrome, menopause, aging, GH-deficiency, depression, smoking and excess alcohol intake. With appropriate interventions against hypercortisolemia and substitution of deficient sex steroids and GH, visceral fat mass is decreasing. Based on this evidence from physiological, clinical, interventional observations and detailed studies of mechanisms at cellular and molecular levels it is suggested that the combined endocrine abnormalities in the syndrome of visceral obesity direct storage fat to visceral adipose depots. Therefore, measurements of visceral fat accumulation.

Hum Reprod. 1997 Oct;12 Suppl 1:21-5.

Hormonal control of regional fat distribution.

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Hormones exert powerful influences on body fat distribution in humans. Studies under fully controlled conditions in vitro have indicated that cortisol and insulin facilitate lipid accumulation by expressing lipoprotein lipase (LPL). Growth hormone (GH) abolishes this and turns metabolism towards lipid mobilization. Testosterone and GH inhibit LPL and stimulate lipolysis markedly. Cortisol effects are mediated via a glucocorticoid receptor, and testosterone effects via an androgen receptor, the density of which appears to be higher in visceral than subcutaneous adipose tissue. The receptor-mediated effects are probably expressed via transcription of appropriate genes. The female sex steroids also regulate adipose tissue metabolism, but apparently not directly in the absence of specific cellular receptors. Oestrogens seem to exert net effects similar to those of testosterone. These results of cellular studies agree well with in-vivo studies of triglyceride uptake and turnover in different adipose tissue regions. Furthermore, clinical entities with characteristic disturbances in hormone levels show the expected redistribution patterns.

Int J Obes Relat Metab Disord. 1997 Aug;21(8):619-25.

The effects of weight loss treatments on upper and lower body fat.

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The intra-abdominal visceral deposition of adipose tissue, which characterises upper body obesity, is a major contributor to the development of hypertension, glucose intolerance and hyperlipidaemia. Conversely, individuals with lower body obesity may have comparable amounts of adipose tissue but remain relatively free from the metabolic consequences of obesity. This raises an obvious question-are there particular weight reducing treatments which specifically target intra- abdominal fat? In theory, surgical removal of upper body fat should be effective. In reality, neither liposuction nor apronectomy ('tummy tuck') have any beneficial metabolic effects, they simply remove subcutaneous adipose tissue which is often rapidly replaced. Vertical banded gastroplasty and gastric bypass operations may be dramatically effective in improving blood pressure, insulin sensitivity and glucose tolerance. However, these benefits result from a parallel reduction in visceral and total body fat. Studies of body fat distribution in postmenopausal women confirm that the marked decrease in adiposity, following a programme of very low calorie diet and exercise, reflects a comparable reduction in visceral and thigh fat. The reduction in waist circumference after a low fat/exercise programme suggests a similar situation in men. Exercise has an important role in treatment but, once again, the fat loss is generalised. Nevertheless, the improved metabolic parameters seen in exercising obese subjects, independent of weight loss, suggest other beneficial actions. Growth hormone (GH) has a marked lipolytic action. GH replacement treatment for GH deficient adults with pronounced abdominal fat deposition, has been shown to reduce intra-abdominal fat by 47% compared to 27% decrease in abdominal subcutaneous fat. Similar beneficial actions on abdominal fat have been reported following treatment with testosterone in obese men. The potential hazards of such treatments make them unsuitable therapy for obesity. Dexfenfluramine is effective in reducing total body fat but the results from a six month randomised controlled trial indicates that it does not specifically influence changes in waist circumference associated with weight loss. In conclusion, any treatment which reduces total body fat will, by its nature, reduce intra-abdominal visceral fat. There are presently no specific treatments which can be recommended for intra-abdominal fat but increasing knowledge of the biochemical aberrations associated with visceral adiposity may lead to more specific therapies for the future.

Am J Hum Biol. 1999;11(2):209-224.

Hormonal changes during puberty and their relationship to fat distribution.

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In adults, abdominal visceral adiposity is related to an increased risk of cardiovascular diseases, Type 2 diabetes mellitus, and stroke. The antecedents of these conditions likely begin with the alterations in body fat distribution during childhood and adolescence. The sexually dimorphic alterations in fat distribution are influenced by sex differences in hormone concentrations, anatomical differences in the number and density of specific hormone receptors, capillary blood flow, and the activity of enzymes promoting lipid synthesis or degradation. Hormones influencing the amount and regional distribution of adipose tissue during puberty include cortisol, insulin, growth hormone, and the sex steroids. Cortisol and insulin promote fat deposition while the sex steroids and GH stimulate lipolysis. An overly sensitive hypothalamic-pituitary-adrenal axis may exist in obesity and disrupt the balance between the lipogenic effects of cortisol and insulin and the lipolytic effects of sex steroids and growth hormone. Leptin is released from the adipocytes and may act as a metabolic signal to the hypothalamic areas controlling satiety, energy expenditure, and the regulation of cortisol, insulin, sex steroid and growth hormone release. The complex issues of the hormonal control of alterations in body fat distribution during puberty are developed and a working model is proposed.

