Hormones, body composition and cardiovascular risk

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Some 20 compartments of the body may be measured by CT and organ areas determined in 28 CT scans. Advantages of CT are described. While there have been extensive studies of hormones in pre- and postnatal growth, apart from evidence from disease, the role of hormones in adults has been less known. Data on growth hormone and sex hormones, from organ-oriented body composition studies, are summarized, together with implications for the relation between body composition and cardiovascular risk. Sex-specific anthropometric equations allow estimation of LBM, visceral and sc AT with <20% error. In the obese such estimates show visceral AT to be a stronger risk predictor than other compartments or W/HR.

Over the last ten years an increased knowledge on the relationships between body composition and health has been achieved. The health hazards of being obese have finally been proven and several studies have also indicated an increased morbidity and mortality among extremely lean subjects[1,2]. Furthermore, relationships between the adipose tissue (AT) distribution and cardiovascular risks have been demonstrated[1,2]. Most of these studies have used just weight and height or, in the case of cross-sectional studies, simple two-compartment models based on density, total body potassium and/or total body water to describe the body composition. Similarly, the AT distribution has been estimated from skinfold- and waist/hip-circumference ratios (W/HR) in most studies. Some cross-sectional studies have used single or a small number of computed tomography (CT) scans to determine visceral and subcutaneous AT areas. In a stricter sense, not even this is sufficient, since AT *areas* can not be expressed as a percentage of the total AT *volume* and therefore regional area determinations can not describe the AT distribution or changes of this distribution. As shortly summarized below we have used CT for total as well as regional volume determinations of AT, muscles and other organs. This *organ*-oriented approach has certain advantages over traditional body composition techniques which only give *constituents* such as fat, water, potassium, nitrogen or calcium.

Body composition techniques based on computed tomography

Determination of AT volumes with CT.
In 1986, we described a multiscan CT technique to determine the total AT volume from the AT areas of 22 CT scans and the distances between the scans[3,4]. Methods for determination of regional AT volumes, including the visceral AT, were described in the same publications.

The reproducibility of the CT method is high. As calculated from complete double determinations, the error was 0.6%[3].

In order to obtain correct results with CT a number of precautions are necessary. These include area corrections due to beam hardening[4,5]. CT studies not performing beam-hardening corrections have most likely reported incorrect AT-area values. Unfortunately, this criticism is valid for the majority of AT studies using CT.

CT-calibrated anthropometry. As mentioned above, most studies of abdominal obesity have used skinfold- or W/HR to characterize the AT distribution. None of these ratios have ever been calibrated against methods determining visceral and subcutaneous AT volumes. The W/HR is influenced not only by visceral AT, but also by other visceral organs, muscles and skeleton. Except for visceral AT, these influences occur both at the waist and the hip levels. The hazard of interpreting a high waist/hip ratio as an increased visceral AT depot is illustrated by our examination of alcoholics in whom the increased ratio was mainly explained by a reduced volume of hip (gluteal) muscles[6].

We have used the CT-based technique for determination of total and regional AT volumes[3-5] as a standard when developing equations predicting the masses of lean body mass (LBM) (i.e., non-AT), visceral and subcutaneous AT from weight, height and the sagittal (antero-posterior) diameter of the trunk at the crista iliaca level of recumbent subjects[7]. The

Table 1. Anthropometric CT-calibrated equations predicting total and visceral AT in men and women. W=body weight, kg. H=height, m. D=recumbent sagittal diameter at the iliac crest, cm. Adapted from[7].

Males Females	Primary group n=17 n=10		Cross-validation group n=7 n=9
	R^2%	error%	error%
Males:			
Total AT litres=1.36·W/H–42.0	93	9	11
Visceral AT litres=0.731·D–11.5	81	18	12
Females:			
Total AT litres=1.61·W/H–38.3	96	7	9
Visceral AT litres=0.370·D–4.85	80	21	18
Males & Females			
AT kg=AT litres·0.923			
LBM kg=BW kg–total AT kg			
Subcut. AT kg=total AT kg–visceral AT kg			

error of these estimates (as compared to CT examinations) was 10-20% in the primary and cross-validation groups (Table 1). Weight, height and sagittal diameter was chosen after screening of several hundred anthropometrically accessible measurements. In the original publication[7], primary as well as validation groups were small (Table 1) but recently the equations have been further validated in larger CT-examined groups of subjects[8]. The associations between cardiovascular risk factors and the CT-calibrated anthropometric estimates of body composition have also been examined in 1006 severely obese subjects (see below).

