Visceral Obesity: A "Civilization Syndrome"

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Abstract

The controversial question of the relationship between obesity and disease has been considerably clearer after the demonstration in several prospective, epidemiological studies that the subgroup of central, visceral obesity is particularly prone to develop cardiovascular disease, stroke, and non-insulin dependent diabetes mellitus.

Visceral obesity is associated with multiple central endocrine aberrations. The hypothalamo-adrenal axis is apparently sensitive to stimuli, sex steroid hormone secretion blunted, and hyperandrogenicity is found in women. In addition, there seem to be signs of central dysfunctions in the regulation of hemodynamic factors after stress, and growth hormone secretion appears to be particularly blunted.

Several of these endocrine abnormalities are associated with insulin resistance, particularly glycogen synthesis in muscle. Fiber composition with low type I/type II ratio might be secondary to the prevailing hyperinsulinemia, but low capillary density in muscle may well be of importance. In combination with elevated turn-over of free fatty acids (FFA) this will probably provide powerful mechanisms whereby insulin resistance is created. Portal FFA, from the highly lipolytic visceral depots may, in addition, affect hepatic metabolism to induce increased gluconeogenesis, production of very low density lipoproteins as well as to perhaps inhibit clearance of insulin. By these mechanisms a Metabolic Syndrome may arise in which visceral obesity is a central part.

Visceral adipocytes seem to have a high density of several steroid hormone receptors, directing steroid hormone effects particularly to these depots. The net effect of cortisol is apparently a stimulation of lipid storage, with opposing effects of sex steroid hormones which also facilitate lipid mobilization, regulations most often found at the gene transcription level. Growth hormone inhibits cortisol effects on lipid accumulation, and amplifies the lipid mobilizing effects of steroid hormones. The combined perturbations of hormonal secretions will therefore probably direct triglycerides toward visceral depots. Circulatory and nervous regulatory mechanisms require, however, more attention.

The multiple central endocrine and nervous aberrations of visceral obesity suggest neuroendocrine dysregulations, and have features characteristic of the hypothalamic arousal seen after certain types of stress, alcohol intake, and smoking. Such factors can be traced to subjects with visceral fat accumulation. Standardized stress, eliciting a “defeat reaction” in primates is followed by an apparently identical syndrome.

This integrated picture of the multiple symptoms of visceral obesity is based on epidemiological, clinical, experimental, cellular, and molecular evidence. The ingredients of positive energy balance, including physical inactivity, stress, smoking, and alcohol consumption are frequent features of modern, urbanized society. Visceral obesity may therefore be an expression of a “Civilization Syndrome.”

Introduction

The early history of the syndrome of abdominal obe-
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Proneness of disease and in psychological characteristics had been noted in previous anthropometric studies. For example, Kretschmer, in his work in the 1920s (65) subdivided somatotypes and noted differences in the prevalence of apoplexia (stroke) and gout with physical habitus. These conditions were often found in pycnic subjects, and it is of considerable interest that anthropometric measurements are provided in his descriptions of somatypes, including the waist and hip circumferences, from which the ratio (WHR) can be calculated. The WHR has provided an important measurement as a basis for epidemiological observations in the modern era of research in this field.

Although these early reports demonstrate sharp-sighted clinical observations, they are of course not treated with the statistical rigor required in modern research. Similar observations have also been made even before this era in for example royalties where a pycnic habitus and hot temperament have been noted to be associated with gout and sudden death in apoplectic conditions. Examples here might be taken from the Royal Swedish family of the Vasa kings, ruling Sweden for about 150 years in the 16th and 17th centuries.

One might then see a development here from historical observations, to anthropometric, more systematized research in the early 20th century. Vague was no doubt the first to place adipose tissue distribution in focus and to apply modern research tools to his clinical observations.

The recent development of this field was emerging from independent observations of the usefulness of the WHR as a method to classify obese subjects (63,68). In our studies this finding came from the combination of several observations in the 1960s and 1970s. First, we noticed the covariation of metabolic complications with abdominal fat cell size (69), which lead to the classification of obesity into hypertrophic and hyperplastic obesities (12). We then observed considerable differences in the prevalence of metabolic abnormalities among men and women with the same degree of obesity (68). To examine this further in relation to anthropometric and adipose tissue variables, several measurements were analyzed as far as their connections with the metabolic complications of obesity, including glucose tolerance, insulin resistance, plasma lipids, and hypertension, a cluster of abnormalities now known as the Metabolic Syndrome or Syndrome X (93). The independent variables tested were adipose tissue thickness, fat cell size and number in different subcutaneous adipose tissue regions, skinfolds alone or in combinations, total body fat, and lean body masses, as well as various circumferences alone or in combination. Although we could confirm the importance of abdominal fat cell size (69), the WHR was found to show even stronger statistical associations to the components of the Metabolic Syndrome (68). The construction of the ratio was the result of deliberations, where the waist circumference would include intraabdominal fat masses, not directly accessible by puncture biopsies and cellular analyses such as the subcutaneous depots. In order to adjust for the frame differences in a large or small person, the hip circumference was placed in the denominator.

Syndrome X (93) has been described as a condition in which hyperinsulinemia and insulin resistance are primary features. Associated characteristics are hypertriglyceridemia, low high density lipoproteins, and hypertension. Visceral obesity is very likely a part of this syndrome because of its close relationship with the components of Syndrome X (63,68). This association has recently been analyzed in quantitative terms in the epidemiological study of women in Göteborg. This material was divided into quintiles of WHR and body mass index (BMI). The presence in these quintiles of elevated blood glucose, insulin, triglycerides, and blood pressure (all defined as values above mean plus 2 SD in the total population) were then determined. Essentially all the women in the highest quintiles of WHR and BMI, signifying abdominal obesity, had one or more of the metabolic abnormalities, including hypertension. In fact, elevated WHR and BMI were phenomena no less frequent than any of the other components of the total syndrome, including hyperinsulinemia (Lapidus and Björntorp, to be published). This analysis strongly suggests that abdominal obesity is an integrated part of the cluster of abnormalities in the syndrome in question.

Syndrome X (93) might not be an optimal name because it is already utilized by cardiologists as a denomination of pain of cardiac origin without visible coronary atherosclerosis. The Metabolic Syndrome seems to be a better label of the condition in question, because of this metabolic nature.