Am. J. Hum. Biol. 11:209-224, 1999. Copyright 1999 Wiley-Liss, Inc. Horm Res. 1993;39 Suppl 3:81-5.

Endocrine-metabolic pattern and adipose tissue distribution.

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The associations between cardiovascular disease (CVD), non-insulin-dependent diabetes mellitus (NIDDM) and abdominal fat distribution are well established. The most important adipose tissue depot in this context is probably the mass of intra-abdominal adipose tissue which has been found to be associated with CVD, NIDDM and their established metabolic risk factors. This type of adipose tissue distribution is also associated with multiple endocrine aberrations, probably comprising an increased responsiveness of the hypothalamo-adrenal axis and a parallel or secondary decreased activity of the hypothalamic-gonadal axis. Epidemiological studies in both men and women indicate that this may be a consequence of psychological stress. Recently, indirect evidence for decreased production of growth hormone in this condition has also been recognized. These multiple and interrelated abnormalities comprise a syndrome where the primary disturbance could be localized to the hypothalamus and the main peripheral consequences would be metabolic effects on the mass and function of intra- abdominal adipose tissue. This in turn, probably by the effects of elevated concentrations of portal free fatty acid levels on the liver, could result in insulin resistance and other metabolic risk factors known to be strongly associated with CVD and NIDDM.

Int J Obes Relat Metab Disord. 2000 Jun;24 Suppl 2:S18-21.

Hormones and body composition in humans: clinical studies.

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Leptin in relation to body fat and hormonal regulation of body fat distribution will be treated. Leptin circulating levels are strongly related to the percentage of body fat and in women leptin values are always twofold those observed in men. A role of androgens has been suggested to explain this gender difference. Insulin resistance may contribute to the wide variation in leptin levels. Leptin levels and insulin resistance are increased at the end of pregnancy and normalize after delivery. Furthermore, insulin resistance is associated with elevated plasma leptin levels independent of body fat mass and leptin levels are significantly related to insulin sensitivity independent of BMI. Energy restriction can strongly influence leptin levels, overcoming the effects of body composition changes. The shift from a state of triglycerides storage to a state of release could down-regulate leptin production. Triglyceride flux at the intra-abdominal level depends on the balance between insulin and corticosteroids, which have liposynthetic activity, and between sexual and growth hormones, which have lipolytic activity. Both hormonal and body composition change with ageing, primarily due to a decrease in lipolytic activity, with consequent prevalence of liposynthesis and visceral fat accumulation. Enlargement of intra-abdominal adipose cells is more gradual in men and more abrupt in women after menopause.

Obes Res. 1995 Nov;3 Suppl 4:609S-612S

Testosterone and regional fat distribution.

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The effects of testosterone treatment of abdominally obese men have been assessed by evaluating the following parameters: The metabolic activity of different adipose tissue regions in vivo (using lipid label as a tracer) and in vitro (measuring lipoprotein lipase (LPL) activity), the total and visceral adipose tissue mass, insulin sensitivity, fasting blood glucose, blood lipids, and blood pressure as well as prostate volume. Middle-aged men with abdominal obesity were treated with transdermal administration of testosterone (T), dihydrotestosterone (DHT) or placebo (P) during 9 months. The study was double-blind. Treatment with T was followed by an inhibited uptake of lipid label in adipose tissue triglycerides, a decreased LPL-activity and an increased turn-over rate of lipid label in the abdominal adipose tissue region in comparisons with the DHT and P groups. These effects on adipose tissue metabolism were not detected in the femoral adipose tissue region in any of the groups. T treatment was also followed by a specific decrease of visceral fat mass (measured by CT-scan), by increased insulin sensitivity (measured with the euglycemic glucose clamp), by a decrease in fasting blood glucose, plasma cholesterol and triglycerides as well as a decrease in diastolic blood pressure. In the DHT group an increased visceral mass was detected. No other changes in these variables were found in the DHT and P groups. There were no detectable changes in prostate volume (measured by ultra- sound), prostate specific antigen concentration, genito-urinary history or urinary flow measurements in any of the groups. It is suggested that T substitution to a selected group of men results in general metabolic and circulatory improvements. The prostate area needs further careful attention.

Curr Opin Clin Nutr Metab Care. 2001 Nov;4(6):499-502.

Gender differences in fat metabolism.

