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THE ROLE OF NUTRITION IN ABDOMINAL OBESITY

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ABSTRACT

Recognition of the biological and health importance of abdominal fatness has stimulated researchers, clinicians and public health workers. Most work and interest so far has focussed on how it might account for health outcomes, with increasing attention to its preferred measurement. Its aetiology and pathogenesis is thought to reflect gender, age and energy balance which, if positive, leads to increased total body fatness, including abdominal fatness. But these contributors themselves, when considered mechanistically, raise possibilities about other potentially important modulators of abdominal fatness, such as adipocyte differentiation and apoptosis, the kinetics of cell fat content, its hormonal and neural control, along with underlying genetic predisposition and expression. In turn, the ways in which environmental factors may influence fat distribution come into focus; these include nutritional factors, which may be as broad as the food cultural (given ethnic differences in abdominal fatness) or as located as specific food factors like those which are thermogenic (eg. capsaicin-like), hormone-like (notably the candidate phyto-estrogens) or essential fatty acids which affect receptor function (like omega-3 fatty acids). There is a prima facie case for food intake, aside from its energy value, in its own right, or in conjunction with early life events and/or physical activity and/or substance abuse having a determinant role in the development of abdominal fatness. To what extent, and how, it is now opportune to ask.

Keywords: Body fat, abdominal obesity, adipocyte, lipogenesis, lipolysis, insulin like growth factor-1, fatty acids

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Genetics and environment are involved in the determination of fatness and fat distribution. The focus of this review is on nutritional and other environmental factors associated with fat distribution and abdominal fatness in particular. The role of modulators of body fat in the regulation of fat distribution is discussed briefly, together with their relationships with nutritional and other environmental factors associated with abdominal fatness.

Abdominal obesity has been associated with various diseases and disorders, but of major interest has been its relationship with non insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD). Abdominal obesity together with hyperinsulinaemia, insulin resistance, lipoprotein abnormalities and hypertension constitute a metabolic syndrome which increases the risk of NIDDM and CVD (1). The role of total body fat in accounting for abdominal fatness must be acknowledged. However, abdominal obesity is now recognised as the most consequential aspect of obesity as far as its metabolic complications are concerned.

A prima facie case can be made through ethnic comparison, that food intake, aside from its contribution to energy balance, may modulate body fat distribution (2).

Measurement of abdominal obesity. Abdominal obesity is distinct from simple obesity in that it relates to the distribution of adipose tissue rather than total body fatness. Much of the recent obesity research have focused on the accumulation of abdominal visceral fat because of its association with other metabolic disorders of the metabolic syndrome, and with its possible causal role in increasing risk of NIDDM and CVD (1).

Anthropometric measurements such as skin folds, and circumferences measured at the waist and hip are often used to assess body fat distribution. The most commonly used measure of body fat distribution is the waist to hip circumference ratio (WHR). Unfortunately, the term "waist" has had many definitions, and the World Health Organisation (WHO) expert committee on anthropometry has recommended that the term "abdominal circumference" (A) be used, and that this be taken as the point midway between the two bony landmarks of the lower ribcage and the superior iliac crest. The hip circumference is now defined as the maximum gluteal circumference (3). WHR or abdominal hip ratio (AHR) provides an indication of abdominal fat deposition, and is useful for epidemiological studies. The abdominal circumference and abdominal sagittal diameter may be better indicators of abdominal visceral adipose tissue than the AHR (4). However, these simple anthropometric indices do not provide an index of visceral relative to subcutaneous abdominal fat (5). Computed tomography (CT) is an accurate method for measurement of the amount of subcutaneous and visceral fat in the abdominal area (6,7). It also allows an assessment of the location of visceral fat such as that in the omental region and that which is retro-peritoneal. More recently magnetic resonance imaging (MRI) (8) and ultrasound (9) have also been used to measure visceral fat. Omental intraperitoneal fat, with its splanchnic and portal circulation, is a tissue of considerable interest from the point of view of metabolic disorders, which might be hepatic-dependent. Its nutritional determinants are likewise of interest.

Modulators of body fat. The metabolic control of lipid deposition and mobilisation will influence both total body fat and body fat distribution. Energy-rich free fatty acids are continuously stored as triglycerides in adipocytes through esterification, and released from adipose tissues through hydrolysis of triglycerides in adipocytes. Small changes in the turnover rate of free fatty acids in adipocytes may in the long-term cause marked accretion or redistribution of body fat mass. Factors that control the deposition and mobilisation of triglycerides in adipocytes have been considered to be important candidates for the regulation of adipose mass accretion and regional fat distribution profile.