Epidemiology

In a series of analyses from the ongoing epidemiological studies in Gothenburg, Sweden, we have now been able to demonstrate the independent power of the WHR as a risk factor for cardiovascular disease (73,75) (CVD), stroke (75), and non-insulin dependent diabetes mellitus (NIDDM) (80,88) in both men and women. The predictive strength of the WHR is comparable to that of other previously established risk factors for the mentioned diseases such as cholesterol, blood pressure, and insulin. These observations have subsequently been confirmed in studies in Paris policemen (37), the
Framingham study (105), in the Honolulu heart study (36), a study of American veterans (107), Japanese-Americans (8), Mexican-Americans (46), and of Indian immigrants in London (Marmot, personal communication, 1992). Having been observed now in a number of studies in which measurements of regional distribution of body fat have been available, it seems reasonably safe to conclude that an elevated WHR, or related measurements, are powerful predictors of some of the most prevalent diseases in urbanized society.

At this point, however, it is pertinent to critically evaluate the significance of the WHR. If we start with an analysis of the waist circumference, this is obviously a composite measurement of several body components, of which abdominal fat masses (both subcutaneous and intraabdominal) are only a part, which may well be trivial in relation to the total abdominal contents in lean subjects. This is particularly the case in premenopausal, lean women who have very little visceral fat (70). Furthermore, most normal young men and athletes have only a few kg of body fat mass (20), presumably spread out in a thin layer in the subcutaneous and intraabdominal depots. In these instances the WHR could not possibly be a measurement of body fat distribution.

It is of course also necessary to analyze the significance of the hip circumference, which might contribute with information other than being just an adjustment for frame size. For example, hip circumference is most likely covarying with height, a known predictor of longevity. A low WHR might thus be due to a large hip circumference, associated with tallness. Height is, however, not a "protective" factor in the prospective, epidemiological studies in Gothenburg.

Furthermore, the hip circumference includes the large gluteal muscle. An elevated WHR might consequently be due mainly to a relative atrophy of gluteal muscle. An example of this is an analysis of the components of the elevated WHR in alcoholics (71). Analyzed by detailed computerized tomography (CT) scans at different levels, the elevated WHR of alcoholic men seems equally dependent on increased visceral fat masses and a relative atrophy of the gluteal muscle. The influence of muscle mass on the WHR should therefore be carefully considered. For example, insulin resistance is a cardinal symptom of abdominal obesity, and muscle mass and function are major regulators of insulin sensitivity. Insulin resistance in relation to an elevated WHR may thus well be associated with a relative muscle atrophy rather than adipose tissue distribution factors, particularly in non-obese subjects.

In summary, the WHR is not a measurement of body fat distribution in lean subjects with a few kilograms of body fat. In lean men waist circumference alone might be more useful (34). In the studies of middle-aged men and women in Gothenburg, the average body fat mass is about 15 and 20 kg respectively (16,17), and at this level of body fat mass, as well as in obese subjects, the WHR probably provides an approximation of body fat distribution. However, caution must be expressed as to the potential influence of factors other than adipose tissue distribution in the WHR measurements, particularly muscle mass.

The Biological Significance of Abdominal Obesity

With the cautions discussed above, it is likely that a major part of the significance of an elevated WHR is due to an enlargement of abdominal fat masses. In fact, the component of main importance is probably the subcompartment of visceral fat mass, defined as the mesenteric omental adipose tissues, rather than total abdominal fat mass. This statement is based on the following observations. The WHR is closely statistically associated with several of the established metabolic risk factors for CVD, stroke and NIDDM, viz. plasma lipids, and insulin resistance as well as blood pressure. These statistical associations are, however, more closely connected with the mass of visceral fat indicating that this component of the WHR is the critical factor (10,15,16,17,31,32,33,34,48,59,60,62). This is not to suggest that a cause-effect relationship is necessarily at hand, although observations indicate that this might be the case (14), particularly since the correlations between metabolic risk factors are stronger with visceral adipose metabolism than mass (81). As will be reviewed in a following section, it seems at least equally likely that an increase of visceral fat masses might be a parallel phenomenon to the occurrence of the metabolic perturbations in question. There is also clearly a genetic susceptibility to visceral fat accumulation (23).

Unfortunately, there is only limited information on the risk of visceral fat masses, determined precisely with computed-tomography (CT) scans, in prospective epidemiological studies. An exception is a study on second generation Japanese-Americans, where visceral fat mass has been shown to be a more powerful risk factor for the development of NIDDM than other adipose tissue compartments (8).

The strong relationship between visceral fat mass, or surrogate measurements thereof, and the risk factors for CVD, stroke, and NIDDM has now been amply demonstrated by in essence all groups that have performed such studies. This relationship may then, with a rather high degree of certainty, be considered established.

Cause-Effect Relationships

We have now a well established statistical relationship between visceral fat mass and risk factors for CVD, stroke, and NIDDM. The next question then is to try to
establish or refute potential cause-effect relationships between these associations. Two principal possibilities are apparent. The first is that visceral obesity is generating the risk factors. This alternative has been considered previously (14). The other possibility is that both visceral obesity and the risk factors appear independently of each other, and in parallel, caused by another, independent factor. As will be reviewed in following sections, there is now considerable evidence supporting such a mechanism. In short, there is accumulating evidence suggesting that a neuroendocrine aberration, resulting in multiple peripheral endocrine perturbations, may be a central feature in the syndrome of visceral obesity.

**Neuroendocrine-Endocrine Peturbations in Visceral Obesity**

**Cortisol**

The similarities between Cushing's syndrome and visceral obesity are quite apparent. Both conditions are characterized by visceral obesity with the associated Metabolic Syndrome. The question then arises whether an increased secretion of cortisol is involved in the syndrome of visceral obesity. This possibility has also been previously considered (10,15,25).

Early studies suggest that cortisol levels are elevated in abdominal obesity (67,109). To elucidate this further we have devoted considerable effort to this question, due to its potential central importance. The results of studies show, in brief, that subjects with visceral obesity excrete more urinary cortisol than normal when measured on a 24-hour basis. This finding is, however, not particularly robust, and seems to require measurements of cortisol output under "field conditions," that is, with the examined subjects in their ordinary work and/or home milieu. When the hypothalamo-adrenal axis is subjected to standardized stress, however, the amenability to increased cortisol secretion in visceral obese subjects seems to appear more clearly. After stimulation of the adrenal cortex by ACTH the increase of cortisol secretion in visceral obese subjects seems to appear more clearly. Furthermore, with stimulation by physical or mental stressors, cortisol secretion is accentuated in parallel with visceral obesity (83). In recent unpublished experiments we have now also observed that the secretion of various stress hormones, including not only cortisol but also prolactin and growth hormone (GH) seems to be more stimulated in visceral obese women than in controls after the stress of cigarette smoking (Szostak et al., unpublished). Other recent studies have shown that stimulation of cortisol secretion by cortisol releasing factor (CRF) is also elevated in visceral obesity (R. Pasquali, personal communication, 1992).