Multicompartmentation with CT.

Recently our CT-technique has been further developed so that the body can be compartmentalized in some 20 different compartments[9,10]. Organ areas are determined in 28 CT scans. Air, gas and lungs are determined in the attenuation interval –1001 to –191 HU, AT in the interval –190 to –30 HU, all other soft tissues in the interval –29 to +151 HU, and spongy plus dens bone in the interval +152 to +2000 HU. Different tissues in the soft tissue interval (–29 to +151 HU) are separated by various types of cursor work[9,10]. Corrections for beam-hardening are performed whenever needed[4,5]. All tissue and organ volumes are calculated in the same way as AT (see above). The result of these procedures are illustrated by Fig. 1. Since five scans are examined in the diaphragmatic region and since precautions are taken to collect all scans after an identical degree of expiration, it is possible to separate abdominal from thoracic organs (Fig.1).

The *validity* of the multicompartment technique has been examined by multiplying each organ volume with its density as reported in the literature. Estimated organ weights so obtained have been summed up to a CT estimated body weight (BW). The error calculated on the differences between CT-estimated BW and actual BW is in the order of 1%[9,10]. The net change of CT-estimated organ weights has agreed closely with the change in body weight in several intervention studies (see below).

In contrast to the CT-based AT technique[3,4], the multicompartment technique may be dependent on subjective judgements during the cursor work. The intra-individual *reproducibility* was examined by performing the analytical work twice in the same examinations. Based on the difference between the two examinations, the error was in the order of 0.6 to 3% depending on which organ that was under consideration[10].

From the observations discussed above it is concluded that our CT-based multicompartment technique has a high validity as well as a high reproducibility.