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Women generally have a higher percentage of body fat than men. Also, women store more fat in the gluteal-femoral region, whereas men store more fat in the visceral (abdominal) depot. This review focuses on differences in regional fatty acid storage, mobilization and oxidation that may contribute to gender-related differences in body fat distribution. There are pronounced regional differences in the regulation of regional fatty acid metabolism between men and women. Firstly, there is evidence that in vivo, catecholamine mediated leg free fatty acid release is lower in women than in men, whereas free fatty acid release from the upper body depots is comparable. These data correspond to in-vitro adipose tissue biopsy data, which indicate a more pronounced difference in catecholamine mediated lipolysis between upper body and lower body fat depots in women than in men. Secondly, free fatty acid release by the upper body subcutaneous fat depots is higher in men than in women, indicating a higher resistance to the antilipolytic effect of meal ingestion in the upper body fat depots in men. Thirdly, there are indications that basal fat oxidation (adjusted for fat free mass) is lower in females as compared to males, thereby contributing to a higher fat storage in women. Finally, postprandial fat storage may be higher in subcutaneous adipose tissue in women than in men, whereas storage in visceral adipose tissue has been hypothesized to be higher in men. All the above differences may play a role in the variation in net regional fat storage between men and women, but the number of in-vivo studies on gender-related differences in fatty acid metabolism is very limited and most findings require confirmation. Furthermore, there is abundant evidence that the proportion of energy derived from fat during exercise is higher in women than in men. With respect to total body fat, this finding seems counterintuitive, as percentage body fat is increased in women. Further studies are necessary to investigate the significance of differences in exercise-induced fat oxidation on 24-h fat balance

Int J Obes. 1991 Sep;15 Suppl 2:37-40.
Endocrine disorders and body fat distribution.
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To evaluate the role of hormones in formation of regional fat distribution, the ratios of visceral fat (V) to subcutaneous fat (S) in the abdomen of rats with various endocrine disorders were determined by computer tomography. Abdominal fat index (AFI), which was obtained by ultrasonography, correlated with V/S. In Cushing's syndrome, seven out of nine patients showed visceral type and V/S ratio positively correlated with cortisol levels. In acromegaly, three out of four patients showed visceral type and V/S ratio correlated not only with growth hormone level, but also with insulin level. All three insulinoma patients showed visceral type. During pregnancy, AFI decreased at the late stage of pregnancy. These results suggest that in visceral fat formation, insulin is the most important factor, and estrogen is an important factor for subcutaneous formation. In vitro experiments showed that visceral fat was much more sensitive to insulin in terms of glucose uptake and triglyceride synthesis than visceral fat. Fibroblast-like cells derived from adipose tissue were cultured. Estrone enhanced cell growth of fibroblast-like cells derived from subcutaneous fat tissue more than that from visceral fat tissue. The results suggested that hyperinsulinism primarily promotes visceral fat tissue enlargement and that estrogen might promote subcutaneous fat tissue enlargement.

Aesthetic Plast Surg. 1984;8(1):13-7.
Site differences in human subcutaneous adipose tissue metabolism in obesity.
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The results of several recent studies indicate that there are regional differences in the metabolism of subcutaneous fatty depots in obesity. Fat cells are larger in the femoral than in the abdominal region. Lipids are mobilized at a slower rate but synthesized at a higher rate in the former than the latter region. Fasting is accompanied by an increased rate of fat mobilization and a decreased rate of fat synthesis in all fat depots. These changes are, however, more pronounced in abdominal than in femoral fat. There are also regional differences in the hormonal regulation of fat metabolism in obesity. The action of insulin is most pronounced in the femoral region whereas that of catecholamines is most marked in the abdominal area. The regional differences in hormone action are further enhanced during therapeutic fasting. These differences may partly explain why adiposity is more catching in some fatty regions than in others and also why some obese areas are resistant to slimming.

J Clin Endocrinol Metab. 1996 Mar;81(3):1018-22.
Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissues in vivo in men: effects of testosterone.
Marin P, Lonn L, Andersson B, Oden B, Olbe L, Bengtsson BA, Bjorntorp P.

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To determine the effects of testosterone (T) on lipid assimilation in different adipose tissue depots, T (250 mg, im) was given to 17 middle-aged men 5 days before abdominal surgery. Twenty-four hours before surgery, 10 microCi labeled oleic acid in 80 g milk fat were administered orally. Lipid radioactivity was measured in adipose tissue biopsies from abdominal ac, omental, and retroperitoneal adipose tissues. Subcutaneous, visceral (omental plus mesenteric), and retroperitoneal adipose tissue masses were determined using computerized tomography scans at 22 levels. Sixteen men who were not treated with T served as controls. T administration was followed by an increase in serum concentrations from

17.7 +/- 1.1 to 32.6 +/- 1.8 nmol/L (P < 0.001) and a marked (> 50%) reduction compared with controls in lipid radioactivity in omental and retroperitoneal adipose tissues, but not in sc adipose tissue. In controls, sc, visceral, and retroperitoneal adipose tissues assimilated 59.2 g (73.4%), 16.9 g (20.9%), and 4.6 g (5.7%), respectively, of the orally administered fat. In the T- treated men, this was changed to 73.5 g (88.8%), 6.4 g (7.7%), and 2.9 g (3.5%), respectively. It was concluded that T inhibits triglyceride assimilation in intra- abdominal depots and apparently directs this lipid to sc fat in men.