The current and previous observations are thus compatible with an increased sensitivity of the hypothalamo-adrenal axis in visceral obesity. Interestingly, this is parallel to observations in the obese fa/fa rat, which is also particularly sensitive to stress stimuli, of the same kind as those applied in the human experiments (43). In the rat, further studies, not possible to perform in humans, have revealed functional and even structural abnormalities in the hypothalamic area (9).

In this context it should be observed that an increased cortisol secretion has previously been observed to be a characteristic of obesity in general, not subdivided into subgroups determined by the regional distribution of excess adipose tissue (106). This increased secretion has been considered to be of questionable biological significance, because it is parallel to and elevation of lean body mass. Glucocorticoids exert their activity via binding to a specific glucocorticoid receptor (GR), and then generally induce stimulation of transcription of appropriate genes. The stimulation of various glucocorticoid-dependent metabolic pathways is thus probably dependent on the traffic over the GR, which in turn is dependent on the rate of production of cortisol. It thus seems apparent that the increased production of cortisol in obesity should also be followed by functional consequences. The results of the studies where obesity has been subdivided into abdominal and peripheral obesity therefore suggest that visceral obesity is the subgroup of human obesity where the effects of cortisol are particularly pronounced. The observations available indicate that this is mediated mainly via a hypothalamo-adrenal axis, which is particularly sensitive to stress stimuli at different levels.

**Sex Steroid Hormones**

Sex steroid hormones are clearly involved in the syndrome of visceral obesity. Seidell et al. (102) found that visceral fat mass, determined with CT-scan, was negatively correlated to free T in men from a health screening center. This observation has subsequently been confirmed in population studies (45,58).

Women often have irregular or absent menstruations, which might be due to an involvement of a disturbance of gonadotropin secretions (97). Secondarily, this probably results in a low production of progesterone. Measurements of estrogens have not so far revealed any abnormalities (39), but estrogen concentrations have not been followed through the menstrual cycle. The increase of the WHR with menopause and associated metabolic perturbations suggest that estrogen might be of importance for the regulation of visceral fat mass and metabolism, indicating that estrogen should be studied in further detail in this syndrome. A repeatedly described important abnormality is, however, a hyperandrogenicity of central obese women (21,39,109). The origin of this is not known. This field has been reviewed repeat-
edly recently (10,15,21).

**Other Hormonal or Nervous Perturbations**

Low circulating concentrations of GH are well established in obesity in general. In recent studies, we have found that IGF-I concentrations are inversely related to visceral fat mass, but not to total fat mass or to other subcompartmental adipose tissue measured with CT-scan technique (86). These observations suggest that the blunted GH secretion in obesity is particularly pronounced in visceral obesity. Furthermore, the hemodynamic response to stress seems abnormal (57). The expected, normal “fight-flight” type of reaction is an increased blood pressure due to elevated cardiac output with a compensatory decrease of peripheral resistance. In young moderately obese, normotensive men with an elevated WHR, however, stress-stimulus was followed by a primarily increased peripheral resistance, and a depression of heart rate and blood pressure. This is the response pattern of rats subjected to “uncontrollable” stress, labeled a “defeat”-reaction (47,49). Although not interpretable in detail, these observations suggest that the centrally regulated hemodynamic response to stress is altered with central distribution of body fat. This might well mean that the central regulation of the autonomic nervous systems might also be involved as a part of the hormonal and nervous perturbations of visceral obesity.

A recent study has shown that the apnea syndrome, often associated with obesity, is also seen more pronounced in visceral than peripheral obesity. In parallel, oxygen tension is low and hemoglobin concentration compensatorily elevated (G. Enzi, personal communication, 1992). Whether this syndrome is more prevalent in visceral than peripheral obesity due simply to mechanical or other factors cannot be determined at present.

**Summary of Endocrine and Nervous Aberrations in Visceral Obesity**

It thus appears that several hypothalamo-peripheral axes are disturbed in visceral obesity. First, the hypothalamo-adrenal axis seems to be abnormality sensitive to stress stimuli, resulting in frequently elevated cortisol concentration in peripheral circulation. Furthermore, sex steroid hormone secretion is inhibited, probably due to a disturbed gonadotropin secretion.

Finally, GH-secretion is blunted and the central response to stress of hemodynamic regulation apparently abnormal. These multiple disturbances of central endocrine and nervous regulations strongly suggest that central neuroendocrine dysregulations are involved.

Another interesting conclusion seems to be possible from this series of observations. Obesity in general has long since been known to be associated with a number of metabolic, endocrine, and other abnormalities. These include the metabolic disturbances associated with the Metabolic Syndrome and increased cortisol secretion, blunted sex steroid hormone and GH secretions, as well as sleep apnea and a tendency toward polyglobulinemia. All these abnormalities are apparently more pronounced in visceral than peripheral obesity as reviewed above. Interestingly, this statement holds true also for the development of cardiovascular disease, stroke, and NIDDM. This then clearly separates out visceral obesity as a malignant nucleus of the condition of human obesity. A question which follows automatically is whether or not peripheral obesity is innocent from an endocrine-metabolic-disease point of view, and only a cosmetic worry. First of all, it must be pointed out that locomotor problems, as well as varicose veins, are following peripheral obesity (101). Furthermore, several adverse factors associated with visceral fat mass seem to be amplified by an increased total body fat mass. An example here is the risk to develop NIDDM (80). Therefore, it cannot be stated that peripheral obesity is totally harmless, particularly not in extreme forms. Clearly, however, in moderate forms peripheral obesity seems to be mainly a cosmetic problem. In women this corresponds to an increased mass of adipose tissue in harmonious physiological proportions, and may therefore be considered as other phenomena of physiological tissue or organ enlargement with mainly cosmetic consequences, such as a big nose, feet, or ears.

**Associations Between the Endocrine and Metabolic Aberrations**

Several of the endocrine aberrations following visceral obesity seem to be able to cause insulin resistance in the periphery. These include hypercortisolism, hypogonadism in men, and hyperandrogenicity in women, as reviewed previously (11). These abnormalities may then, by themselves, contribute to the insulin resistance of visceral obesity. Clearly, visceral obesity clearly, is also a condition with high circulating concentrations of free fatty acids (FFA) both in the systemic circulation (56) and most likely in the portal circulation (14). This probably also contributes to the insulin resistance in the periphery as well as in the liver. (For review, see 10,13,61).