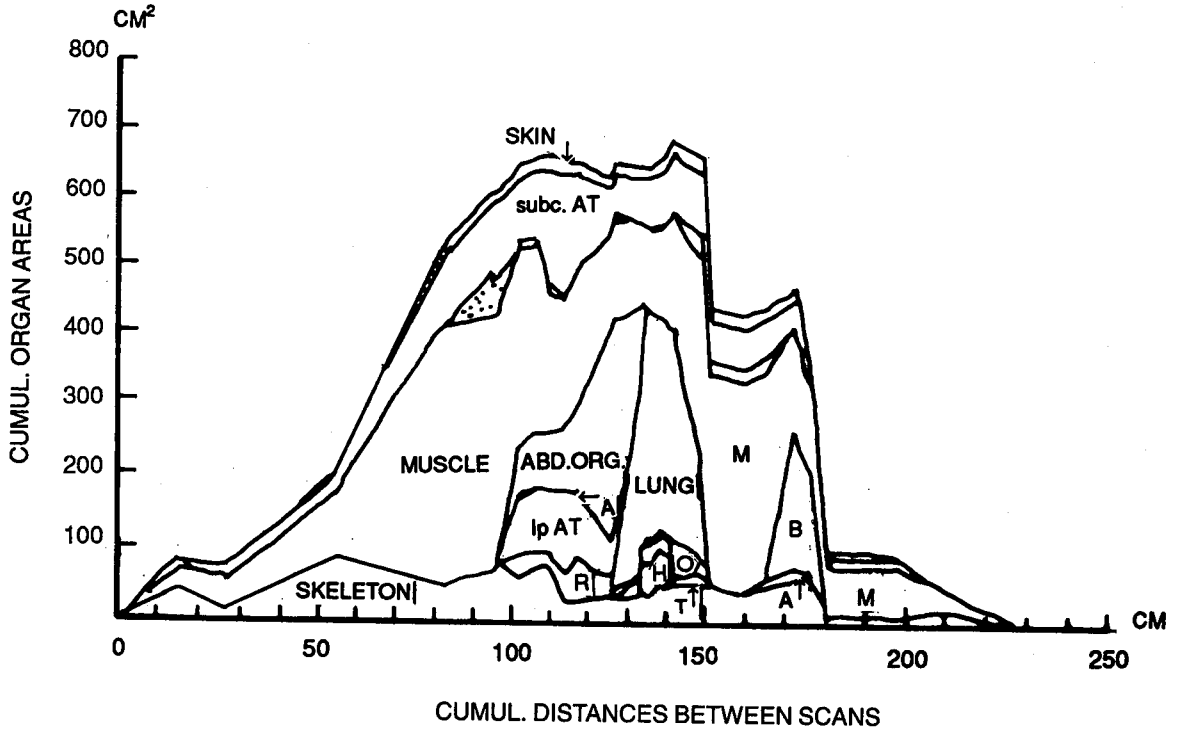

Figure 1. The human body compartmentalized in several organs and tissues by means of the multiscan CT technique[9]. Tip toes at 0, tip of fingers at 230 cm. Since cm^2 times cm is equal to cm^3 different areas of the plot represent tissue volumes. These volumes are also automatically given by the computer. Abbreviations: Oth. Th. org. = other thoracic organs: R = retroperitoneal AT: ipAT = intraperitoneal AT.

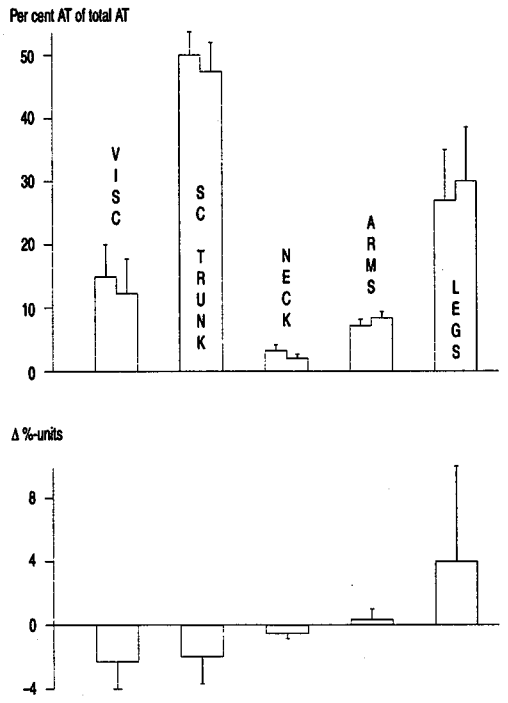

Figure 2. Changes of the AT distribution after treatment of Cushing's syndrome. *Upper panel:* AT depots expressed in per cent of total AT before (left part of each column) and after (right part) treatment. *Lower panel:* The number of %-units each depot was changed. Analysis of variance proved a changed AT distribution ($P<0.005$). Copyright: Sjöström, Lönn and Kvist.

Hormonal regulation of body composition in adults

The importance of several hormones for normal pre- and postnatal growth has been extensively studied. Well-known examples are the growth-promoting effects of growth hormone, growth factors, insulin and thyroid hormones. Several of these hormones also interact in a complicated way during growth. One classical example is the depancreatized and hypophysectomized young rat in which neither insulin nor growth hormone supplementation can induce growth, whereas a combined treatment with the two hormones results in a rapid weight development.

In contrast, much less information is available on the hormonal regulation of body composition in adults and in aging subjects. Some knowledge has been obtained from clinical experiences of endocrine diseases. For instance the trunk obesity of patients with Cushing's disease, the leanness of acromegalics and the muscle wasting of thyreotoxic patients are well-known features. However, due to the lack of organ-oriented techniques such disturbances in body composition have not previously been possible to quantitate. In the following we are summarizing some of our experiences regarding hormones and body composition.

Cortisol

In a study on seven subjects with Cushing's disease/syndrome we examined body composition before and one year after surgical treatment (unpublished data and ref 11). Body weight was reduced by 10.2 kg after treatment. AT, muscles and visceral organs were reduced by 8.9, 1.2 and 0.6 litres corresponding to reductions of 8.2, 1.3 and 0.6 kg, respectively. The sum of changes in organ weights was -10.1 ± 7.8 kg which was not significantly different from the change in BW. The error calculated on individual differences between change in organ weights and change in BW was 2.8 %.