Br J Nutr. 2000 Mar;83 Suppl 1:S71-7.

Visceral fat and insulin resistance--causative or correlative?

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The association between abdominal fat accumulation and risk of chronic diseases, including type II diabetes and coronary heart disease, has long been recognized. Insulin resistance may be a key factor in this link. Many studies have pointed to an association between insulin resistance and intra-abdominal fat accumulation (visceral obesity). However there is no clear proof of a causal link between visceral fat accumulation and insulin resistance. In assessing the probability of a causal link, it is useful to consider potential mechanisms. One such potential causal link is the release of non-esterified fatty acids from visceral fat into the portal vein, so that they have direct effects on hepatic metabolism. Visceral fat has been shown in many studies to exhibit a high rate of lipolysis compared with subcutaneous fat depots. However, if the idea that visceral fat releases fatty acids into the portal vein at a high rate is examined critically, a number of difficulties appear. Not least of these is the fact that continued high rates of lipolysis should lead to the disappearance of the visceral fat depot, unless these high rates of fat mobilization are matched by high rates of fat deposition. There is far less evidence for high rates of fat deposition in visceral adipose tissue, and some contrary evidence. Evidence for high rates of visceral lipolysis in vivo from studies involving catheterization of the portal vein is not strong. If this potential link is discounted, then other reasons for the relationship between visceral fat and insulin resistance must be considered. One is that there is no direct causal link, but both co-correlate with some other variable. A possibility is that this other variable is subcutaneous abdominal fat, which usually outweighs intra-abdominal fat several-fold. Subcutaneous fat probably plays the major role in determining systemic plasma non-esterified fatty acid concentrations, which are relevant in determining insulin resistance. In conclusion, there is at present no proof of a causal link between visceral fat accumulation and insulin resistance, or the associated metabolic syndrome. The possibility of co-correlation with some other factor, such as subcutaneous abdominal fat accumulation, must not be forgotten.

J Clin Endocrinol Metab. 1995 Jan;80(1):239-43.

Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: effects of androgens.

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Studies on regional differences of adipose tissue metabolism have mainly been performed in vitro. To allow measurements of lipid uptake in vivo in man, radioactive label from [9,10-3H]oleic acid in 80 g orally administered milk fat was measured after 4 h in abdominal and femoral sc adipose tissues in 28 middle- aged, abdominally obese men. Radioactivity was measured in adipose tissue triglycerides extracted from needle biopsies. Lipoprotein lipase (LPL) activity was also measured. Uptake of label in triglycerides and LPL activity were higher (20% and 15%, respectively; P < 0.05) in the abdominal compared to the femoral adipose tissue region. The men were then randomly assigned to three groups, receiving testosterone (T), dihydrotestosterone, or placebo, for 9 months. After 2 months of treatment, the procedure of administration of label was repeated, this time using [U-14C]oleic acid as a marker. Measurements of radioactive label was then performed after 4 h and monthly up to 7 months.

Supplementation with T was followed by an inhibited uptake of label in triglycerides (34%; P < 0.05), lower LPL activity (48%; P < 0.05), and a shorter t1/2 (30%; P < 0.05) in the abdominal adipose tissue region compared with the dihydrotestosterone and placebo groups. No significant effect of T on triglyceride uptake, LPL activity, or t1/2 was found in sc femoral adipose tissue. It was concluded that the turnover rate of depot triglycerides is more rapid in abdominal compared to femoral sc adipose tissue in men. Furthermore, T supplementation inhibits triglyceride uptake and LPL activity and causes a more rapid turnover of triglycerides only in the sc abdominal adipose tissue region. These results demonstrate the marked effects of T on adipose tissue metabolism in vivo and suggest that T is an important regulator of the proportion of depot fat mass in central and peripheral adipose tissue in men.

Endocr Rev. 1993 Feb;14(1):72-93.

Genetic and nongenetic determinants of regional fat distribution.

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The role of inherited and nongenetic factors in individual differences observed in the level of sc fat on the trunk and abdominal areas and in the abdominal visceral deposit is reviewed. First, the metabolic and clinical implications of variation in body fat topography are summarized. Second, the results of genetic epidemiology studies on the heritability and other evidence for a role of the genotype in the amount of truncal-abdominal sc fat and abdominal visceral fat are reviewed. Third, the impact of total body fat, age, and gender on regional fat distribution is highlighted. Fourth, adipose tissue lipoprotein lipase activity is considered as a determinant of fat topography, with a discussion of site and gender differences, the effects of steroid hormones, and evidence from genetic epidemiology. Fifth, the contribution of adipose tissue lipolysis is reviewed with an emphasis on the various regulatory factors of the lipolytic pathways including catecholamines, insulin, adenosine, steroids, and other modulators. The role of lipolytic characteristics on fat topography is further assessed by considering changes with age, differences between men and women, effects of excess body fat, and data from heritability studies. Although the study of regional variation of in vitro adipose tissue metabolism has provided valuable information, a better understanding of variation in fat topography and of the role played by adipose tissue in the regulation of whole body carbohydrate and lipid metabolism will likely require extensive in situ and in vivo investigations. Sixth, as enlargement of a specific fat deposit is associated with increases in fat cell size and number, these topics are considered with an emphasis on the role of adipose cell differentiation. Seventh, the importance of blood levels of sex steroids and glucocorticoids for regional fat distribution is discussed. Then, a unifying hypothesis, defined as the hypothalamic arousal and neuroendocrine dysregulation model, is briefly described. Finally, the issue of whether body fat distribution can be altered by caloric restriction or regular exercise is addressed.