Interesting features of visceral obesity are the morphological changes of the insulin resistant muscle. These include a larger than normal proportion of relatively insulin insensitive type II, particularly II b fibers at the expense of the more insulin sensitive type I fibers. Furthermore, capillary density is decreased (66). Both of these phenomena would be expected to be followed by an insulin resistant muscle (22,51,53,54,64,115). They can, however, simply be another consequence of the
endocrine aberrations, because cortisol and androgens in females, as well as cortisol and a relative hypogonadism in males, seem to be followed by these changes in skeletal muscle structure (11,51,53,54).

The mechanism for the regulation of insulin sensitivity in muscle by steroid hormones is of course of considerable interest and has been studied surprisingly little. We have examined this utilizing the euglycemic, hyperinsulinemic clamp technique in combination with analyses of regulatory steps at the level of different muscles in rats. As far as androgens are concerned, glycogen synthesis and the insulin sensitive part of the glycogen synthase are severely inhibited by both absence (males) or excess (males and females) of T. There is also some inhibition of the insulin stimulation of glucose transport, as estimated by 2-deoxyglucose uptake in vivo, and it is therefore not possible to state which is the primary locus of inhibition (51,53,54). The insulin receptor number and function in terms of tyrosine kinase seem to be intact, and the total number of glucose transporters 4 is not affected (unpublished). At the level of the muscle cell it thus seems that the insulin effect on glycogen synthesis and/or glucose transport might be the common lesion for the insulin resistance in conditions of abnormal T concentrations.

This is closely associated with morphological changes in muscle, viz. a low ratio of percentages of fiber type I / type II and a low capillarization (54). Muscles with such a fiber composition, or with a low number of capillaries, are known to have a low degree of insulin sensitivity (22,51,53,54,64). The mechanisms for this are probably different for fiber composition and capillary density. As far as the fiber type shift the lower insulin sensitivity has been thought to be due to a lower density of insulin receptors in white than red muscles (22). The potential role of capillary density in regulating insulin sensitivity might be apparent from several pieces of information, recently available. First, the magnitude of the effect of insulin in muscle shows a much stronger correlation with extracellular, extravascular than intravascular insulin conceptions. The former concentrations are considerably lower than those in circulation (115). The equilibration space for insulin in muscle is larger than for inulin, a molecule with similar volume, suggesting that insulin is bound to an intravascular pool before appearing in the extravascular space (50). Taken together, this information suggests that insulin is first bound to capillary endothelium from where it is released to the extravascular space and the cellular receptors on muscle. Thus, there is evidence that this transendothelial transport of insulin might be rate limiting for cellular insulin effects. The parallelity between insulin sensitivity and capillary density in various clinical conditions (66,78) as well as after hormone manipulations (51,52,54) may therefore mean that insulin sensitivity is at least partly regulated by the capacity of the capillary bed to bind and subsequently transport insulin to its active site.

The effects of perturbations of androgen secretion on insulin sensitivity in muscle are apparently, in the order of appearance, first a decreased capacity of the binding to capillary endothelium, then a decreased density of insulin receptors, suggested by the low type I / type II fiber ratio, and finally a decreased glucose transport and/or glycogen synthesis. Interestingly, the effects of other factors that alter muscular insulin sensitivity seem to be similar. Excess corticosteroids (95), as well as physical inactivity, are characterized by similar morphological changes in combination with a decreased insulin sensitivity of glucose transport and glycogen synthase (100). This chain of events is depicted schematically in Figure 1.

Similarities in these adaptations of muscle in relation to insulin sensitivity among different conditions automatically leads to the question of whether or not the listed regulatory steps might be interdependent. If we start at the distal end of the presumed chain of events (cf. Figure 1) it seems logical that a low density of insulin receptors on the muscle cell would be associated with a diminished capacity of intracellular events to dispose of glucose. It is, however, less evident why a low transcapillary transport or binding of insulin to capillary endothelium would be associated with a low type I / type II muscle fiber ratio and presumed low density of

![Figure 1: Potential rate limiting steps for insulin action in muscle. The final effects on cellular metabolism are dependent on the signaling from insulin receptors, in turn dependent on the cellular density of receptors and available concentration of extravascular insulin. The latter is dependent on insulin concentrations in circulation and the capacity of the endothelial barrier to transfer insulin to the extravascular space.](image)
insulin receptors. Since there is evidence that insulin regulates its own receptor density inversely (89), one would presume an opposite situation to that observed, namely, that a low insulin concentration in the extracellular space would cause an upregulation of insulin receptor density.

An experiment was therefore performed to examine the effects of insulin to regulate insulin sensitivity in the muscular system. Rats were chronically exposed to insulin, while counterregulatory hormones were controlled (52). This had several unexpected but potentially informative consequences. Capillary density increased by about 50%, paralleled by an increased insulin sensitivity, systemically and in muscle. This was associated with a decrease of the type I/type II fiber ratio, in other words, a shift in the direction of what from other studies would be expected to be characteristic of an insulin resistant muscle; instead the opposite was found. These findings may be interpreted to mean that muscle fiber composition has little to do with regulation of insulin sensitivity. Insulin receptor density was not measured in this experiment, and it may well be that changes in insulin receptor density and in myosin composition did nor parallel each other. Whatever the correct sequence of events, muscle fiber composition seems to be a poor indicator of insulin sensitivity. It may well be that the reverse chain of events is correct, namely, that insulin is regulating the turn-over of the different types of myosins in muscle.

These experiments then further established the importance of capillary density in muscles for maintaining insulin sensitivity. Furthermore, the results suggest that insulin may increase capillarization. Changes in myosin composition of muscle are probably misleading as an index of muscular insulin sensitivity, and might be a consequence rather than a cause of changes in insulin sensitivity. Insulin receptor density may not be coupled to the composition of muscular myosins. These results seem to reemphasize the importance of capillarization for insulin sensitivity in muscle. Decreased, capillarity density and/or faulty function may therefore be factors of importance in insulin resistant conditions, including visceral obesity. At least two pieces of indirect evidence suggest this possibility. First, with increased insulin secretion, such as in obesity, the muscular capillarization may be expected to increase in parallel, as seen in the experiments with rats subjected to chronic hyperinsulinemia. Instead, in visceral obesity it is decreased (66). Visceral obesity may be considered as a precursor condition to NIDDM. In insulin resistant NIDDM muscle, capillaries have been found not only to be low in number, but also not to change after physical training (1), and apparently to have abnormal functional features (87). The regulation of capillary density and function is therefore a question of considerable interest in insulin resistant conditions, such as visceral obesity.