Adipocyte size and number. Changes in adipocyte size and number occurs during growth and development of adipose tissue depots. Lipogenesis in adipocytes is of importance in the expansion of adipose tissue. The major source of fatty acids for triacylglycerol deposition in adipocytes is from plasma, where fatty acids circulate either bound to albumin or as components of lipoproteins, and delivered at the concentration and turnover operating in the systemic arterial circulation. Lipoprotein lipase activities in tissues appear to be correlated well with adipocyte cell size (10). Recently a great deal of attention has been focused on the potential for controlled adipocyte cell number increases, and on the contribution of this process in relation to the expansion of the tissue both during development and in response to dietary manipulations. Many effectors that either facilitate or inhibit the conversion of adipocyte precursor cells to mature adipocytes have been reported. Hormonal factors affecting the differentiation of adipocyte precursor cells include insulin, corticosteroids, thyroid hormones and growth hormone (GH) (11).

Apoptosis of adipocytes may also be another way of regional fat regulation through cell death (12). How the myriad of food factors now being studied as phytochemicals may affect the adipocyte population should be of considerable future interest (13).

Lipogenesis. Adipose tissue may obtain free fatty acids directly from plasma from hydrolysis of circulating triglycerides by LPL. This lipase is synthesised and secreted by adipocytes (14) and its activity is rapidly increased by feeding and decreased by energy deprivation (15). Insulin and glucocorticoids are thought to be the primary mediators of these changes (16). Glucorticoids in the presence of insulin markedly increase LPL activity (17). The variations in LPL activity parallel differences in adipocyte size, suggesting a role of LPL in control of local fat accumulation (18). Lipoprotein lipase (LPL) is a key factor involved in triacylglycerol deposition into adipocytes, which suggests that differences in LPL activity between sites could have implications for body fat distribution (19).

Hormonal factors also appear to be important in the control of lipogenesis. Differences in LPL activity between sites and between genders may relate to sex steroids. Testosterone inhibits the expression of LPL activity, an effect which seems to be magnified by GH (20). However many of the effects of the sex steroids on LPL activity may be indirect, perhaps mediated through corticosteroids (21). The increased secretion of cortisol in obesity is well known (22). At the same time, glucocorticoids in excess can contribute to truncal fat deposition. Cortisol binds to the glucocorticoid receptor in human fat cells, and visceral fat cells have a higher density of glucocorticoid receptors. The cortisol-receptor complex induces

increased LPL activity (23). Cortisol and thyroid hormones are also reported to have conditioning effects on adipocytes. Women exposed to exogenous corticosteroids for therapeutic purposes have smaller gluteal adipocytes than untreated age-related controls (24,25). Changes in the concentrations of cortisol, insulin and the sex steroids might therefore influence LPL activity and lipogenesis. The importance of GH in the control of lipogenesis has also been defined (26,27).

Lipolysis. Several factors may be involved in the control of lipid mobilisation, and might therefore influence body fat distribution. The lipolytic activity varies between the adipose depots in man (28). In both men and women, femoral and gluteal fat cells exhibit a lower lipolytic response to catecholamines than subcutaneous adipocytes. This effect is independent of total body fatness (29). Intra-abdominal adipocytes tend to have a higher lipolytic response than either femoral or subcutaneous adipocytes. The mechanisms behind these variations have been partly elucidated and involve a number of hormones and growth factors (30,31). Catacholamines have pronounced lipolytic activity (32) acting via beta-1 and beta-2 adrenoceptors (33). A higher lipolytic response to catecholamines in omental than in subcutaneous abdominal or femoral adipocytes is probably due to a reduced alpha- and an increased beta- adrenergic receptor density in the omental adipocytes. (34).

Insulin has an anti-lipolytic effect, and subcutaneous adipocytes appear to be more sensitive to this than either femoral or omental fat cells, which is consistent with a higher insulin receptor affinity in subcutaneous adipocytes than in omental adipocytes (34,35). There are also sex differences in insulin anti-lipolytic responsiveness (15,19). Obesity, abdominal obesity and, more particularly, visceral obesity have all been associated with disturbance in plasma insulin-glucose homeostasis, and with increased risk of cardiovascular disease (36).

GH, insulin like growth factor-1 (IGF-1), and cortisol also seem to be significant regulators of lipolysis. GH treatment results in increases in lean body mass and decreases in fat mass (7), and also causes redistribution of fat from the visceral to the subcutaneous truncal regions (37,38). The lipolytic actions of GH may partially explain its effects on lean body mass. Metabolic pathways through other factors such as insulin, IGF-1 and cortisol are also likely to be involved. For example, the anabolic actions of GH require the presence of insulin (7).