Acta Med Scand Suppl. 1988;723:143-6.

Steroid hormones and distribution of adipose tissue.

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Several descriptive studies, performed in women before and after menopause, in young and older men and in women with Cushing's disease, have suggested that steroid hormones have a role in the regulation of regional fat metabolism. Femoral lipoprotein lipase (LPL) activity seems to be increased by progesterone, while it might be inhibited by testosterone. Estradiol and testosterone might be lipolytic in the abdominal region. Long-term exposure to corticosteroid might increase femoral LPL activity and decrease abdominal lipolysis. These conclusions, however, are only tentative. Corticosteroid hormones bind to the cytosolic fraction of human adipose tissue, while no binding was observed with estradiol or progesterone. The relationship between steroid hormone receptors and biological effects in unknown. Further work should be performed to investigate the mechanisms by which steroid hormones might

influence human adipose tissue metabolism and distribution.

Diabetes Metab Res Rev. 1999 Nov-Dec;15(6):427-41.
Neuroendocrine perturbations as a cause of insulin resistance.
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Insulin resistance is followed by several prevalent diseases. The most common condition with insulin resistance is obesity, particularly when localized to abdominal, visceral regions. A summary of recent reviews on the pathogenesis of systemic insulin resistance indicates that major factors are decreased insulin effects on muscular glycogen synthase or preceding steps in the insulin signalling cascade, on endogenous glucose production and on circulating free fatty acids (FFA) from adipose tissue lipolysis. Contributions of morphologic changes in muscle and other factors are considered more uncertain. Newly developed methodology has made it possible to determine more precisely the neuroendocrine abnormalities in abdominal obesity including increased cortisol and adrenal androgen secretions. This is probably due to a hyperactivity of the hypothalamic- pituitary-adrenal (HPA) axis, amplified by inefficient feedback inhibition by central glucocorticoid receptors, associated with molecular genetic defects. Secondly, secretion of gender-specific sex steroid hormones becomes inhibited and the sympathetic nervous system activated. At this stage the HPA axis shows signs of a 'burned-out' condition, and cortisol secretion is no longer elevated. Cortisol counteracts the insulin activation of glycogen synthase in muscle, the insulin inhibition of hepatic glucose production and the insulin inhibition of lipolysis in adipose tissue, leading to the well-established systemic insulin resistance caused by excess cortisol. This is exaggerated by increased free fatty acid mobilization, particularly with a concomitant elevation of the activity of the sympathetic nervous system. Furthermore, capillarization and fiber composition in muscle are changed. These are the identical perturbations responsible for insulin resistance in recent reviews. The diminished sex steroid secretion in abdominal obesity has the same consequences. It is thus clear that insulin resistance may be induced by neuroendocrine abnormalities, such as those seen in abdominal obesity. These endocrine perturbations also direct excess fat to visceral fat depots via mechanisms that are largely known, indicating why abdominal obesity is commonly associated with insulin resistance. This possible background to the most prevalent condition of insulin resistance has been revealed by development of methodology that allows sufficiently sensitive measurements of HPA axis activity. These findings demonstrate the power of neuroendocrine regulations for somatic health. Copyright 1999 John Wiley & Sons, Ltd.

Acta Physiol Scand Suppl. 1997;640:144-8.
Stress and cardiovascular disease.
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The statistical associations between stress and cardiovascular and other prevalent diseases have not been explained. Perceived stress, resulting in an uncontrollable defeat reaction, has been shown by James Henry (Henry 1993) to be followed by specific endocrine abnormalities, including sensitization of the hypothalamo- pituitary-adrenal (HPA) axis, and inhibited sex steroid and growth hormone secretions. With an elevated waist/hip circumference ratio (WHR)--a simple, surrogate, measurement of intraabdominal, visceral fat masses--combined with insulin resistance, similar endocrine perturbations are found. Based on considerable evidence, such endocrine abnormalities seem to be followed by accumulation of intraabdominal, visceral fat masses and insulin resistance, both powerful risk factors for cardiovascular disease, diabetes and stroke. A postulated chain of events is therefore that the endocrine perturbations are primary factors, followed by visceral fat accumulation, insulin