**Associations Between the Endocrine Abnormalities and Accumulation of Visceral Depot Fat**

There is considerable evidence to suggest that the endocrine perturbations of visceral obesity might be followed by accumulation of depot fat in visceral adipose tissues. Cushing's syndrome is a dramatic example of visceral accumulation of body fat with hypercorticolemia. The mechanism here seems to be that cortisol, in the presence of adequate insulin concentrations, induces lipoprotein lipase (LPL) activity via a combination of effects on gene transcription stimulation and post-translational stabilization of the enzyme (4,29,91,95).

The exact effects on the lipid mobilization side are not yet known, but the net effects seem to be, surprisingly, an inhibition of lipolysis in abdominal regions (95). These effects are probably mediated via a specific glucocorticoid receptor (GR) (96, and Ottosson, unpublished). Available evidence suggests, but does not prove, that the density of the GR is particularly high in visceral adipose tissue (96). This then might explain the lipid accumulating effects of cortisol specifically in visceral adipose tissue. The "functional" oversecretion of cortisol in visceral obesity would thus be expected to be followed by accumulation of depot fat specifically in visceral adipose tissues.

Androgens also exert marked effects on adipose tissue metabolism. T is clearly lipolytic. The mechanisms here are multifactorial, and include transcription effects on the lipolytic β-adrenergic receptor genes, as well as interactions at the level of the protein kinase and/or the hormone-sensitive lipase (112,113). In addition, LPL expression is inhibited by both T and dihydrotestosterone (Xu, unpublished). These effects are mediated via a specific androgen receptor which is positively autoregulated by androgens (30). Indirect evidence suggests that the density of this receptor is also, similar to the GR, higher in visceral than other adipose tissue (13).

The net cellular effects of T are thus clearly to stimulate lipid mobilization, and to inhibit lipid uptake by inhibition of LPL expression. The end result would thus be a marked prevention of triglyceride storage. In addition, by autoregulation of its own receptor, the T effects will be amplified. The androgen effects on adipose tissue are probably most pronounced on visceral depots. With a deficiency of T, such as in men with visceral obesity, visceral triglyceride accumulation would be an expected consequence as a result of a subnormal T effect on the mechanisms reviewed above. However, it is totally unclear why women with the visceral obesity and a relative hyperandrogenism are accumulating tri-
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glycerides in visceral depots. In accordance with the effects to prevent lipid accumulation, reviewed above, T would be expected to diminish the visceral fat depot in visceral obese, hyperandrogenic women. Clearly the adipose tissue effects of T have to be studied not only in male but also in female adipose tissue.

GH deficiency seems to be another endocrine perturbation of visceral obesity (86). GH has several effects on adipose tissue metabolism, which interestingly seem to be mainly synergistic with or antagonistic to the steroid hormone effects. Starting with cortisol, GH inhibits the LPL-expression exerted by cortisol (Ottosson, unpublished). It has been known for a long time that cortisol and GH in concert provide a "permissive" effect on lipolysis (40).

Finally, GH amplifies the effects of T to prevent lipid accumulation, both by enhancing the T-inhibitory effect on LPL-expression, as well as the T-stimulatory effect on lipolysis (Xu, unpublished). Taken together, GH then is preventing lipid accumulation by mechanisms which seem concerted, antagonistic, or synergistic, with steroid hormone actions. It is then conceivable to consider that the relative GH-secretion deficiency in visceral obesity would further enhance the visceral fat accumulation, accomplished by the combination of cortisol excess and relative lack of T in men.

There are thus observations indicating that the different impact of hormonal effects on metabolic regulation varies in different adipose tissue regions due to the density of their specific hormonal receptors. There is, however, also considerable evidence to suggest that circulatory factors are of importance for the regional distribution of body fat stores. For example, measurements of lipid uptake in vivo does not always parallel the activity of LPL, the rate limiting enzyme for triglyceride uptake (81). This finding indicates that other than cellular, metabolic factors are of importance for lipid uptake such as circulation. This is rather obvious when one considers that the net uptake of circulating lipid in a depot is dependent not only on the cellular factors, such as LPL, but also on the availability of substrate for the enzyme. As a matter of fact, the LPL seldom or never operates at maximal velocity in vivo, therefore the delivery of substrate to an adipose depot through capillaries is probably more important than LPL activity as a regulator of regional fat deposition. This has been demonstrated in previous work (10).

Circulatory factors are also of fundamental importance for lipid mobilization from an adipose tissue depot (99). Glycerol and FFA are the products of triglyceride hydrolysis. If the FFA are not removed from the site of hydrolysis by circulatory factors, further hydrolysis will be inhibited by feedback mechanism exerted by the reaction product, the FFA. In other words an efficient lipid mobilization requires a sufficiently efficient circulation. A brisk circulation through an adipose tissue will thus probably result in a rapid turn-over of triglyceride in that depot, because both uptake and mobilization mechanisms are critically dependent on blood flow for supply respective to lipid removal. As a matter of fact the currently available information and the considerations above strongly suggest that circulatory factors are rate limiting for the turn-over of triglycerides in a depot. Whatever efficiency the cellular enzymic systems possess for lipid uptake or mobilization, they are critically dependent on circulation for the execution of their activities.

This important factor is evident also from another aspect. As mentioned above, the regional differences in adipose tissue metabolism have been considered to be influenced by the cellular densities of specific hormonal receptors. Such differences in characteristics of adipocytes might be considered to be due to inherent, genetic differences to express such receptors, or rate limiting enzymic regulators. In recent experiments we have tested this possibility by isolating adipocytes precursors from different adipose tissue regions, and then allowed them to develop into fully mature adipocytes under standardized, equal cell culture conditions. Their basic metabolic characteristics, as well as their sensitivity to corticosteroids and expression of GR were then compared. The results were no differences between the depots (114). In other words, there was no evidence for the expression of phylogenetically different adipocyte populations in different adipose tissue regions. Nevertheless, we know from numerous previous studies of adipocytes or shreds of adipose tissue in vitro, obtained directly from the donor, that there are marked regional differences in metabolism (for review see 94). These regional difference may then be acquired through specific effects of factors in the milieu from which these adipocytes have been taken. In a recently finalized study of regional triglyceride turn-over in vivo, it was found that mesenteric adipose tissue has a rapid triglyceride turn-over due to a combination of a high cellular density, phylogenetic characteristics of adipocytes, as well as factors in their microenvironment (77). All these factors need to be taken into consideration when regional differences of adipose tissue metabolism are sought.