The AT reductions of subcutaneous trunk, viscera, legs, arms and head plus neck were 4.9, 2.0, 1.3, 0.4 and 0.3 litres, respectively. Expressed in per cent of the initial AT depot volume, visceral AT was reduced with 36%, followed by reductions of 34% (head & neck), 26% (subcut./trunk), 18% (arms) and 8% (legs). These figures indicated a changed fat patterning, and a final evidence for this was obtained by expressing each AT depot as a percentage of the total AT volume both before and after weight reduction.Visceral AT occupied 15.4% of the total AT volume both before and 12.9% after weight reduction (Fig. 2, upper panel). The visceral AT depot was thus reduced by 2.5%-units on the average, while the AT of subcutaneous trunk and neck plus head regions were reduced by 1.8 and 0.3%-units, respectively. AT of arm and leg regions were increased by 0.4 and 4.2 %-units respectively. These changes were significantly different between regions (Fig. 2, lower panel) and thus the AT distribution was in fact altered. As expected, the net change over all regions was 0.0%-units.

Growth hormone (GH).

In a cross-sectional study of 27 healthy men we found a negative correlation between insulin like growth factor 1 (IGF-1) and the visceral AT mass but not between IGF-1 and the subcutaneous AT mass[12]. To the extent IGF-1 concentrations reflect GH secretion, a deficient GH secretion thus seems to be associated with visceral rather than subcutaneous fat accumulation.

These cross-sectional indications have been strengthened by results from two intervention studies. In one of these trials, 10 subjects with adult onset pituitary deficiency were treated with recombinant human growth hormone (rhGH) for six months in a placebo controlled double-blind cross-over study (unpublished data and ref. 13). The details of this study are given in the paper on growth hormone deficiency by Brummer et al. elsewhere in this issue. Briefly, this study demonstrated that rhGH increased skeletal muscle and visceral organs with 2.4 and 0.7 kg respectively and decreased AT with 4.7 kg. AT was also redistributed from visceral and subcutaneous trunk regions to peripheral depots. Again the average net change of organ weights (–1.6 kg) was in good agreement with the average change in BW (–1.5 kg).

In the other intervention study of growth hormone effects, eight males and seven females with acromegaly were examined before and one year after adenectomy[14]. GH and IGF-1 were dramatically decreased by this treatment. The results were opposite to those observed in patients with pituitary deficiency treated with rhGH. In acromegalic males treatment resulted in the following changes: BW + 1.0 kg; AT +6.6 kg; muscle plus skin –3.8 kg; visceral organs –1.6 kg. In women the corresponding figures were –0.8 kg, +3.6 kg, –3.4 kg and –1.0 kg, respectively. In acromegalic men the treatment resulted in a changed fat patterning with increases of the fractions of AT in subcutaneous trunk and viscera and a decrease of the fraction of AT in legs ($P<0.005$, analysis, of variance). a similar but insignificant change of AT distribution was observed in women.

Testosterone.

In a cross-sectional study on 25 males aged 25–50 and with an average BMI of 26 we observed a negative relationship between free and total testosterone on the one hand and the CT-determined visceral fat area at the L4/5-level on the other ($r=-065$; $P<0.01$)[18]. Testosterone was also negatively related

to fasting and summed (OGT) insulin and C-peptide values.

These observation[15] have recently been followed up in two placebo-controlled intervention studies with testosterone[16–17]. In one study 25 moderately obese middle-aged males were randomized to testosterone undecanoate (80 mg x 2 perorally) or placebo[16]. Sex hormone binding globuline (SHBG) and FSH dropped in the treatment but not in the placebo group. The visceral AT and the sagittal diameter dropped in the testosterone but not in the placebo group. Subcutaneous AT and W/HR did not change in any of the groups. Glucose disposal rate (GDR), insulin, cholesterol as well as systolic and diastolic blood pressure were significantly improved in the testosterone group. In the placebo group systolic blood pressure was improved. The most pronounced improvement of GDR was observed in those subjects having the lowest testosterone values before treatment ($r=-0.645$, $P<0.05$).

In another intervention study 35 moderately obese males were randomized to transdermal preparations of testosterone (T), dihydrotestosterone (DHT) or placebo[17]. Before treatment all three groups had similar BMI (29.4, 29.6 and 28.6 kg/m^2, respectively) and age (55.8, 57.9 and 56.3 year, respectively). Treatment decreased FSH and LH in the T and DHT groups but not in the placebo group. Total and free testosterone were increased in the T-group but decreased with more than 50% in the DHT group. In the T-group the visceral AT was decreased from 6.6 to 6.0 kg ($P<0.05$) whereas in the DHT group, visceral AT was increased from 7.9 to 8.4 kg ($P<0.05$). GDR, fasting blood glucose, serum cholesterol, serum triglycerides and blood pressure were improved in the T- but not in the DHT-group.