The fate of fatty acids and glycerol released on lipolysis from abdominal fat depends on the site of the fat and its venous drainage - systemic in the case of subcutaneous and retroperitoneal, and splanchnic (portal and hepatic) in the case of omental fat.

Age, gender and the sex steroids. An increase in both total body fat and body fat relative to lean body mass is seen with increasing age up until about 60 to 70 years of age. This increase occurs in normal weight and obese individuals, and in both genders. An increase in abdominal visceral fat would appear to be a major contributor to the increase in total body fatness with increasing age in both men and women. However men generally have more abdominal visceral fat than women, and the increase with age is greater in magnitude in men (15,19)

Gender is one of the strongest indicators of type of body fat distribution. Accumulation of subcutaneous fat on the upper body is regarded as "male type" obesity, and gluteo-femoral obesity is considered to be "female type" obesity. The mechanisms for the differences in body fat distribution probably relate to sex steroid differences and other hormonal differences between men and women . In girls, the appearance of female type obesity coincides with an increase in oestrogen production, and in women, higher levels of oestrogens and progesterone are associated with lower body obesity (19). In women, androgen levels have been associated with upper body obesity (39). In boys, the appearance of male type obesity coincides with an increase in androgen production, but in men lower androgen levels are generally associated with upper body obesity (19,24,40). In men, testosterone increases lipolysis in abdominal adipocytes, but not femoral adipocytes (41), and would appear to result in a reduction in visceral fat. In women, the relationship between testosterone and body fat distribution would appear to be in the opposite direction. The effects of the various sex steroids on body fat distribution are therefore likely to be different between genders, and may not be linear within one gender.

The effects of sex steroids on human adipose tissue have been examined in several studies. Sex steroid levels are altered in upper body obesity. Abdominally obese women have low levels of sex hormone binding globulin (SHBG) and high levels of free testosterone (42). Sex steroid levels are associated with variations in insulin sensitivity and plasma lipid transport in women (43). SHBG produced by the liver has a profound impact on metabolism and action of bound steroids. The mechanism by which obesity decreases the production of SHBG is unclear. The hypothesis that insulin may regulate the hepatic production of SHBG is supported by the finding of a direct inhibitory action of insulin on SHBG secretion by human hepatoma cells (44). The serum levels of SHBG changes inversely with that of insulin (45).

Energy intake and expenditure. The AHR is regarded as an independent indicator of CVD risk. However the role of total body fatness as a determinant of the presence of abdominal fatness must be acknowledged. Energy intake and expenditure will therefore influence both total body fatness and its distribution. Studies discussed include those which have observed changes in fat distribution with alterations in energy intake and/or expenditure.

At least two studies have reported a preferential mobilisation of abdominal visceral fat with energy restriction (46,47). Another study reported a loss in both abdominal visceral and subcutaneous fat (48). An increase in the anti-lipolytic effect of insulin in the gluteo-femoral region compared to the abdominal subcutaneous region (27,49) and possibly the visceral region may help to explain these changes. The adipose tissue LPL activity in obese individuals remains high after weight loss. Further studies are required to verify whether regional variation in LPL activity and responsiveness to insulin are involved in the apparent preferential abdominal fat loss observed during fasting and energy restriction (45,47). Alterations in catecholamines and other modulators of body fat may also be involved. Nutrient availability influences both lipogenesis and lipolysis by altering the concentration of modulators of these processes (50).

Changes in energy expenditure usually involve changes to physical activity. A reduction in abdominal fatness with exercise has been observed in both men and women (51,52). In a

study of obese women where CT scanning was used to assess changes in visceral fat, a reduction in visceral fat was only observed in women who lost a large proportion of body fat (51). A significant reduction in visceral fat has also been observed in men with exercise training and energy restriction (51,53). In addition, a negative association between physical activity and WHR has been reported (54). This evidence suggests that exercise results in preferential mobilisation of abdominal fat. Changes in catecholamine induced lipolysis in response to exercise may help to explain changes in body fat distribution. The influence of exercise on lipolytic response to catecholamines is site and gender dependent (55). Other modulators of fat distribution may also play roles in response of body fat to exercise. For example, both resistance (56) and endurance (57) exercise can result in an elevation in plasma GH concentration.

Total fat intake. The relative macronutrient composition of the human diet appears to be an important factor in the development of obesity (58,59,60). There is a greater physiologic control of the intake of protein and carbohydrate than for fat. This may lead to positive energy balance if the fat content of the diet is high. This is consistent with the link between a high consumption of dietary fat and obesity (61). The mechanisms involved in the link between fat intake and total body fatness may relate to satiation (61,62), or to the fact that dietary fat does not promote its own oxidation as does protein and carbohydrate (61). At this time there is no evidence that the total or relative fat content of the diet can influence body fat distribution independent of total body fatness.