To sum up, circulatory factors are probably of fundamental importance for the regulation of metabolism in different adipose tissue regions. This factor is not taken into account in conventionally performed studies of adipose tissue in vitro. Such studies are therefore probably of overestimated value if information is sought about regulation of adipose tissue metabolism in different regions. Although more complex, methods have to be
developed in which these events are studied in vivo in the fully integrated system. Such Methodological development is possible (18,77,81), although the results have to be interpreted with caution.

There is apparently no information available on the effects of hormones and other factors on the regulation of regional adipose tissue circulation and innervation. Such information is badly needed, not least in clinical conditions where adipose tissue distribution is altered, such as in the syndrome of visceral obesity. A previous sector has pointed out the critical importance of capillary circulation for the regulation of insulin sensitivity in muscle. Capillarization of adipose tissue might be of equal importance for the distribution of body fat to different regions. The regulation of capillary density or function might be deranged in visceral obesity, either as a result of endocrine perturbations, or as primary fault. This area appears to be of considerable importance to explore further.

A Summary of the Consequences of the Endocrine Aberrations

A previous section has pointed out the potential possibilities that the endocrine aberrations of visceral obesity may in fact contribute to the insulin resistance seen in that syndrome. Furthermore, visceral fat accumulation seems to a large extent to be explainable by the hormonal changes. Finally, not only the insulin resistance of muscle but also the morphological changes in muscle may well be secondary to the endocrine aberrations.

The picture is far from complete, but as reviewed in previous sections there is no doubt considerable evidence suggesting that the endocrine abnormalities of visceral obesity may indeed explain the major symptoms of that condition, viz. peripheral insulin sensitivity, muscular changes in fiber composition and capillarization as well as visceral fat accumulation. The latter may secondarily amplify the metabolic symptoms by effects of systemic and portal FFA on hepatic and muscle metabolism (14).

There is thus a number of pieces of evidence that fit into the hypothesis that the endocrine aberrations of visceral obesity may actually be followed by the most important features of that syndrome. It therefore seems reasonable to believe that the endocrine aberrations play a central pathogenetic role in the syndrome of visceral obesity.

Neuroendocrine Aspects

The cluster of endocrine aberrations in visceral obesity most probably has a central origin. For example, central, mental stressors have been shown to cause both increased cortisol secretion and an aberrant hemodynamic response (47,49). Furthermore, sex steroid hormone secretions are directly dependent on gonadotropins, the secretion of which probably is deranged in visceral obesity as suggested by clinical and laboratory observations (11,21,39). Gonadotropin secretion is regulated by gonadotropin hormone regulating hormone (GnRH), a neuropeptide. Finally, GH secretion is regulated by GH releasing hormone (GHRH), in turn regulated by neuroendocrine mechanisms. In summary, the endocrine aberrations in visceral obesity clearly point to the possibility that a neuroendocrine dysregulation might be a central feature of that syndrome.

An interesting question then is to try to understand whether or not the endocrine disturbances observed may indeed be interdependent at the central, neuroendocrine level. Several interactions between the CRF and the GnRH peripheral axes as well as GH secretion have been described (27). There is considerable evidence to suggest that an increased CRF secretion inhibits GnRH secretion (90). An increased CRF production would consequently be expected to be followed by abnormalities also in sex steroids. GH secretion is dependent on steroid hormones (38). One may then speculate and suggest that an increased CRF production might be a start of a chain of events, the next step of which is decreased GnRH and GHRH secretions. The resulting deficient or abnormal sex steroid concentrations might be thought to further inhibit the deficient GH secretion.

This seems, at first glance, to be a reasonable working hypothesis, and we have therefore tested it in several ways. First, T substitution of men with low T and GH levels seems to change their insulin like growth factor I concentrations in a normalizing direction (unpublished). It has previously been shown that androgens influence GH secretion in male hypogonadism (79). This is in apparent accordance with the hypothesis above. A more direct way to test potential abnormalities in the secretion of central nervous system neuropeptides and transmitters is to analyze their concentrations in the cerebrospinal fluid. With the background provided above, we considered it ethically possible to perform lumbar puncture in obese subjects to directly analyze these questions. Although final analyses are not available as yet (November, 1992) it seems currently clear that the CRF concentration is actually lower than normal in obese subjects. This is in apparent contradiction with the presumed increased sensitivity of the CRF-ACTH-cortisol axis, referred to above. On the other hand, animal models of obesity also seem to be characterized by the same seemingly contradictory results, a high activity along the CRF-peripheral axis, but a low CRF concentration in the central nervous system (43,98). This apparent contradiction remains to be resolved. The animal models may be helpful from this
aspect, particularly now that a close parallelism seems to be found between the neuroendocrine aberrations in the human and experimental animal models.

The Origin of the Neuroendocrine Abnormalities

A major question then of course is to try to understand the nature of the neuroendocrine aberrations presumably associated with visceral obesity. There are several similarities between the neuroendocrine and circulatory reactions to stress in visceral obesity with certain types of stress, which are well characterized in animal experiments (49). The response to stressful stimuli may express itself in different ways, depending on whether the individual is able to cope with the stress-challenge or not. In a first phase of reaction, the animal strives to obtain control, and this may be successful or unsuccessful. When successful a typical neuroendocrine-hemodynamic response follows with elevated catecholamine levels, as well as increased heart rate and blood pressure. When the animal is facing a threat which is overwhelming, and when attempts to control fail, the reaction pattern is moved into a defeat-type of reaction characterized by a general depression, low blood pressure and heart rate, as well as increased cortisol secretion, and low sex steroid hormone secretions.

The similarities between the neuroendocrine and circulatory phenomena noted in visceral obesity and the defeat-type of reaction in animals are quite striking, they are in fact largely identical. Recent animal experiments, utilizing primates, have repeated these observations and utilized a standardized stress model, involving psychosocial modifications of the environment of the animals. A female in a defeated, uncontrollable situation develops enlarged adrenals, decreased sex steroid secretion, insulin resistance, decreased glucose tolerance, hyperlipidemia, hypertension, and coronary atherosclerosis. Furthermore, triglycerides are accumulating in visceral depots (104, and Shively, personal communication 1992). This is a picture then which is similar in essentially all parts to that seen in a woman with visceral obesity.