resistance and other risk factors dependent on the hyperinsulinemia following insulin resistance. This highlights the importance of elucidating the cause(s) to the endocrine abnormalities. These are identical to those described by Henry (1993) to follow a stress reaction of a defeat type. Findings of several psychosocial and socio-economic handicaps might provide a basis for such a reaction, supported by experimental studies in primates. Furthermore, depression, anxiety, alcohol consumption and smoking, all known activators of the HPA axis, are also often found. The low sex steroid and growth hormone secretions might be secondary to the hypersensitive HPA-axis. They could also be caused by other factors, and are, each alone, capable of causing both visceral fat accumulation and insulin resistance. Visceral fat accumulation is only an indirect, surrogate measurement of the underlying endocrine abnormalities, but is useful for screening purposes on a population basis. Developments of novel techniques for sensitive, yet simple measurements of HPA axis activity under undisturbed conditions seem to allow a better definition of pathogenetic factors. Utilizing such methods, subgroups of the syndrome including visceral fat accumulation, insulin resistance and other associated risk factors (Metabolic Syndrome), are beginning to emerge. A more detailed information on noxious factors in society leading to a defeat reaction to perceived stress, endocrine abnormalities and the Metabolic Syndrome, with increased risk for prevalent disease may hopefully be developed by these new methods.

Metabolism. 2000 Jan;49(1):6-10.

Postabsorptive resting metabolic rate and thermic effect of food in relation to body composition and adipose tissue distribution.

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One hundred thirty subjects were studied to investigate relationships between the body composition and fat distribution as evaluated by computed tomography and the resting metabolic rate (RMR) as evaluated by indirect calorimetry: 82 premenopausal women (age, 18 to 52 years; body mass index [BMI], 27 to 52 kg/m2), 27 postmenopausal women (46 to 71 years; 28 to 49 kg/m2), and 21 men (18 to 70 years; 31 to 43 kg/m2). The thermic effect of food (TEF) was evaluated in all men and in 2 subgroups of 55 and 19 women. The best-fitting equations for predicting RMR, obtained by multiple regression, included the following as covariates: fat-free mass and both subcutaneous and visceral adipose tissue in premenopausal women (R2 = .55, P = .0001), fat-free mass and visceral adipose tissue in postmenopausal women (R2 = .58, P = .001), and age, with minus sign, and visceral adipose tissue in men (R2 = .44, P = .0051). Fasting insulin and fat- free mass, with minus sign, and both visceral and subcutaneous adipose tissue were the predictors of the TEF (R2 = .25, P = .0055) in premenopausal women. This study demonstrates that visceral fat distribution is important in determining the RMR in postmenopausal women and men. In premenopausal women, total adipose tissue is a main determinant of both the RMR and TEF This last effect could be counterbalanced by insulin resistance.

Baillieres Clin Endocrinol Metab. 1994 Jul;8(3):549-75

Hormones and obesity.

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This chapter has reviewed the evidence for obesity being characterized by distinct patterns of hormonal changes related to both the degree of obesity and the distribution of fat tissue. Many of these changes are also seen in subjects with Cushing's and polycystic ovary syndromes, in particular hyperinsulinaemia, alterations in adrenocortical activity and sex steroid secretion and binding. Animal models of obesity provide evidence to suggest the possibility of a primary abnormality of hypothalamic-pituitary function as a basis to corpulence and this cannot be excluded in the human situation. Nevertheless, abdominal distribution of adiposity plays a significant role in establishing a vicious cycle of metabolic events which may perpetuate both the obese state and PCOS. It is of interest that the additive genetic effect for total body fat is about 25% whereas the heritability of subcutaneous truncal-abdominal fat is about 30-35%, and may possibly be higher (Bouchard et al, 1993). Upper body obesity is characterized by large adipose cells with higher LPL activity, elevated basal and stimulated lipolysis but a low antilipolytic effect of insulin. The results from preliminary investigations of potential candidate genes suggest a possible genetic basis to hyperinsulinaemia/insulin resistance found in upper body obesity but further studies of greater numbers are required for confirmation. It is hoped that the findings from such molecular studies will shed additional light on both the genetic background to obesity and the complex hormonal alterations seen at the tissue level. This should provide the confirmation of a unifying theory for the causal factors associated with obesity and related conditions.

Growth Horm IGF Res. 2002 Jun;12(3):147-61.

Impact of the GH-cortisol ratio on the age-dependent changes in body composition.

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Aging is associated with a decrease in GH levels and this is paralleled by changes in body composition, i.e., increased visceral fat, and decreased lean body mass and bone mineral density. Similar changes in body composition are seen in the state of hypercortisolism. Increasing age has been shown to be associated with elevated evening cortisol levels in men. An increased exposure of several tissues to glucocorticoids with aging, i.e., visceral fat cells, in combination with the reduction of the lipolytic effects of declining GH levels, may contribute to the age-dependent increase of visceral fat accumulation. We hypothesize that the age- dependent changes in body fat are the result of an age-dependent decrease of the GH/cortisol ratio at the level of the adipocyte. This is caused by the decline in GH concentrations and the increase in cortisol levels and/or metabolism at the adipocyte.