Body composition and cardiovascular risk

The waist/hip ratio (W/HR) and risk.

During the last ten years the consequences of abdominal obesity have been extensively studied all over the world. Several important observations have been made but much research remains to be done.

In 1983 we published a cross-sectional study on the relationship between the W/HR and cardiovascular risk factors in 930 subjects covering a wide range of body weights (BW)[18]. In this study males had a more pronounced risk factor pattern than women in all body fat (BF) classes (10 to 100 kg BF). Furthermore, *within* both sexes, subjects with a W/HR above the median had higher glucose, insulin, triglycerides and blood pressure than subjects below the median and this was true in the majority of BF classes studied. Kissebah and his group published similar results[19].

The cross-sectional studies were followed up by prospective population studies in men[20] and women[21]. In these studies total mortality and the incidence of myocardial infarction and stroke were strongly related to a large W/HR, while these end-points were not at all (men) or only weakly (women) related to body mass index (BMI).

Later, our results[18,20,21] have been confirmed by a large number of cross-sectional and longitudinal studies (for review[1,2]).

CT-calibrated anthropometry

As discussed above, the body can be compartmentalized in lean body mass, subcutaneous and visceral AT by means of CT-calibrated sex-specific anthropometric equations. These equations have been used in 450 obese males and 556 obese females.[8] In Table 2 systolic blood pressure among men is used as an example. As in most studies, age and body weight were related to systolic blood pressure. When weight was compartmentalized into LBM and total AT, it became evident that systolic blood pressure was related to AT but not to LBM (regression no 2 of Table 2). The third regression of Table 2 indicates that visceral AT was a stronger predictor than subcutaneous AT. In fact, visceral AT was the strongest predictor for almost all cardiovascular risk factors and for a number of diseases and symptoms[8]. Table 2 also illustrates that the W/HR was not related to systolic blood pressure in these severely obese subjects. The W/HR was a weaker predictor than the estimated visceral AT for most but not all risk factors[8]. Finally, Table 2 shows that BMI (regr. no 4) was related to blood pressure. However, an obvious disadvantage with BMI is that it can not distinguish between the influences of LBM and AT (cf, regr. no 1, Table 2).

Table 2. T ratios of indicated x variables versus systolic blood pressure (y). Multivariate regressions of 450 obese males. Adapted from [9].

	CT-calibrated Regression no			Conventional Regression no
	1	2	3	4
(x)				
	t	t	t	t
Age	4.4	4.4	4.4	4.2
Weight	5.3			
LBM		–0.2	0.1	
Total AT		3.6		
Subcutaneous AT		2.0		
Visceral AT		3.6		
BMI				5.3
Waist/hip			0.1	

Discussion

Hormonal regulation of body composition.

The studies summarized above illustrate that GH and testosterone are causing a reduction of the AT volume as well as a redistribution of AT from central to peripheral depots. The volumes of skeletal muscle and visceral organs are markedly increased by GH, but these changes did not reach significance in our testosterone studies, probably due to the fact that supraphysiological plasma concentrations were avoided. Cortisol causes an increase of the AT volume as well as a redistribution of AT from peripheral to central depots. Using two-compartment models or area determinations of single CT scans, similar GH[22-29] and cortisol[30] effects have recently been reported by other groups. Cellular and gene mechanisms responsible for the hormonal regulation of the body composition are only partly understood.