These strikingly parallel findings clearly make it of interest to examine whether stressful stimuli of the same type as those utilized in the animal experiments might be identified in humans with visceral accumulation of depot fat. In population studies, we have found that an elevated W/H ratio in men is associated with a poor education, physical types of work, and a low income. Both men and women are often on sick leave and frequently utilize free sick insurance facilities. Among diseases causing this close contact with health facilities are peptic ulcers, gastric bleeding, depression, and anxiety. Drugs for are often used such conditions (72,74).

From this, a picture seems to emerge with subjects in a socioeconomic situation that they might have difficulties coping with, resulting in psychosomatic disease as well as signs of psychological insufficiency or psychiatric symptoms. Obviously the individual capacity to cope with socioeconomic difficulties varies, but once cornered into a situation that is pressing and difficult to control, several individuals might well be thought to react similarly to the animals in the primate experiments referred to above, viz. with a neuroendocrine reaction that is followed by metabolic and body fat distribution symptoms.

Such abnormalities have thus been observed in human studies (72,74). Recent reports have now confirmed the association between an increased accumulation of abdominal fat and psychosocial handicaps with sign of abnormal psychological reactions (76,111). A situation with frequent environmental stress challenges would presumably result in an increased sensitivity and readiness of the neuroendocrine mechanisms involved. Subjects with visceral obesity show such a sensitivity. Upon psychological or somatic stress stimuli they secrete excess amounts of cortisol, detectable also under field conditions during ordinary work days (83).

In addition to the possibility that in visceral obesity, psychosocial and socioeconomic handicaps might provide a background to develop a neuroendocrine response typical of a defeat reaction, there might also be other factors involved. Both excess alcohol consumption and tobacco smoking are known to be followed by increased cortisol secretion (28,42). Excess alcohol consumption is also followed by a decreased secretion of sex steroid hormones (28).

Tobacco smoking as well as excess alcohol consumption are both associated with visceral fat accumulation (71,74,72,103). Subjects in the population with elevated W/H ratio smoke and use alcohol more often than the rest of the population (74,72). Furthermore, they seem more sensitive to this type stress than non-obese controls (Sztostak, unpublished, 1992). It therefore seems likely that alcohol and tobacco smoking may contribute to a hypothalamic arousal of similar type as that caused by a presumed defeat type of reaction to psychosocial stress in visceral obesity.

The susceptibility to visceral adipose tissue deposition has been shown to have a strong genetic component (23). The impact of the environmental factors mentioned above may thus vary individually.

Therapeutic Implications

The introduction of negative energy balance is the first choice of therapy for visceral obesity. This might be performed by diet or exercise or a combination of both. There is now evidence that both these modes of treatment are more effective in visceral than peripheral
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obesity (26,35,66), particularly the insulin resistance and other components of the Metabolic Syndrome seem to respond well to exercise treatment (19, 35, 66).

The possibility reviewed above that visceral obesity is associated with a multiple neuroendocrine abnormality opens up new potential ways of treatment of the metabolic abnormalities associated with the syndrome. At the same time, such intervention studies provide an opportunity to test whether the presumed pathogenetic chain of events is correct.

Drug treatment can in principle be introduced at different "levels" of the abnormalities of the condition. To start in the periphery the hypertension, hyperlipidemia, or NIDDM may be treated by separate, specifically constructed drugs, and this is the current mode of therapy. It is, unfortunately not unusual that each "symptom" is treated separately without adequate observation being paid to other metabolic perturbations. For example, a patient with visceral obesity and hypertension as a dominating symptom may not always be adequately diagnosed and treated for an associated hyperlipidemic condition.

If the endocrine aberrations of visceral obesity are of pathogenetic importance for the metabolic symptoms, then intervention at this level would be desirable. We have performed several such attempts, of which T-substitution of visceral obese men clearly has been promising. T has been administered in moderate doses to substitute such men to the normal T-levels of the age in question, utilizing T-preparations bypassing the portal circulation to prevent the liver from direct hormonal exposure. The studies have for security reasons been increased in duration gradually up to 8 months. Improvement of insulin resistance seems to be one of the earliest events occurring, reaching a degree of improvement of about 25%, and seems to be most pronounced in men with the lowest T-values. Blood glucose decreases as well as total cholesterol (about 20%) and triglycerides (about 60%), without change in high density lipoproteins. Blood pressure decreased by 4-5 mm Hg, and visceral fat mass by 10-15% (82,84).

The men were carefully selected not to have any prostate or urinary problems before being included in the studies, as examined by rectal ultrasound measurements of prostate size and structure, as well as prostate specific antigens (PSA). In one study, a 10% increase in prostate size was recorded without symptoms or PSA elevation. This might be an expected result, the prostate parenchyma is a major target for T effects, but is of course a cause for further careful observations.

There were also other effects of T treatment. Muscle strength improved, particularly in athletic type of power tests (isometric strength), paralleled by increased muscle fiber diameter of "athletic," type II fibers. Several psychological beneficial effects were reported, including better energy, sleep, and general well-being (82,84,85).

Double-blind technique has of course been applied in these studies. Furthermore, a parallel group treated with a dihydro-T has provided an additional control for potential effects on metabolism mediated via psychological variables. Dihydro-T was, in essence, without effect in the metabolic variables. It thus seems that the effects noted are those of T, particularly since 17-estradiol concentrations did not increase (82,84,85).

The substitution of men with visceral obesity and a relative hypogonadism with T has thus shown promising effects. Although the results so far seem to be compatible with the conclusion that a relative deficiency of T is a part of visceral obesity in men, this treatment is not recommended yet for general use. We need to know more about indications and side-effects.

There is of course an analogy here with sex hormone replacement therapy of women. Such treatment has recently been shown to prevent an increase of central fat masses with menopause (44) and is improving risk factors for CVD (5). We have also recently treated post-menopausal hyperandrogenic NIDDM women with visceral obesity with 17-estradiol to elevate sex hormone binding globuline and decrease free T concentrations. The results were marked improvements in their blood glucose homeostasis, hemoglobin A1C, and plasma insulin concentrations (2).

There is thus now evidence that replacement therapy with sex steroid hormones is effective against visceral obesity and its associated metabolic aberrations in both sexes. This in turn also strengthens the presumed pathogenetic importance of deficiencies of these hormones in the syndrome of visceral obesity.

A sensitive hypothalamo-adrenal axis seems to be a prominent feature of visceral obesity. Treatment of this phenomenon has therefore had a high priority in our intervention studies, aimed both at seeking further evidence for cause-effect relationships, and to find novel principles of therapy. The apparent similarities between the fa/fa rat and visceral obese humans as far as a sensitivity along the hypothalamo-adrenal axis and metabolic aberrations were pointed out in a previous section. It is of considerable interest that adrenalectomy in the rat in question ameliorates essentially all the metabolic aberrations as well as the obesity (24). Adrenalectomy can of course only be performed in humans on very strict indications.