Horm Res. 1996;46(4-5):188-91.

Growth hormone, insulin-like growth factor-I and lipid metabolism: interactions with sex steroids.

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Steroid hormones usually act via specific receptors and the hormone-receptor complex then influences the transcription of genes. These effects are often permissive for the actions of peptide hormones such as insulin and growth hormone (GH). The best known effects are those of cortisol. Since cortisol is always present, the sex steroids often modify cortisol effects. In adipose tissue, lipoprotein lipase (LPL), in the presence of insulin, is expressed via a glucocorticoid receptor, increasing transcription and

stabilizing the enzyme. This process is efficiently inhibited by GH via posttranslational effects, and lipolysis is markedly stimulated. Testosterone inhibits LPL expression and, in the presence of GH, markedly increases lipolysis via multiple interactions along the lipolytic cascade. In human adipose tissue, direct effects of estrogen and progesterone cannot be demonstrated, probably because of the apparent absence of specific receptors. These hormones presumably via indirect mechanisms, perhaps by interaction with other hormone receptors.

Diabetes Care. 1996 Mar;19(3):287-91.

Insulin resistance and body fat distribution.

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Body fat distribution can be assessed by computed tomography (CT). The ratio of umbilicus was used to classify obese subjects as having visceral fat obesity (VFO) or subcutaneous fat obesity (SFO). Serum triglyceride and total cholesterol levels and plasma glucose area in an oral glucose tolerance test were higher in patients with VFO than in those with SFO. Significant positive correlations were demonstrated between V/S ratio and plasma glucose area, serum triglyceride level, and total cholesterol level as well as systolic or diastolic blood pressure. VFO was more frequently associated with coronary artery disease. Moreover, VFO was more often accompanied by multiple risk factors than was SFO. Steady-state plasma glucose (SSPG) level was significantly higher in patients with VFO than with SFO, suggesting that insulin resistance may be more remarkable in VFO than in SFO. Furthermore, visceral fat accumulation was also associated with these complications even in nonobese subjects. Visceral fat area (VFA) was significantly correlated with fasting plasma glucose, serum triglyceride, and total cholesterol levels. Animal models such as Goto-Kakizaki (GK) rats with ventromedial hypothalamus (VMH) lesions and Otsuka-Long-Evans-Tokushima- Fatty (OLETF) rats were accompanied by visceral fat accumulation and an early stage of aortic atherosclerosis. Aging, sex hormone, genetic, and dietary factors and physical inactivity may induce visceral fat accumulation. Visceral fat is characterized by its high lipogenic activity as well as its accelerated lipolytic activity. High levels of portal free fatty acids (FFAs) may eventually result in an enhancement of hepatic triglyceride synthesis, causing hyperlipidemia. High portal FFA levels would also induce insulin resistance, thereby causing glucose intolerance, hypertension, and finally atherosclerosis. We propose a term, "visceral fat syndrome," as a highly atherogenic state, which includes visceral fat accumulation, glucose intolerance (insulin resistance), hyperlipidemia, and hypertension.

Ann N Y Acad Sci. 2002 Jun;967:500-5.

Endocrine regulation of subcutaneous fat metabolism during cold exposure in humans.

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Increased oxidation of carbohydrates and free fatty acids is a well-known phenomenon during cold stress. Nevertheless, sources of the fuels used have not been fully clarified as yet. Thus, the aim of our study was to evaluate the effect of acute cold exposure on lipid and carbohydrate metabolism in human subcutaneous adipose tissue and to identify the possible regulatory mechanisms involved. Ten volunteers were exposed for 30 min to an ambient temperature of 4 degrees C. Interstitial metabolism was assessed with the aid of the microdialysis technique. Lipolysis intensity was evaluated from changes of glycerol concentration in plasma and in dialysate. Cold exposure induced a significant increase of glycerol concentration both in plasma (by 199 +/- 16%, $p < 0.01$) and in dialysate (by 308

+/- 58%, p < 0.001). No changes in glucose concentration were found whether in plasma or in the dialysate. Ethanol concentration in dialysate increased (148 +/- 15%, p < 0.01), indicating a slower blood flow in the subcutaneous region. Plasma concentrations of various gluco- and/or lipid-regulatory hormones remained unaffected by the cold exposure, except for norepinephrine, which rose about threefold (309 +/- 41%, p < 0.001). The data indicate an important role for subcutaneous adipose tissue in mobilization of free fatty acids during cold exposure. This process seems to be regulated by the sympathetic nervous system, whereas hormones involved in the regulation of lipid metabolism, such as epinephrine, insulin, cortisol, and growth hormone, may play a less significant role-at least under the conditions studied.

J Physiol Biochem. 2002 Sep;58(3):151-60.

Interrelationship between serum lipid profile, serum hormones and other components of the metabolic syndrome.