As far as *cortisol* is concerned it is clear that the hormone binds to a cytoplasmic glucocorticoid receptor in human fat cells.[31] As compared to adipocytes from other depots, visceral fat cells have a higher density of glucocorticoid receptors[31] and receptor depots, visceral fat cells have a higher density of glucocorticoid receptors[31] and receptor mRNA[32]. The cortisol-receptor complex induces increased lipoprotein lipase (LPL) activity, probably both by increased synthesis[33] after transcription of the LPL gene and by decreased degradation[34] via unknown mechanisms. A reduced cortisol secretion after treatment of Cushing's disease may thus result in

decreased lipid storage via a reduced LPL activity, particularly in the visceral AT depot. LPL activity is also modulated by sex steroid hormones and GH[32,33]. Finally, cortisol suppresses the secretion of corticotrophin releasing factor (CFR)[35]. CRF enhances sympathetic activity and thus lipolysis in rodents[36] as well as in men[37]. Obese subjects tend to have increased serum cortisol levels and recently Strömbom et al. (personal communication) have demonstrated decreased CRF concentrations in cerebrospinal fluid of the obese. The reduction of AT after treatment of patients with Cushing's disease may hypothetically be related to a CRF-induced increase of sympathetic activity. This may be in line with increased sympathetic nerve fibre activity and increased energy expenditure after treatment of patients with Cushing's syndrome (Sjöström et al. to be published).

Growth hormone. The reduction of the AT volume induced by GH may be due both to a decreased reesterification of fatty acids and to an increased lipolysis[38]. Additionally, the expression of LPL by cortisol in human AT is markedly inhibited by GH (Ottosson, M., Edén, S., Björntorp. P. et al. unpublished). However, the lipolytic effect of GH is potentiated by glucocorticoids[38]. Unlike catecholamines, the lipolytic effect of GH is delayed for at least one hour and abolished by inhibitors of RNA and protein synthesis[38]. Experiments with monoclonal antibodies have indicated that the lipolytic effect of GH is not mediated via IGF-1[38]. The lipolytic effect of IGF-1 per se seems to be mediated through the suppression of insulin secretion[39]. Evidently, the GH-dependent acceleration of lipolysis requires an activation of the hormone-sensitive lipase but exactly how this is achieved seems not to be known. Similarly, no data seem to be available explaining why the AT-reducing effect of GH is most pronounced in the visceral AT depots.

Most of the studies cited above were performed in vitro but the lipolytic effect of GH has also been demonstrated in vivo after a single GH pulse treatment in humans[40]. The increased lipolysis was associated with increased lipid and decreased carbohydrate oxidation while the total energy expenditure was unchanged in acute experiments[40]. The isotopically determined appearance rate of glucose decreased, and plasma concentrations of glucose, insulin. C-peptide and glucagon were unchanged[40]. The well-known diabetogenic effect of GH requires sustained elevation of circulating GH[41].

The GH effects on LBM (i.e. mainly skeletal muscles and visceral organs) are remarkably consistent between studies[13,14,22-29] and have been reported to occur in the absence of any training or increased daily activity as assessed by pedometer recordings and activity questionnaires[42] and without changes in dietary intake[23]. The GH- induced expansion of LBM is associated with an increased energy expenditure (unpublished data) that at least partly may be paid by increased oxidation of lipids from the 'melting' AT stores.

The anabolic actions induced by GH require the presence of insulin which has a permissive role[43]. In the absence of insulin, the effects of GH are mainly catabolic[43]. Although rhIGF-1 has been available for some years it is not yet settled to what extent the GH effects on the human LBM are exerted through IGF-1.

GH treatment causes a marked nitrogen retention as measured with neutron activation techniques[13]. The simplest refection of this is reduced blood urea concentrations. In the liver, the GH-induced reduction of urea synthesis is achieved by deviating glutamine nitrogen away from urea synthesis by increased glutamate synthesis from glutamine.[44] Glutamate is then exported to muscles and visceral organs (including liver)[45]. In these organs, GH stimulates amino acid uptake and protein synthesis.[46,47] In muscles, for instance, the amino acid uptake is associated with enhanced accumulation of muscle myosin heavy chain mRNA[47].

Testosterone. Our observation in males that plasma testosterone concentrations are negatively associated with insulin sensitivity[15] has recently been confirmed in a population-based study[48]. Our two intervention studies with testosterone clearly demonstrate that the visceral AT is decreased and that the risk factors are improved by testosterone supplementation to middle-aged men[16,17]. However, it is also clear that an excessive use of testosterone results in insulin resistance and diminished glucose tolerance.[49] Taken together, these observations[15-17, 48, 49] are in line with experiments in male rats demonstrating that castration as well as administration of high doses of testosterone are followed by a marked insulin resistance[50]. Substitution of the castrated rats with testosterone up to normal serum concentrations results in a rapid normalization of insulin sensitivity[50]. It is not clear whether the improvement of cardiovascular risk factors after testosterone treatment of middle-aged men[16,17] was secondary to a reduced visceral AT or primarily explained by improved insulin sensitivity. Both mechanisms may have been operating in parallel. As far as the AT is concerned, it is known that testosterone increases the lipolytic responsiveness of adipocytes by expression of β-adrenergic receptors in rat adipocytes[51]. However, it is not known if this mechanism is more pronounced in viscera than in other human depots. Testosterone also inhibits the cortisol induced expression of LPL (Ottosson, M., Björntorp, R. et al. to be published). This mechanism may be of particular importance in the visceral AT due to the higher density of glucocorticoid receptors in this depot (see above).