Fatty acid unsaturation. Many studies which have investigated the relationships between diet and chronic diseases, or risk factors for these diseases, have focused on saturated fat. A higher intake of saturated fats has been associated with increased risk of NIDDM and CVD (63). A higher saturated fat intake is also related to insulin resistance, hyperinsulinaemia, glucose intolerance, hypertension, and dyslipidaemia (64). The presence of abdomial obesity is strongly related to all these metabolic complications (65). Whether or not a higher intake of saturated fat is causally related to accumulattion of abdominal visceral fat is not clear from the results of studies presently available.

Little data are available on the relationships between intake of particular fatty acids and body fat distribution. A cross-sectional study which collected retrospective data about food habits found a significant association between the consumption of cod liver oil during childhood and adolescence, and the WHR. Those subjects who consumed cod liver oil had a significantly lower AHR (66). Cod liver oil is high in long chain omega-3 fatty acids, as well as vitamin D. Feeding studies in rats have compared the effects of feeding fish oil, sunflower oil and lard for their effects on rat adipose tissue mass (67). In this study it was found that there was no significant difference in fat cell number, but adipocytes were significantly smaller in fish oil fed rats. Whether there were significant differences between individual fat depots was not clear. In another study Parrish and others (68) investigated the metabolic basis for their previous findings. They suggest that a reduction in plasma triglycerides in conjunction with an increase in hormone stimulated lipolysis may explain in part the selective reduction in adipose tissue trophic growth accompanying fish oil consumption. More recently it has been

found that body fat distribution in rats can be influenced by the type of dietary fat. Fish oil resulted in decreased total body fat as well as decreased intra-abdominal fat (69).

A major role of fatty acids in the body is as structural components of membranes. Greater or lesser levels of particular fatty acids in membranes might result in significant differences in membrane function. Alterations in sensitivity to the action of insulin, catecholamines, androgens and oestrogens may result. Results from a study of Borkman and others (70) suggest that a higher concentration of the long chain polyunsaturated fatty acids in skeletal muscle phospholipid is associated with better insulin sensitivity. Alterations in membrane function of adipocytes may have implications for body fat distribution.

Alcohol. Positive relationships between alcohol consumption, or a marker of alcohol intake, and WHR have now been observed in several studies (54,71,72). In addition, Prijatmoko (72) found an interaction between alcohol consumption, cigarette smoking and WHR. In a cross-sectional study by Bjorntorp (71), men with higher alcohol consumption were also found to have lower plasma testosterone concentrations. Bjorntorp (71) hypothesised that a heavy alcohol consumption may lead to higher levels of corticosteroids relative to sex steroids, resulting in greater lipid accumulation in visceral fat depots compared to subcutaneous fat depots.

Thermogenic factors in food. The ingestion of a mixed meal results in an increase in energy expenditure. This is known as nutrient induced thermogenesis (NIT) or the thermic effect of feeding (TEF). The thermogenic effects of particular nutrients differ. It is known that amino acids are potent thermogenic nutrients with thermic effects of approximately 23% (73). This is compared to a thermic effect of glucose of about 9% (74). The thermic effect of lipids has been estimated at 4% (75), but the thermogenicity of different fatty acids may be different. Polyunsaturated fatty acids, and the long chain omega-3 fatty acids in particular probably have thermic effects significantly greater than saturated fats (76).

Particular non-nutrients in food also have thermogenic action. The compounds studied in most detail are capsaicin and its analogues. Capsaicin is a major pungent principle of hot pepper, and is consumed widely as a flavour for foods. Rats fed a high fat diet together with capsaicin, at about the same dietary concentration which several human populations currently consume, were found to have decreased peri-renal adipose tissue weight (77). In humans spiced food containing capsaicin has been found to increase resting metabolic rate (RMR) by 25% (78). Whether NIT is associated with increased lipolysis occurring preferentially in the more metabolically active visceral fat deposits is not known.

Other thermogenic factors. Cigarette smoking is known to have an acute effect of raising RMR (79). Several studies have now shown a positive relationship between cigarette smoking and abdominal fat distribution (54,80). After adjusting for BMI, male smokers have a larger waist circumference without a reduced hip circumference, and this is due to an increase in visceral fat (54,81). The mechanisms for this relationship are not clear, although there is some evidence that sex steroids may be involved (82). It has also been suggested that cortisol, and changes in LPL activity between sites is involved (54).