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The aim of the present study was to investigate the association between the serum lipid profile and components of the metabolic syndrome, such as central obesity (anthropometric, computed tomography and fat cell data), insulin, sex-hormone- binding-globulin (SHBG) and different hormones influencing this important syndrome, e.g. sex steroids, leptin and tumor necrosis factor-alpha (TNF-alpha). The sample consisted of 85 obese patients (30 men and 55 women) who had undergone abdominal surgery. Fasting serum lipids were analysed, as well as anthropometric and computed tomography data, perivisceral and subcutaneous fat cell size and serum glucose and hormones. Abdominal fat revealed itself as an important correlator of the adverse changes in plasma lipoprotein levels, the waist-to-hip-ratio and waist-to-thigh-ratio being the best morphological correlators in men and women, respectively. Intra-abdominal fat (VA) correlated significantly and positively to perivisceral fat cell size in women, while no correlation was found between subcutaneous fat accumulation (SA) and adipocyte size in both genders. Perivisceral fat cell size showed the greatest number of correlations with the adverse plasma lipid profile compared to that in the subcutaneous depot. SHBG and sex steroids showed a negative correlation with serum lipids considered a cardiovascular risk. In contrast, TNF-alpha and C- peptide were inversely correlated with potential protector lipids. In conclusion, abdominal obesity, adipocyte hypertrophy from visceral fat, serum TNF-alpha and C-peptide seem to be the best correlators of the lipoprotein disturbance characteristic of the metabolic syndrome, whereas SHBG and sex steroids could play a protective role regarding the lipid profile associated to this syndrome.

Med Hypotheses. 2004;63(5):783-6.

Facial fat and its relationship to abdominal fat: a marker for insulin resistance?

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Reports of relationships between measures of insulin sensitivity and measures of body fat and fat distribution suggest that abdominal fat accumulation is a predictor of insulin resistance. It has been previously suggested that facial fat (primarily in the cheeks and neck) is strongly associated with visceral abdominal fat accumulation. The facial fat is a rich vascular region, that seems to be metabolically active and resembles abdominal white adipose tissue. We, therefore, hypothesize that facial fat could be a good predictor of insulin resistance. Whether facial fat can be used as an accurate marker for insulin resistance remains to be determined.

Ann N Y Acad Sci. 1995 Dec 29;771:665-76.

Hypercortisolism and obesity.

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Obesity is a multifactorial heterogenous condition. The location of excess fat on the body determines the risk of morbidity and mortality for significant disease. Visceral, or intraabdominal, fat is the fat depot most highly associated with illness and death from cardiocerebrovascular disease and diabetes. Visceral fat is also associated with a quartet of metabolic disturbances. Referred to as the metabolic syndrome, these abnormalities include hypertension, hyperlipidemia, hyperinsulinemia, and insulin resistance. The metabolic syndrome is also present in Cushing's syndrome, which is characterized by primary hypercortisolism as well as profound visceral adiposity and obesity. The interrelationship between hyperactivation or hypersensitivity of the stress axis and disease can be elucidated by an understanding of the effect of excess glucocorticoids upon energy storage and metabolism. The complex interactions of the stress axis upon the growth and reproductive axes, as well as upon the adipose tissue, suggest that chronic stress, whether psychological and/or physical, exerts an intense effect upon body composition, which, in turn, significantly affects the longevity and survival of the organism.

Metabolism. 1995 Feb;44(2 Suppl 2):38-41.

Neuroendocrine abnormalities in human obesity.

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Recent research has indicated that visceral obesity is associated with multiple endocrine disturbances. Insulin resistance, as well as visceral fat accumulation, may be consequences of these abnormalities. The complex endocrine aberrations are probably of central origin, and suggest a neuroendocrine background with a "hypothalamic arousal" syndrome. Such a syndrome has been found after excess alcohol intake, tobacco smoking, and certain types of stress reactions. Subjects with visceral obesity might be characterized by a high prevalence of such factors, although only indirect evidence is available for the stress component, maybe caused by a poor socioeconomic and psychosocial situation. In primate experiments, a submissive stress reaction is followed by a syndrome essentially identical to that seen in humans with visceral obesity, including visceral fat accumulation. These observations strongly support a similar chain of events in humans. Recent studies have indicated several abnormalities in cerebrospinal fluid (CSF) concentrations of catecholamines and neuropeptides. In particular, serotonin metabolites and corticotropin-releasing factor (CRF) concentrations are apparently lower than normal. In women with visceral obesity, these low concentrations are associated with food choices that indicate a preference for carbohydrates. This finding emphasizes the importance of serotonin agonists in the treatment of human obesity. It seems possible that such drugs may have effects on metabolic and other symptoms particularly prevalent in abdominal obesity, and that these effects might be independent of the decrease in energy intake. It would seem highly desirable to explore these possibilities further. Such observations may also provide a link between the abnormalities of low serotonin and CRF concentrations in the central nervous system on one hand and peripheral metabolic and other abnormalities on the other.