We have, however, tried reversible blockade of adrenal cortical hyperfunction. We first used RU 486 (Roussel UCLAF, Paris, France), a compound blocking the GR in a competitive way. Although very efficient in blocking cortisol effects on human tissues in vitro, the
effects in vivo were transient or absent as far as for example influence on insulin sensitivity or LPL expression in adipose tissue. This is probably due to a build-up behind the blockade of endogenous cortisol in high concentrations, which presumably suffice to break the receptor blockade (unpublished).

There are, however, other pharmacological possibilities. Ketoconazol (Janssen, Belgium) is changing cortisol synthesis to largely inactive compounds. This is now under study in order to see whether cutting excess cortisol effects might improve the symptoms of visceral obesity.

GH-deficiency is the most recent addition to the list of endocrine aberrations in visceral obesity (86). Other studies, several years ago, have shown that total GH insufficiency in man is followed by accumulation of CVD risk factors and an increased incidence of CVD (41). Recent studies have now also shown that GH regulates accumulation of visceral fat (6,7). Interestingly, substitution of totally GH-insufficient patients with GH for 6 months was followed by a diminution of CVD risk factors, except insulin sensitivity which was temporarily decreased, but then returning to initial values. Visceral fat decreased by about 30% (7). With this background from total deficiency of GH we have now embarked into a similar study in visceral obesity, a syndrome with relative GH deficiency (86).

Finally, FFA may well be an intermediary mediator of symptoms in visceral obesity by effects both on peripheral (muscle) and hepatic metabolism. To our knowledge, however, a trial of FFA-release blockade has not been performed. Such a study would be of considerable interest, if a compound were available to provide a FFA-release blockade of sufficient duration.

Several attempts to treat the endocrine aberrations at an “intermediary” level of the syndrome of visceral obesity have thus been promising. The question is then whether or not interventions with the presumed central abnormalities are possible. Theoretically, an intervention at the level of the presumably deranged CRF secretion would be of considerable interest, but the possibilities here appear to be limited. We have tried a 5-

Figure 2: The "Civilization Syndrome." The primary factors are stress, smoking, alcohol, overeating, and physical inactivity. Stress might result in poor coping, with a neuroendocrine response that in combination with overeating and physical inactivity leads to insulin resistance and visceral obesity, which constitute the base for hypertension, hyperlipidemia, cardiovascular disease (CVD), and non-insulin dependent diabetes mellitus (NIDDM).
hydroxytryptamine antagonist, which was followed by a
decrease of blood pressure (3). Beta-adrenergic block-ade showed no effects (unpublished).

This complex area is difficult to approach, but the theoretical potential of correct and sufficiently specific interventions at this level may have considerable potential future significance.

Conclusions and Aspects for the Future

Research in the field of visceral obesity has no doubt been helpful in sorting out the hazardous nucleus of human obesity. This has already made the associations between human obesity and metabolic disturbances and disease considerably clearer. The marker of this syndrome, the specific accumulation of fat in visceral depots, has been helpful insofar as it has brought into focus a number of new potentially important pathogenetic endocrine factors. These factors may well be of importance for the pathogenesis of visceral obesity, including insulin resistance, hypertension, and hyperlipidemic conditions. Through the new developments pathogenetic mechanisms may have a better possibility to be revealed. Thereby new avenues into the understanding of the development of NIDDM and CVD may develop. Furthermore, as briefly summarized above, new means for prevention and treatment may develop.

The syndrome of visceral obesity, as described above, has several features of the unhealthy life-style that has developed in urbanized countries. Positive energy balance, physical inactivity, smoking, alcohol, and stress seem to be important ingredients of the syndrome of visceral obesity. These are the components of what might be labeled a "Civilization Syndrome." It is hypothetically suggested that these life-style factors are closely connected via neuroendocrine disturbances to prevalent diseases such as NIDDM, CVD, and stroke as well as their risk factors, and that visceral accumulation might be a marker for this syndrome. The expression of the specific symptoms and end-points might be determined by the individual genetic susceptibility to develop these abnormalities (23, 32).

Figure 2 shows an attempt to construct an integrated picture of the observations. Although in total this is still a hypothesis, it should be noted that there is evidence for most of its integral parts. To start from the periphery of the relationship between visceral obesity, insulin resistance, hypertension, and hyperlipidemia with NIDDM as well as CVD is now well established. The insulin resistance as a background factor to hyperlipidemic conditions, NIDDM and CVD also rests on a rather solid basis. The relationship to hypertension is, however, less well established.

Information is now available from several studies indicating that the endocrine abnormalities might at least contribute to the creation of insulin resistance. These studies comprise experimental work at the intact organism, cellular, and molecular levels in the rat and human as well as clinical observations and intervention studies in the human. The linkage of these endocrine aberrations to visceral accumulation of fat rests on a similar basis. The possibility of amplification of the disease risk by visceral fat depots seems reasonable, but is unproven.

To come next to the more proximal parts of the attempt to integration, obesity is certainly caused by a positive energy balance by overeating and/or physical inactivity. The stress-linked chain of reactions is, however, more speculative, and the evidence for this is mainly circumstantial in man. It is doubtful for ethical reasons whether it will be possible to arrive at conclusive evidence in humans for this important part of the potential chain of events. However, data in primates strongly indicates that the suggested background factors in humans are indeed correct, because in primates the entire syndrome can be developed by stress in well-controlled experiments.

A philosophical consideration might be in order at this point. Medical research is time-consuming, expensive, and labor-intensive. "Data collection" without a working hypothesis is therefore not an acceptable way to try to approach important problems in medical research. In the worst case such research might be meaningless and a waste of time, effort, and resources. With a working hypothesis as a background, it is of course of fundamental importance to interpret the results obtained in an objective manner in relation to the hypothesis and change the approach to the problem when indicated. Another problem is to decide when sufficient information has been considered to be available to accept a hypothesis as proven. This varies to a large extent among researchers. A practical yard stick here might be to aim at sufficient information allowing prevention or treatment of the disorder in question. The information on the syndrome of visceral obesity is far from this first goal, but no doubt much important information has been gained during recent years, and the intensive work in this area of research in many laboratories promises to yield more useful information within a limited period of time. The importance of the problem makes such further efforts highly appropriate.

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