Non-nutrient food factors and environmental factors with hormonal like properties. The relationship between oestrogen and body fat distribution has been discussed. In addition to natural oestrogen, there are several other environmental sources of compounds with oestrogenic properties. These relationships are summarised in Figure 2. The compounds with oestrogenic (or androgenic) properties can be separated into two classes: those derived from plants (phytoestrogens), and industrial products which enter the food chain as environmental pollutants. Many plants contain compounds with oestrogenic activity (83), which may have effects in humans (84,85). Phytoestrogens in the human diet are likely to influence oestrogenic functions through competition for binding to oestrogen receptors, resulting in anti-oestrogenic effects (86,87). There are also other classes of oestrogenic compounds to which humans are exposed through the diet (84). Environmental pollutants such as nonylphenol and related compounds (derived from degradation of surfactants) which are often added to a range of products such as detergents and pesticides, have been shown to have oestrogenic activity in fish, birds, and other animals (88,89).

If the sex steroids play a role in the determination of body fat distribution, then factors which effect sex steroid concentrations or activity might also influence body fat distribution. Several studies have assessed the relationships between dietary fat and plasma oestrogen levels. Higher total fat intakes are associated with higher plasma oestrogens in both pre-menopausal (90) and post-menopausal (91) women. Whether this effect is mediated by total dietary fat or saturated fat is not clear. The influence of different fatty acid classes on plasma oestrogens needs to be assessed. A reduction in the percentage of dietary fat in men has also been associated with changes in sex steroid concentrations. In a study where the percentage of dietary fat was reduced from 40% to 30%, serum concentrations of testosterone, SHBG, and non-SHBG-bound testosterone increased significantly (92). Another dietary factor which may effect plasma oestrogen concentrations is dietary fibre. A high fibre diet has been shown to reduce serum oestrogen concentration in pre-menopausal women (93). The effects of these dietary changes on body fat distribution have not been investigated, and are of interest (94).

Physical constitution. A reduced growth rate in childhood can result in failure to attain genetic height potential. Genetics and environment, and nutrition in particular, determine childhood growth rates and adult height (95). The major interest in childhood growth rates has been as an index of nutritional status, and a reflection of acute disease. There is now some evidence that early life experience *in utero*, during infancy, and in childhood can influence the risk of chronic disease later in life (96,97). An inverse association between birth weight and death from CVD has been found. The relationships between height and disease specific morbidity and mortality have been examined in several studies (95). Because of the genetic influence on height potential, more convincing evidence for relationships comes from within population studies. Waaler (98) found that all cause mortality declined with increasing height for both men and women and for all age groups in a large population study of Norwegians. A reduced mortality from obstructive lung disease and cardiovascular disease in taller people was also observed. No significant relationship with non-site specific cancers was found. Data such as this are supported by the observation that as population heights have increased, so too has life expectancy.

Short stature may be an adaptation to protein energy malnutrition and/or specific nutrient deficiencies. This may effect body fat distribution later in life, particularly if food becomes more abundant. With increasing affluence, food becomes more abundant, and those with shorter stature who require less energy may be at increased risk of obesity. In a study by Hsu-Hage and Wahlqvist amongst Melbourne Chinese (unpublished), height was not associated with BMI, but was negatively associated with WHR (2). Yip and others (personal communication) have also found a negative relationship between height and WHR in prospective studies in Tianjin, China. These studies suggest that short stature may increase the risk of abdominal obesity. Further work is needed to determine whether short stature is associated with increased risk of abdominal visceral or subcutaneous fat deposition, and whether or not this relationship is found in other nutritionally divergent populations.

Nutritional pathways: a concise view. The inter-relationships between factors involved in the metabolic control of lipogenesis and lipolysis are likely to be many and complex. There are therefore many pathways to abdominal obesity where nutrition influence may be possible. The effects of nutrition on the regulation of lipogenesis and lipolysis are likely to be mediated via the various modulators of these processes. Several nutritional factors, such as total energy intake, total fat intake and the type of dietary fat, might influence modulators of body fat, and thus total body fat and its distribution (50,99).

Given that the heritability of abdominal fatness is less than 50% (19), environmental factors would appear to have a significant influence on abdominal fatness. Lifestyle factors such as lack of exercise and cigarette smoking are likely to contribute to increased risk of abdominal obesity. Total energy intake, total fat intake and the degree of fatty acid unsaturation, alcohol intake, and non-nutrient food factors with hormonal like properties may also influence body fat distribution. Specific nutrients may influence body fat distribution through effects on the various modulators of body fat. Figure 3 describes the hypothetical relationships between food intake and body composition, and potential nutritional pathways to abdominal obesity.

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