It seems unlikely that estrogens, formed by aromatization of testosterone, would be involved since plasma concentrations of 17-β-estradiol were not changed in our intervention studies with testosterone[16,17]. Testosterone as well as DHT reduced the gonadotropins[17]. Unlike testosterone, DHT increased visceral AT and cardiovascular risk factors and reduced testosterone levels. These observations indicate that elevated testosterone levels rather than reduced gonadotropins are involved in the beneficial effects of testosterone treatment in males.

Estrogens. By using dual energy X-ray absorptiometry (DXA) it has been demonstrated that estrogen administration to postmenopausal women decreases trunk AT.[52] In contrast to the situation in males[15], abdominal obesity in women is associated with a hyperandrogenic state[53]. Therefore, the reduced trunk AT in ref. 52 may well have been caused by an estrogen induced increase of SHBG and thus by decreased free testosterone plasma concentrations (Andersson, B., Björntorp, P. et al, unpublished).

Body composition and cardiovascular risk.

This topic, which has recently been reviewed, is summarized below (for references, see[1]): Among several possibilities, a prevailing explanation for the relationship between risk and an increased visceral AT depot is that the resulting increase in portal free fatty acid (FFA) concentration causes elevated hepatic gluconeogenesis and very-low-density lipoprotein

(VLDL) secretion as well as a decreased hepatic insulin clearance. The resulting hyperinsulinemia and insulin resistance, together with increased gluconeogenesis as well as an FFA-induced reduction of peripheral glucose uptake will cause a reduced glucose tolerance and ultimately non-insulin-dependent diabetes. Although the clinical impact is unclear, elevated glucose concentrations may be related to reduced removal of low-density lipoprotein (LDL) and VLDL due to glucosylation and thus to hypercholesterolemia, dypertriglyceridemia, and low high-density-lipoprotein (HDL) cholesterol levels. A reduced fibrinolytic activity in obesity was observed by us 20 years ago and more recently, hyperinsulinemia has been shown to be positively related to the concentration of plasminogen activator inhibitor (PAI-1). High VLDL concentrations may also contribute to increased PAI-1 activity, a state known to be associated with myocardial infarction and reinfarction in young subjects. Finally, hyperinsulinemia or insulin resistance may have a permissive role for the development of hypertension, and high insulin levels may even promote the development of hypertension[54] directly by increasing sodium reabsorption and sympathetic tone. Interestingly, hypertension can be ameliorated by improving insulin sensitivity pharmacologically at a postreceptor level without changing the degree of obesity. Thus, it seems at least hypothetically possible to link diabetes, hypertriglyceridemia, hypercholesterolemia (?), low HDL levels (?), reduced fibrinolysis, and hypertension to elevated portal FFA concentrations due to an increased visceral AT depot[1].

CONCLUSIONS

- The multiscan CT technique permits the determination of a large number of body compartments with a high accuracy and reproducibility.
- In a stricter sense area determinations of visceral and subcutaneous AT can not describe AT distribution because AT areas can not be expressed as a percentage of the total AT volume.
- It is possible to estimate LBM, visceral and subcutaneous AT with errors smaller than 20% by using CT-calibrated sex-specific anthropometric equations.
- In obese subjects the anthropometrically estimated visceral AT mass is a stronger predictor of cardiovascular risk factors than other compartments or the waist/hip ratio.
- Several hormones are involved in the regulation of body composition in adult subjects. Growth hormone and sex steroids reduce the AT and redistribute AT from central to peripheral depots. Cortisol has an opposite effect. Growth hormone also increases the mass of skeletal muscles and visceral organs.

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